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Abstracts
The Israel Society for Neuroscience
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Eilat, Israel, Dec. 12 - 14, 2010
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The effects of Carnitine on histological, biochemical and behavioral parameters in a novel model of chronic kidney disease

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Background: Carnitine is a vitamin-like compound synthesized mainly in mammalian liver, kidney and brain.It serves as an essential factor in the supply of energy to tissues dependant on fatty acid oxidation. The energy originating from this oxidation is quantitatively important as it provide up to 40% of overall need. In patients suffering from advanced chronic kidney disease (CKD), Carnitine has an additional role – lowering the levels of acyl-CoA, which is elevated in these patients and is toxic to many other enzymes. In CKD patients the level of Carnitine in low due to its decreased intake, absorption and biosynthesis. Objectives: we aim to establish a novel rat model to CKD that will enable us to explore whether chronic administration of Carnitine inhibits the development of kidney failure, and affect the metabolic and behavioral CKD complications. Methods: Wistar male rats were randomly allocated to 4 groups: Sham operated; Sham operated + Carnitine; 5/6 nephrectomy (Nx); 5/6 nephrectomy + Carnitine (Nx –Carnitine). Creatinine and blood-urea-nitrogen (BUN) levels as well as qualitative and quantitative morphological analysis were performed to assess kidney function. Moreover, we investigated various behavioral effects of Carnitine, including food and fluids intake, anhedonia (sucrose preference test) and learning (two way shuttle task) performance.

Results: Interestingly, histological analysis demonstrated that the Nx group had more collagen in the kidney than Nx-Carnitine. Moreover, Carnitine treatment reduced Creatinine and BUN serum levels by 25% and 44%, respectively, compared with the Nx group. Food and liquid intake was increased in the Nx group, however, all groups showed similar level of hedonia. Finally, Nx-Carnitine group showed less avoidance and more freezing behaviors in the shuttle box.

Conclusion: chronic treatment with Carnitine had beneficial effects on kidney function in CKD rat model; however it leads to higher freezing level.

Long term in vivo imaging of neuronal networks in the mouse olfactory bulb

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Neuronal circuits are not homogeneous; nor are they stable. Nearly all circuits are composed of a rich repertoire of distinct subpopulations which presumably determines their exact function. Furthermore, neuronal circuits are dynamic as they continuously change and adapt to the never ending demands of the external world. In order to understand the long term plastic changes that neuronal circuits undergo it is useful to develop ways to follow the same networks over time, preferably one component at a time. Here, we developed a novel chronic window preparation in the mouse olfactory bulb (OB), a circuit with unique form of plasticity, because a large portion of its inteneurons (INs) is continuously replaced. This preparation allows in-vivo time lapse two-photon imaging for long periods of time (months) in virtually unlimited number of sessions. We present two applications of this preparation for studying specific subpopulations both anatomically and functionally. Anatomically, we studied the turnover of a distinct subpopulation in the OB - the dopaminergic periglomerular neurons (DA-PGNs). DA-PGNs were rendered fluorescent in a transgenic mouse strain expressing GFP exclusively in DA neurons. We repeatedly imaged the same neurons over months and found a continuous net addition of ~10% in a period of 9 months (n=501 cells from 4 animals). Physiologically, we present in vivo time lapse imaging experiments of calcium responses to sensory stimuli. Specifically, distinct subpopulations of neurons were transduced with different viral vectors to express the genetically encoded calcium indicator GCaMP3.0. Physiological responses to odors of GCaMP3.0-expressing neurons were tracked from identified local networks over months with high reliability. Our experimental design combines imaging and genetic tools to get a hold of anatomical and physiological information from distinct neuronal subtypes over time.

Empathic embarrassment in autistic spectrum conditions: the role of the mirror neuron system

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The neural bases underlying the ability of individuals with autistic spectrum conditions (ASC) to experience empathic embarrassment has never been investigated before. Empathic embarrassment involves situations in which the observer feels embarrassed for a person he observes.

Recent explanatory models of social impairments in ASC center upon a dysfunction in the mirror neuron system. Interestingly, the mirror neurons have been considered to be the foundation for simulation and empathy. It has been shown that some aspects of empathy cannot be accomplished without simulation processes.

Here we examined empathic embarrassment in subjects with ASC using a task that required subjects to view other individuals performing embarrassing tasks and rate their embarrassment as well as the embarrassment felt by the protagonist. Additionally, we examined subjects' performance in the biological motion task, which has been associated with the mirror neuron system. Results indicate that the ASC group is impaired in the biological motion task.

The results in the empathic embarrassment task and their relevance to the mirror neuron system are discussed.

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Imbalanced neural response to basic motivational reinforcers may underlie disturbed cognitive - action interface in obsessive compulsive disorder

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Background: Obsessive compulsive disorder (OCD) is composed of disturbed cognitive relatedness of environmental reinforcers (i.e., obsessions), accompanied by abnormal non-goal oriented behaviors (i.e., compulsions). Notably, motivation, which presumably evolved to guide us to avoid threats but approach rewards in the environment is regarded as the drive to facilitate or inhibit behavior in response to environmental reinforcers. Taken together, it suggests that maladaptive interface between cognition and action, as exampled in OCD, may be driven by disturbed motivational processing.

Methods: 13 OCD patients and 13 age-matched healthy controls underwent fMRI while playing a computerized interactive Domino game that encompasses discrete intervals of threat and reward. This game was shown before to activate the amygdala in response to threat (Kahn et al 2002) and the nucleus-accumbens (Nacc) in response to reward (Assaf et al 2009); corresponding to previous findings on the neuronal foundations of motivational tendencies.

Results: OCD patients compared to controls exhibited heightened amygdala response to threat as well as diminished Nacc response to reward. Furthermore, the functional connectivity between the amygdala and Nacc to the dorsal Anterior Cingulate and medial Pre Frontal Cortex, respectively, was weaker in OCD patients compared to controls. Lastly, weaker functional correlations were related to more severe OCD symptoms.

Conclusions: Our results demonstrate imbalanced neural response to basic motivational reinforcers in OCD. Furthermore, this imbalance seems to be related not only to local regional activation but rather to limbic connectivity with the Pre Frontal Cortex, an area known to mediate innate, self driven information processing. Such imbalanced distributed brain activity may yield inappropriate emotional response towards a stimulus in the environment, as typically evident in anxiety disorders including OCD.

Differentiating alpha and mu suppression during observation of motor acts using PARAFAC and PCA methods

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EEG oscillations between 8-12 Hz are desynchronized and their amplitude reduced in humans while observing biological movement. This EEG modulation, which has been traditionally labeled mu-suppression, is recorded primarily over the sensory-motor cortex and reflects motor activity. The specific sensitivity to motor activity and a presumed source in the sensory-motor cortex distinguish the mu rhythms from the parieto-occipital alpha waves. Nevertheless, since both rhythms share the same frequency range and, at rest, this frequency dominates the EEG across most scalp sites, disentangling mu rhythms from alpha is not trivial. This endeavor is further complicated by the evident sensitivity of alpha to the level of visual attention allocated to processing. This factor might be easily confounded with the perceptual aspects of motor manipulation. Indeed, although mu suppression is expected primarily at fronto central sites, similar (and sometime even larger) EEG modulation can be recorded from traditional alpha-dominated locations at parieto-occipital sites. In the present study we applied two analytic algorithms, Parallel Analysis of Factors (PARAFAC) and Principal Component Analysis (PCA), aimed at separating mu from alpha EEG manifestations, and compared their outcome. These algorithms were applied to data recorded while 24 observers either grasp an object repeatedly or watch a video of a hand grasping different objects. A video of a rolling ball was used as baseline. We will present the results of the two algorithms and discuss the implementation of these methods.

Cognitive control changes with aging

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Cognitive abilities decrease with aging. Aging affects inhibitory processes that control visuo-motor transmission. Hasher and Zacks (1988) suggested that age-related impairments result from weakening of inhibitory processes with aging. In the current study, age differences were tested using the Simon task, commonly used to measure cognitive control recruitment. In this task participants are presented with a blue or red color patch and asked to press a left or right key according to the color (e.g., press left key for red). Presenting the color patch to the left or right of the center of the computer screen creates congruent (e.g., red on the left) or incongruent (e.g., red on the right) conditions. Participants commonly respond slower to incongruent than to congruent trials (i.e., the Simon effect). This task was generally found to involve activation of the dorsolateral prefrontal cortex (DLPFC) and the anterior cingulated cortex (ACC). In a series of 3 experiments, behavioral and fMRI studies were carried out using a Simon task with a neutral condition and inter-trial interval (ITI) jitter. The behavioral results showed a larger Simon effect and interference component for old compared with young adults, and sequential analyses revealed different patterns of control recruitment between groups. Primary imaging data showed different error monitoring processes between young and old adults. Our results strengthen inhibition impairment theories and shed light on brain structures involved in error monitoring that decline with aging.

A unique asymmetrical auditpry stroop effect in absolute pitch possessors

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The Stroop effect is known to be asymmetrical, with words affecting color naming but not vice-versa. Many theories tried to explain this asymmetry. In order to test these theories, in the current work an auditory-visual Stroop like task was devised. In the tone naming task participants were asked to name the auditory tone while ignoring the visual note name. In the reverse task, participants were asked to read a note name while ignoring the auditory tone. Participants could be either absolute pitch (AP) possessors or musically trained controls without AP (nAP). The nAP group showed a significant Stroop effect without a reverse Stroop effect, whereas AP possessors showed a unique asymmetry with a significant reverse Stroop effect only. The results are interpreted as supporting the automaticity account of the Stroop effect. Importantly, the present experiment further demonstrates the strong automaticity of pitch tone labeling in people endowed with AP ability.

The road to neurodegeneration is paved with good intentions: the controversial role of dopamine in a pre-clinical Parkinson's disease model

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Maladaptive response to oxidative stress (OS) is a possible cause of the neurodegeneration of Parkinson's disease (PD), however, the role of dopamine (DA) in compensation and generation of OS is unclear. We have developed a new rat model system to study this problem, consisting of rats with 44% loss of nigral dopaminergic neurons and a novel free radical trap, scavenging extracellular reactive oxygen species (ROS).

Methods: Stable destruction of nigral dopaminergic neurons was produced by intracerebroventricular injection of 6-hydroxydopamine (6-OHDA; 250 μg), and was accompanied by increased striatal DA turnover. The novel marker is a molecule combining tyrosine and linoleic acid (LT), which does not diffuse through the microdialysis membrane, but is attacked by ROS diffusing into the microdialysis probe from the extracellular space. Products of this ROS attack were detected, and quantitated by HPLC/MS.

Results: Perfusion of LT in the striatum of 6-OHDA-lesioned rats resulted in increased generation of hydro peroxide LT derivative (44%±4), reserpinisation or monoamine oxidase (MAO) inhibition by tranylcypromine (TCP) drastically reduced OS by 40%±3 and 47%±3 respectively. The DA compensatory mechanisms in the 6OHDA rats increased the level of OS both in reserpinized and MAO inhibited rats compared to SHAM rats treated with the same substances (24%±5 and 12%±4 increase respectively). Striatal tissue reduced and oxidized glutathione levels showed a decreased level of intracellular OS in the 6OHDA rats, despite the elevated level of OS in the extracellular compartment.

Conclusions: a) Partial dopaminergic denervation is accompanied by elevated extracellular stress but compensatory changes effectively reduce intracellular stress. Failure of this compensatory mechanism may be important

in the accelerated neurodegeneration of PD; b) Oxidation of DA either by MAO or through auto oxidation is a powerful OS generator and is increased by DA neuronal loss in pre-motor PD.

The plastic multisensory human brain: insights from crossmodal plasticity and sight restoration efforts in the blind using fMRI and TMS

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In the talk I will cover research on the combination of functional magnetic resonance imaging (fMRI) and Transcranial Magnetic Stimulation (TMS) to study crossmodal plasticity and multisensory integration in blind and in sighted individuals. These methodologies were applied to study central questions in perception, brain plasticity, large-scale brain dynamics and multisensory integration. I will focus on recent results imaging blind individuals' brain before and after learning to use visual-to-auditory sensory substitution algorithms to 'see' using a webcam and soundscapes (aka artificial vision). Finally, I will present how such methods can be used to start looking into the binding problem: how we integrate information into a coherent percept, an old question in neuroscience which has relatively poor answers, especially in humans.

Supported by the Human Frontiers Science Program Career Development Award, an EU-FP7 MC International Reintegration Grant, an Israel Science Foundation grant and a German Israeli Foundation grant (to AA). Lab website: http://brain.huji.ac.il/ *contact:* amir.amedi@ekmd.huji.ac.il

Prolonged but not acute withdrawal from cocaine following CPP decreases synaptic NMDAR and AMPAR subunits in the Nucleus Accumbens

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Incubation of cocaine craving is a term describing a phenomenon in which a time-dependent increase of cocaine seeking is induced by exposure to cocaine cues during the first months of withdrawal. Behavioral studies conducted in our laboratory demonstrated that rats that undergo conditioned place preference (CPP) displayed preference 1 day after withdrawal, and maintained their preference even 13 days following withdrawal. In light of these findings, our aim was to explore the molecular mechanisms underlying this phenomenon.

CPP is a classical (Pavlovian) conditioning model which reveals the rewarding effect of a drug. Using CPP as a behavioral paradigm, we found that after one test, made 13 days after conditioning, there was a significant decrease in NR1, NR2A and NR2B subunits of the ionotrophic glutamate N-methyl-D-aspartate receptor (NMDAR), the GluR1, GluR2 and GluR3 subunits of the a-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR) and the scaffolding protein postsynaptic density 95 (PSD95), in the nucleus accumbens (NAc), compared to rats that undergo one test, 1 day after conditioning. We also found a decrease in ERK activity which correlated with the decrease in NMDAR and AMPAR subunits in the NAc after 13 days of withdrawal. Interestingly, all of the above changes were seen in the synaptosomal membrane fraction (LP1), and not in the total homogenate (H), indicating that withdrawal from cocaine didn't affect the expression of these proteins but alter their intracellular localization.

Taken together these results suggest that the desensitized response of glutamatergic NMDAR and AMPAR systems are part of long time neuroadaptations involved in the rewarding properties of cocaine following prolonged withdrawal.

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The mechanisms underlying the paradoxical protective and pathological effects of apoE4 in the retina

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#Both authors contributed equally to this research.

Background: ApoE4, the most prevalent genetic risk factor of Alzheimer's disease is protective of Age Related Macular Degeneration, the major cause of visual impairments and blindness in the older population (> 50 years). We hypothesize that a unifying neuronal and vascular mechanism may explain this apparent paradox. As a first step of unraveling these mechanisms we examined the effects of aging on apoE4 retinas.

Methods: Morphological and biochemical measurements of the neuronal and vascular systems in retinas of neonatal, 3 and 9 months apoE3/apoE4 targeted replacement mice as well as of ERG in 9 months old mice.

Results: Immunoblot assays revealed that synaptophysin levels of apoE4 retinas were lower than those of apoE3

in neonate and 9, but not in 3 months old mice. The glycolytic enzyme GAPDH and the inhibitory pre-synaptic marker GAD-67 showed similar results, suggesting that apoE4 has synaptic and energy related pathological effects during development and aging. ERG measurements revealed that the loss of inhibitory synapses was associated with elevated ERG.

Assessment of the retinal vasculature revealed transient occurrence of tufts in the apoE4 neonatal retinas, accompanied with increased expression of VEGF-B. Such tufts have been previously associated with impaired penetration of blood vessels into the developing retina. Further studies revealed decreased density of the vasculature at 9 months but not at 3 months apoE4 retinas.

Conclusions: These findings show that during development and aging the retina is pathologically affected by apoE4. The mechanisms underlying these effects and the extent to which they underlie the apparent paradoxical effect of apoE4 in AMD will be discussed.

Changes in behavioral performance and memory-related mechanisms in the rat Hippocampus following a contextual reminder of an underwater trauma

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Studies have shown that stress can affect neural plasticity. Most studies dealing with the effects of stress on neural plasticity focused on synaptic plasticity and long-term potentiation (LTP) of principle cells. However, following stress, modifications can also take place at the level of complex interactions with interneurons, i.e. at the local circuit level. In the present study, we set out to examine the possible impact of re-exposure to the context of a traumatic experience (i.e. underwater trauma) on the plasticity of the principle cells but also on local circuit activity within the dentate gyrus (DG). To analyze the effects of re- exposure to stress, rats were first exposed to underwater trauma and 24 hrs later were re-exposed to its context. Immediately following context re-exposure, rats were anesthetized and DG responses to perforant path stimulation were recorded. Two protocols, Frequency-dependent inhibition (FDI) and paired-pulse inhibition (PPI) were employed to reflect the activity of GABAergic interneurons in the DG. Measuring both population spike amplitude and field-EPSP, all groups showed similar input-output and baseline responses. Rats that had been exposed to underwater trauma and had been re-exposed to its context 24 hr. later showed significantly higher inhibition in both PPI and FDI protocols compared to control rats. Additionally, compared to control rats, traumatized rats showed reduced level of dentate gyrus LTP. Furthermore, compared to control rats, rats that had been exposed to underwater trauma and had been re-exposed to its context 24 hr. later showed increased anxiety behavior in the elevated plus maze and in the open field tests. Taken together, these findings indicate that the re-exposure to a contextual reminder of a trauma affects not only aspects of plasticity of principle cells, but also aspects of local circuit activity in the DG. These alterations may underlie some of the behavioral consequences of the traumatic experience.

Hyperploid neurons in the normal human brain and in Alzheimer´s disease

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Hyperploidy, i.e., neurons with a more than diploid DNA content, might be a significant source for neuronal complexity, intercellular diversity, and evolution. Genomic instability associated with hyperploidy, however, can also lead to developmental abnormalities and decreased cellular fitness. In the normal human brain, the number of hyperploid neurons, amounts to about 10%. In Alzheimer´s disease (AD), however, this number is more than doubled. Hyperploid neurons are increased already at preclinical stages of AD and are selectively affected by cell death during progression of the disease. These findings show that neuronal hyperploidy in AD is associated with a decreased viability. Hyperploidy of neurons, thus, represents a direct molecular signature of cells prone to death in AD. This adds hyperploidy to the list of critical molecular events that are shared between neurodegneration and malignant cell transformation. Irrespectively of whether hyperploidy results from a lack of aneuploidy clearance during brain development or an aberrant attempt of cell cycle re-entry and DNA replication in the adult, it directs our attention to a failure of neuronal differentiation as the critical pathogenetic event and potential therapeutic target in neurodegeneration.

Neuroprotective potential of human umbilical cord blood stem cells for ischemic brain

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Human umbilical cord blood (CB) is a known source for hematopoietic stem cell transplantation. It is also considered an accessible and less immunogenic source for mesenchymal, unrestricted somatic and other pluri/multipotent stem cells. We isolated a unique population of progenitors from the CB, using their collagen adherent properties and positive expression of alpha1 and alpha2 collagen-receptors. Microarray gene expression analysis indicates that the cells are negative for common hematopoietic markers and positive for common mesenchymal markers, supporting their mesenchymal or unrestricted origin. Our approach to induce differentiation towards a neuronal phenotype was based on supplementation of growth factors, mainly of nerve growth factor and interferon-gamma. The cells differentiation was evaluated by the activation of MAPK signaling and by the expression of a wide range of neural markers. The neuroprotective potential of CB-progenitors was evaluated using a neuronal ischemic in vitro model adjusted to measure cell-cell induced neuroprotection. We found these cells to confer neuroprotection by a mechanism involving the release of antioxidants, the decrease in numbers of free radicals in the injured neuron and the accumulation of neurotrophic and angiogenic growth factors in the media, supporting a "bystander" neuroprotective strategy. The ability of CB-derived progenitors to confer protection against in vivo neurological deficits caused by brain ischemia was evaluated using a closed head injury model in mice. We demonstrated that upon intra-cerebral administration of CB cells, many of the physical and behavioral deficits associated with this disease were ameliorated. The improvement in the neurological score was achieved under cell administration of 1 and 7 days after injury. These results indicate a wide range for intervention and emphasize the clinical relevance of the use of CB cells as a potential therapeutic approach for brain ischemic injuries.

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Parent-Infant Bonding Mechanism: Neuro-Behavioral Insights

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Background: We assessed parent's brain response to two-minute films of the infant to provide an ecological assessment of the neural process underlying parental attachment. Uniquely, we also obtained a behavioral analysis of parent-infant interactive synchrony. The integration of the two measures is novel and may provide insight on the dynamic patterns of brain activations which coordinate to specific attachment markers.

Method: Families were recruited and videotaped. Movies were behaviorally-analyzed to evaluate the parent-infant interaction. The behavioral analysis yielded a measure of parent-infant synchrony: synchronous moms (N=8), intrusive moms (N=8).

fMRI data was analyzed using brain voyager 2.1.

Results: Two regions of interest were found to be differentiated by the groups: the R-Amygdala and L-NAcc.

Functional connectivity maps:

Seed region: L-NAcc

Intrusive mothers displayed subcortical correlations (thalamus, hypothalamus, brainstem, midbrain, cerebellum, insula), yet almost no cortical correlations in IFG, MPFC, ACC, and PCC. Synchronous mothers demonstrated limbic, as well as cortical correlations.

Seed region: R-Amygdala

conversely, the right amygdala map illustrates an inverse outcome: Invasive mothers display subcortical as well as cortical correlations. Synchronous Mothers display only lower areas correlations and almost no cortical correlations.

Discussion: Parents' brain responses to baby stimuli involve two networks: affective areas may process the intuitive approach of a parent to a baby, while cognitive areas integrate a synchronous relationship with the baby. Here, we demonstrate that the outcome of maternal behavior depend on the combination of these two networks. Parent-infant synchrony is an important index of attachment, and has shown to contribute to the child's mental health. Thus, the delineation of the neural pathways underlying a healthy attachment may provide insights into healthy and high-risk parenting.

Interaction between seminal proteins and the female mediates post-mating behaviors in Drosophila

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Even after mating has ended, molecules from male animals continue to interact with molecules and pathways within the female, ensuring the reproductive success of the mated pair. The fruit fly Drosophila melanogaster offers an excellent model system in which to characterize these interactions and their consequences. In particular, seminal fluid proteins that are transferred from males to females during mating affect females' reproductive physiology and behavior. Through the use of Drosophila genetics, genomics and

biochemistry, coupled with behavioral observations, the field is learning the molecular and neural pathways through which male-derived molecules act on, and with, the female. After an overview of those studies, this talk will focus on some recent results from our lab that dissect pathways through which seminal proteins interact with one another, and with the female, to regulate sperm storage and/or ovulation for days after mating. Although these interactions are often synergistic, the sequences of many seminal proteins, and some aspects of their expression, reveal effects of male-male competition or sexual conflict.

We are grateful to the US NIH/NICHD for support of this work

Indication for P/Q type voltage dependent Ca2+ channel resistance to hyperbaric pressure

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Background: Professional deep sea divers experience High Pressure Neurological Syndrome (HPNS) when exceeding depths of 100 m. HPNS includes various motor, sensory and cognitive deficits. Impaired synaptic transmission has been previously implicated with HPNS. Our recent work suggested the involvement of presynaptic voltage dependent Ca^{2+} channels (VDCCs), and that hyperbaric pressure (HP) selectively affects different types of presynaptic VDCCs. To further investigate the role of VDCCs in HPNS mechanisms we tested currents of the $Ca_V2.1$ (P/Q) channel, suspected to be almost HP resistant.

Methods: cRNAs of $Ca_V2.1$ subunits (human α1A, rabbit $\alpha2\delta$, rat β3) were injected to *Xenopus laevis* oocytes, followed by 4-5 day incubation. Using two electrodes voltage clamp experiments we measured the voltage - Ba^{2+} current relation inside a pressure chamber, helium compressed up to 0.6-2.6 MPa (5-25 ATA) at 24-26°C.

Results: Preliminary results suggest that HP does not significantly affect currents amplitude in $Ca_V2.1$ channels, since maximal currents measured under HP did not exhibit a substantial or repeatable change from control level. Normalized maximal currents was 10±1.06% (n=4, p= 0.20) above control. The voltage dependent inactivation also seems insensitive to HP.

Discussion: These preliminary results further support previous findings demonstrating selective HP effect on VDCCs. Unlike $Ca_V1.2$ (L, potentiated) and $Ca_V3.2$ (T, depressed), $Ca_V2.1$ channel seems to be pressure resistant. Recent work in rat dentate gyrus (Talpalar et al.2010) has demonstrated that although elevated $[Ca^{2+}]_o$ at presynaptic terminals increases probability of release, it can only partially compensate for the HP-induced reduction of total release. This compensation may occur through synaptic release sites adjacent to VDCCs which are less sensitive to HP, such as the $Ca_V2.1$.

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The role of the medial prefrontal cortex in consolidation of recent and remote extinction of conditioned odor conditioning

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Conditioned taste aversion (CTA) and conditioned odor aversion (COA) are based on the association between the chemosensory characteristics of food [conditioned stimulus (CS)] with visceral malaise [unconditioned stimulus (US)]. The neural circuit mediating CTA acquisition and extinction is well defined and it includes the amygdala, the insular cortex and the medial prefrontal cortex (mPFC). However, the neural circuit mediating COA is less well known. In this study we wanted to examine (1) the role of the mPFC in the extinction of COA and (2) to examine whether there is a differential involvement of the mPFC in recent as compared to remote memory of COA. To test these questions we evaluated the effects of reversible inactivation of the mPFC on extinction of COA. Lidocaine was microinfused into the mPFC immediately after the first retrieval test on either 2 days (recent memory) or 28 days (remote memory) after COA acquisition. Our results show that (1) odor conditioning can be reliably established in the laboratory, (2) the mPFC and mainly its subregion the infralimbic cortex has a role in the extinction of recent memory of COA, since inactivation of the IL immediately after the first extinction training 2 days after COA acquisition impairs extinction and (3) the IL does not seem to have a role in the extinction of remote memory of COA. These results suggest that the mPFC has a differential role in recent and remote extinction of COA and it further suggest that the role of mPFC is different in extinction of CTA as compared to COA.

Mechanical tension is instrumental in neuronal and network development

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A bewildering series of dynamical processes participate in the proper development of the complex architecture of the nervous system. Complete understanding of this process will be achieved only by taking into account the effects of physical-mechanical forces. Recent years have seen significant contributions, including the role of axonal tension in the development of neuronal morphology, the effects of

mechanical cues from the substrate, the role of tension in axonal pruning, synaptogenesis, and neuronal migration. Work in this direction has benefited much from the use of insect neuronal cultures. Insect neurons are relatively large and can be plated in low density. Using specially prepared culturing substrates and time lapse observation, we were able to explore various developmental processes in networks composed of cultured locust neurons. Utilized substrates included clean quartz surfaces applied with isolated anchoring sites consisting of carbon nanotube (CNT) islands to which the cells and neurites could mechanically attach. We investigated and validated the important role of mechanical tension in determining the final morphology of neuronal networks and suggest an equally important effect on neuronal and network function. This is an exciting field of multidisciplinary study that encompasses biology, physics and engineering and enjoys both conceptual and technical recent advances in all of these. Recent results will be presented and the validity of these results to other in-vitro and in-vivo data will be discussed.

Overcoming intuitive interference: A preliminary tDCS study

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Background: Students encounter difficulties in science and mathematics, which may stem from intuitive interference with analytic reasoning. In a previous fMRI study participants compared the perimeters of two geometrical shapes in two conditions: 1) congruent, in which correct response is in line with the intuitive reasoning and 2) incongruent, in which correct response is counterintuitive. Success rate was lower in the incongruent condition and correctly answering it specifically activated bilateral prefrontal areas known for their executive control over other brain regions. Recently we showed that, students with strong executive control outperform their peers in this task.

In this preliminary study we explored how accuracy in this task is affected by tDCS (transcranial Direct Current Stimulation).

Methods: Participants were twenty-seven young adults. All performed the comparison-of-perimeter test (T1) after Sham (S), and later performed the test again (T2) after Sham or Anodic stimulation (A) [control (n=10), SS; experimental (n=17), SA]. Stimulation was in the right prefrontal region. Neuropsychological tests showed that the groups were similar in their short-term memory and visuospatial abilities.

Results: In the experimental group a significant improvement in accuracy from T1 to T2 was found in incongruent complex trials (64% to 79%, p=0.042) while in the control group similar success rates were observed for these trials (from 54% to 56%). In addition, in the experimental group accuracy in incongruent simple and complex trials increased from T1 to T2 (73% to 86%, p=0.073), while in the control group similar success rates were observed for these trials (from 60% to 62%).

Conclusions: These preliminary findings suggest that stimulating the right prefrontal cortex improves participants' ability to overcome intuitive interference, possibly due to activation of inhibitory-control-mechanisms and/or other relevant cognitive functions. Educational implications will be discussed.

Anchoring – a potential link between perception, memory and early reading skills

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Good phonological skills and alphabetic knowledge in the preschool period positively contribute to the acquisition of adequate reading skills once formal reading instruction begins in the first grade. Nevertheless, the cognitive underpinnings of these elementary skills in the preschool period remain poorly understood. Our goal was to test, in kindergarten children (n=43), the Anchoring Deficit Hypothesis which suggests that reading development may be impaired due to reduced sensitivity to contextual cues (Ahissar, Lubin, Putter-Katz and Banai, 2006). To that end, we asked whether the availability of contextual cues contributes to frequency discrimination, verbal memory and rapid naming, and whether there is an association between sensitivity to contextual cues and early reading skills. Sensitivity to contextual cues was determined by assessing frequency discrimination, rapid naming and verbal memory span in two conditions varying in stimulus set size and thus providing different amounts of contextual cues. Early reading acquisition was assessed with phonological awareness and letter identification tasks. We found that in the small-set conditions frequency discrimination was better, naming speed was faster and memory spans were longer relative to the large-set conditions, suggesting that across domains kindergarten children can use contextual information to facilitate performance. Furthermore, children with better contextual facilitation (based on the rapid naming tasks) identified more letters and had longer memory spans compared to the children with poorer contextual facilitation, suggesting that anchoring is related not only to reading difficulties in older children but also to emerging reading skills. Further longitudinal studies are required to determine if preschool children's anchoring predicts reading acquisition in school.

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State dependent modulation of neuronal activity during magnetic stimulation

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Transcranial magnetic stimulation (TMS) is used extensively in cognitive psychology studies and in clinical treatments of multiple neurological and psychiatric conditions. Despite its growing popularity, little is known about the effect it exerts on the underlying neurons of the central nervous system (CNS). Unraveling the mechanism of TMS effects requires a multi-level approach combining multidisciplinary studies on the biophysical, cellular neurophysiology, system neurophysiology and cognitive neuroscience levels. As part of such a combined effort we set out to investigate this question by combining magnetic stimulation using our novel magnetic mini-coil with simultaneous recordings of neuronal activity in the behaving primate. This mini-coil fits into a chronic recording chamber and provides focal activation of cortical areas while enabling simultaneous extracellular multi-electrode recordings in multiple brain structures. This allows, for the first time, to record in multiple areas of the CNS during magnetic stimulation. This configuration enabled us to study the temporal and spatial activation patterns of cortical neurons directly activated by the induced electrical field and of sub-cortical neurons activated synaptically by the cortical neurons. The study was performed in two states: normal and parkinsonian (MPTP treated). The study demonstrates that equivalent modulation of cortical activity in the two states leads to drastically different activation patterns of basal ganglia neurons. The large stereotypic indirect modulation of the sub-cortical targets occurring in the parkinsonian state was completely missing in the normal state. This modification of the descending cortical activity transmission led to changes in both the single neuron level and the neural network level. These results emphasize the need to customize both scientific and clinical stimulation protocols to the underlying brain state.

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Losartan prevents BBB opening / albumin-induced epileptogenesis

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Epilepsy, affecting 0.5-1% of the population, is one of the most common brain disorders. Almost any injury to the brain, including traumatic, ischemic and infectious injuries may lead to epilepsy. These insults are also associated with blood-brain barrier (BBB) dysfunction. Recent studies pointed injury to the vascular bed and specifically to dysfunction of the BBB as key mechanisms sufficient to induce transcriptional program, eventually leading to epileptogenesis. Once the BBB is compromised, albumin diffuses into the brain, binds to TGF-beta receptor II and activates the TGF-beta signaling pathway, leading to atsrocytic dysfunction and inflammatory response. Losartan is an angiotensin II type 1 receptor (AT1) blocker and recently shown to antagonize TGF-beta signaling in-vivo. We thus challenged the hypothesis that administrating losartan to BBB compromised rats will prevent epileptogenesis. Rats were treated with focal neocortical application of the bile salt sodium deoxycholate (n=8) or serum albumin (n=15) in the presence or absence of losartan (n=5, 13). A sham-treated group served as control (n=18). An EEG-telemetric system was used to continuously monitor brain activity and seizures 4-5 weeks after treatment. We show that losartan prevents albumin-induced smad-2 phosphorylation and partly blocks the consecutive transcriptional response. Furthermore, losartan reduces the extravasation of Evans blue-albumin complexes into the brain, suggesting that TGF-beta signaling is involved in BBB dysfunction and repair mechanisms. BBB opening and exposure of the brain neuropil to albumin induce spontaneous "seizure like activity" in 80% of the DOC and in all albumin treated rats. Losartan-treated showed a significant reduction in both the frequency and duration of seizure like events. This work strongly supports the role of BBB dysfunction in epileptogenesis and highlights the potential role of TGF-beta signaling inhibitors in the prevention of injury-induced epilepsy.

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Enriched environment effects on synaptic proteins and micro RNA expression in the mouse hippocampus

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Synaptic transmission is the process by which nerve cells communicate. This process involves many synaptic proteins, and changes in their levels and sub-cellular localization will lead to alterations in brain plasticity and cognitive performance. Such changes may be caused by microRNAs,

endogenous RNAs that make fine-scale adjustments to their targeted mRNAs and proteins levels. Environmental stimulation was shown to induce brain plasticity and improve cognitive performance, though the mechanisms underlying these effects remain mainly unknown.

Utilizing immunohistochemistry we examined the levels and distribution of the synaptic proteins Synaptophysin, and the negative and positive-regulators of the synaptic transmission process Tomosyn and Munc-13-1 in the hippocampus of mice that were exposed to enriched environment for 8 weeks and compared them to those of corresponding mice that were kept in a regular environment. Affymetrix microarray was used to examine the microRNA expression profile in the hippocampus of these mice.

We found that the levels of Synaptophysin and Munc13-1 proteins were significantly up-regulated in the hilus and mossy fibers following environmental stimulation whereas the corresponding levels of Tomosyn, a down-regulator of synaptic transmission, were significantly down-regulated in these hippocampal subfields. Correspondingly, miR-483, predicted to down-regulate Synaptophysin mRNA and protein levels, was highly down-regulated following environmental stimulation. These results suggest that enriched environment increases the synaptic transmission process, and improves its efficiency by concomitantly reducing negative regulatory mechanisms and up-regulating positive regulatory mechanisms. This occurs both at the microRNA and protein level, and provides a novel mechanism via which neuronal and synaptic activity can regulate synaptic transmission.

Thalidomide analog, 3,6'-dithiothalidomide as a potential neuroprotective treatment for minimal traumatic brain injury in mice

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Most minimal traumatic brain injury (mTBI) patients don't show clear structural brain defects and usually don't require any hospitalization. However, some frequently suffer from long-lasting cognitive, behavioral and emotional difficulties. As yet, there is no effective treatment or cure for patients with mTBI. Tumor necrosis factor-alpha (TNF-a) is a cytokine that is fundamental in the systemic inflammation process. TNF-a levels increase after mTBI, which may cause and initiate secondary damage to the brain tissue and apoptotic cascade at the cells. Thio analogs of N-a-phthalimidoglutarimide, which is the backbone of the well-known drug, thalidomide, have been synthesized to reduce the initial synthesis of TNF-a. The present study was aimed to evaluate the effect of the potent experimental drug, 3,6'-dithiothalidomide on the recovery from mTBI. We used a closed head weight-drop experimental model to induce minimal brain injury in mice. Mice received an injection of either vehicle or 3,6'-dithiothalidomide 1 hour prior to injury and 1 or 12 hours post injury in different 2 doses. 72 hours and 7 days post injury; mice were assessed in 3 behavioral paradigms. Mice exhibited lower learning ability following mTBI in the Y- maze and in the Novel object recognition test. These differences reach significance only at 7 days post injury. These impairments were reversed in mice that received 3,6'-dithiothalidomide prior or after mTBI injury. Lower learning ability was seen in the Passive avoidance test, that did not reach significance. Together, these results suggests that 3,6'-dithiothalidomide may act as a neuroprotective drug to minimize impairments associated with mTBI.

A novel fast mechanism for GPCRs-mediated signal transduction control of neurotransmitter release

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Neuronal communication depends on rapid, temporally precise, neurotransmitter release. Neurotransmitter release is accomplished by Ca^{2+}-dependent exocytosis which characterizes also slow release. How, then, can the Ca^{2+}-dependent exocytosis be so fast and precise in nerve terminals? The prevailing dogma is that precision is achieved by the action-potential inducing fast Ca^{2+} influx. However, temporal control of acetylcholine release is achieved by depolarization relieving a tonic block of release imposed by presynaptic M2-muscarinic receptor (M_2R). To date, the molecular mechanism that underlies release control is unknown. Recently it was discovered that M_2R, like voltage-gated channels, displays depolarization-induced rapid charge movement, offering an unexpected avenue to seek for the molecular mechanism by which voltage-sensitive M_2R controls release. Here we show, for the first time, a novel mechanism by which the action-potential triggers release. Using a fast application system we show that manipulating charge movement in the M_2R instantaneously affects the amount of acetylcholine release and its time of initiation. Our findings call for a revision in the long held consensus. Accordingly, physiological neurotransmitter release involves two distinct processes, both induced by the action-potential, but each is handled by

different proteins. One process is activation by Ca^{2+}, as is well established, of the exocytotic machinery, presumably by Ca^{+2} acting on synaptotagmin. The second process, which is somewhat slower, is removal of a "brake" from the exocytotic machinery. This is accomplished by charge movement in the M_2R. Our findings also demonstrate a novel extremely fast mechanism for GPCRs-mediated signal transduction that does not involve G-protein activation. Charge movement in GPCRs is expected to induce signal transduction also in other systems where rapidity and precision is essential.

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Incubation of fear in the conflict model for relapse to cocaine use

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Drug addiction is not just the repeated administration of drugs, but compulsive drug use maintained despite the accumulation of adverse consequences for the user. In laboratory animals, adverse consequences of drug seeking or use are usually not taken into account; and to this end, we have developed the 'conflict model'. This model incorporates adverse consequences of drug seeking and taking by presenting an electrical barrier to the reinforcing lever, which leads to self-abstinence from drug seeking. The objective of the present study was to evaluate whether presentation of discrete cues that have been associated with cocaine or sucrose self-administration, can induce relapse to cocaine or sucrose seeking and whether home-cage withdrawal can facilitate cue-induced relapse in this model. We have utilized the 'conflict model' to test cue-induced relapse after 1 or 14 days of home-cage withdrawal, in groups of rats that were previously trained to self-administer cocaine or sucrose. We found that although similar shock intensity was required to suppress sucrose or cocaine self-administration, subjects exhibited significantly lower response to sucrose-, as compared to cocaine-, associated cues, during the relapse test. Importantly, cue-induced relapse to cocaine was attenuated following withdrawal, both when tested under the abstinence threshold (i.e. the current intensity in which subject stopped responding for the reinforcer), or at 85% of this threshold. Therefore, the incorporation of aversive consequence in the self-administration model enables detection of a compulsive component which is unique to drug reinforcers. Moreover, the aversive consequence seems to dominate the behavioral outcome following drug withdrawal.

Action video games as exemplary learning tools

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Although the adult brain is far from being fixed, the types of experience that promote learning and brain plasticity in adulthood are still poorly understood. Surprisingly, the very act of playing action video games appear to lead to widespread enhancements in visual skills in young adults. Action video game players have been shown to outperform their non-action-game playing peers on a variety of sensory and attentional tasks. Notably changes in early vision such as better contrast sensitivity, enhanced crowding acuity and better ability at external noise exclusion are noted. A common mechanism may be at the source of this wide range of skill improvement. In particular, improvement in performance following action video game play can be captured by more efficient integration of sensory information, or in other words, a more faithful Bayesian inference step, suggesting that action gamers may have learned to learn.

Prevention by ladostigil of the loss of object, and place recognition memory in ageing rats

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Background: Ladostigil is a novel drug currently being developed for the treatment of Alzheimer's disease. The present study showed that ladostigil could prevent the development of age-related deficits in object (OR) and place recognition (PR) memory in rats.

Methods: Both tests were performed in 24 male Wistar rats from the age of 13 months. In the OR test the time taken to explore two identical objects was assessed during 2 min. Two hr later one object was replaced by a different one, and in the PR test, one of the objects was moved to a new location. The difference in the time exploring the familiar (F) and novel (N) object or that in a novel location (N-F sec) was assessed at monthly intervals. At 16 months of age half the rats were given ladostigil (1 mg/kg/day) in their drinking fluid and half, tap water.

Results: 14 month-old rats were able to discriminate between objects (7.0±1.6 sec) and locations (9.6±3.3 sec) but this was lost at 15 months (4.9±2.9 sec) for objects and at 17 months for locations (2.2±1.5 sec). Chronic treatment with ladostigil prevented the decline in OR (8.4±2.3 sec) and PR (7.4±2.0 sec) at 20-21 months of age. Acute administration of ladostigil (4 mg/kg, but not 1 mg/kg) to 21 month-old controls restored memory in the PR (9.8± 2.3 sec) but not in OR (1.9±2.2 sec), while ladostigil (8.5 mg/kg) restored memory in the OR (8.0±3.2 sec).

Conclusion: The data show that in ageing, recognition is lost before spatial memory and requires a larger dose of ladostigil to reverse the loss.

Postnatal interference of Sp1 activity predisposing to chronic stress – implication for schizophrenia

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Background: Schizophrenia is a chronic, severe, and disabling mental disorder which affects 1% of the world population. Schizophrenia is diagnosed on the basis of symptom profiles. The positive symptoms are characterized by a constellation of symptoms of psychosis, such as abnormalities in the perception or expression of reality. The negative symptoms may include affective flattening, avolition, anhedonia and cognitive deficits. Among different hypotheses regarding the etiology of the disease, it is generally hypothesized that susceptible genes combine with each other and/or with environmental stimuli to produce the variance in schizophrenia clinical manifestations. The ubiquitous transcription factor Sp1 was shown to be involved in the regulation of the transcription of many genes implicated in schizophrenia. Early interference with sp1 activity serves as predisposing to pre puberty chronic stress. Our aim is to examine the chronic stress effect on top of early interference with sp1 activity on schizophrenia relevant behavioral-like and hormonal symptoms in schizophrenia.

Method: postnatal rats (PND 7-10) were injected with the Sp1/DNA binding inhibitor, mithramycin (MTR). At prepuberty, rats were exposed to chronic stress during 14 consecutive days and tested at several behavioral tests and hormonal measurements, later on in adulthood.

Results: indict that chronic stress on top of MTR lead to increased anhedonia and anxiety levels. Corticostrone levels increased at the chronic stress and MTR+chronic stress groups but no significant change was observed in the MTR group. In order to clarify the molecular mechanism, we currently examining Sp1 level and proteins that may orchestrate schizophrenia symptoms.

Ambiguity aversion is abolished in decision-making under losses

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Risk and ambiguity are two conditions in which the possible outcomes of choices we make are not certain. Under risk the outcome probabilities can be estimated, whereas under ambiguity these probabilities are unknown. It has been shown that most people are averse to both risk and ambiguity when making choices between different possible gains. For example, most people prefer a certain gain of $10 to a 50% chance of winning $30, a tendency known as "risk aversion". Similarly, most people prefer a 50% chance of winning $20 to an unknown probability of winning as much as $100, a property called "ambiguity aversion".

When the choice is between different possible losses with known probabilities, most people prefer the risky option. For example, people prefer a 50% chance of losing $30 over a sure loss of $10. However, it is still unclear how people treat ambiguity when the choice is between different losses. Since in real life most situations involve at least some level of ambiguity, characterizing this kind of behavior has important implications for understanding human decision-making.

To investigate risky and ambiguous decision-making under both gains and losses, young adults were endowed with money and then asked to make a series of choices between a certain positive or negative amount of money and a lottery. The lottery varied in the amount of money that could be won or lost as well as the level of risk or ambiguity. At the end of the experiment one randomly chosen trial was played for real money.

Analyzing each subject's choice behavior, we characterized their attitude towards risk and ambiguity under gains and losses. As described in the literature we found that most subjects exhibited risk and ambiguity aversion under gains and risk seeking under losses. Interestingly, subjects were on average neutral to ambiguity under losses, suggesting that people are generally more "rational" when they make choices that involve losses compared to choices that only involve gains.

Unitary response of mouse olfactory receptor neurons

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The sense of smell begins with odorant molecules binding to membrane receptors on the cilia of olfactory receptor neurons (ORNs), thereby activating a G protein, Golf, and the downstream effector enzyme, an adenylyl cyclase (ACIII). Recently, we have found in amphibian ORNs that an odorant-binding event has a low probability of activating sensory transduction at all; even when successful, the resulting unitary response apparently involves a single active $G\alpha_{olf}$-ACIII molecular complex. This low amplification is in contrast to rod phototransduction in vision, the best-quantified G-protein signaling pathway, where each photoisomerized rhodopsin molecule is well known to produce substantial amplification by activating many G-protein, and hence effector-enzyme,

molecules. We have now carried out similar experiments on mouse ORNs, which offer, additionally, the advantage of genetics. Indeed, we found the same low probability of transduction, based on the unitary olfactory response having a fairly constant amplitude and similar kinetics across different odorants and randomly encountered ORNs. Also consistent with our picture, the unitary response of $G\alpha_{olf+/-}$ ORNs was similar to WT in amplitude, although their $G\alpha_{olf}$-protein expression was only half of WT. Finally, from the action-potential firing, we estimated that ≤19 odorant-binding events successfully triggering transduction in a WT mouse ORN will lead to signaling to the brain.

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The dark side of the alpha rhythm: fMRI evidence for EEG related attention allocation

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The role of the alpha rhythm (8-12 Hz) in various states of cortical activity is still debated.Classically considered as reflecting idle state (hence synchronized in the absence of sensory input) and recently as inducing inhibition during task performance (hence synchronized in task irrelevant areas).To challenge these hypotheses this EEG/fMRI study examined the effects of sensory input (light\dark) and task (eyes opened\closed) on alpha rhythm modulation.It was assumed that different modulation of the alpha in light vs. dark will support a "sensory-input idle hypothesis",while changing with eyes state, regardless of sensory input,will maintain a "task-related inhibition hypothesis".

14 subjects were requested to open\close their eyes during light and complete darkness while simultaneously recording EEG\fMRI data.A ridge regression classifier was trained to infer eyes state using EEG data and an alpha band regressor was calculated for an SPM analysis.

The classifier results revealed significant alpha rhythm contribution to eyes-state inference during both light and dark conditions,rejecting a pure "sensory-input idle hypothesis".FMRI activation maps obtained by the alpha regressor in the dark revealed negative correlation of alpha with activity in right Fronto-Parietal network known to mediate alertness.In the light alpha was positively correlated with activity in primary auditory cortex and DLPFC,possibly reflecting inhibition of irrelevant executive regions during internally focused attentiveness [i.e. eyes closed].

Our findings support a "task-related inhibition hypothesis" revealing alpha modulations without sensory input (in complete darkness) and corresponding fMRI activations in alert-related regions.In addition our results imply to a possible role of alpha synchronization in inhibition of task irrelevant areas.Altogether our results point to a possible role of alpha modulation in allocating attention resources,thus improving task related brain functioning.

Offline Encoding of Naturalistic Experiences

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Some of our daily experiences are remembered whereas others are forgotten, with many factors determining which events will be remembered. Previous studies have shown that brain activity elicited during presentation of stimuli predicts subsequent recollection, indicating that online encoding processes play a crucial role in determining the fate of an item in memory. However, these studies have typically focused on short-lasting, noncontextual stimuli. The encoding of complex experiences that require binding of information over time may involve more elaborate processes that only come into play after an ongoing episode is perceived as a cohesive event. In order to examine whether offline encoding processes play a role in the registration of real-life-like experiences to memory, we examined brain activity time-locked to the offset of short narrative movie clips. We found such activity to be correlated with subsequent memory performance in a set of regions including the hippocampus and caudate nucleus. We propose that this offline activity reflects the registration of an episode to memory as a cohesive representational unit.

'Healing' monocyte-derived macrophages are required for neuroprotection and progenitor cell renewal in the injured mammalian CNS

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Background: Neuronal cell death is a hallmark of many neurodegenerative diseases in the eye, brain and spinal cord. Neuroprotection and cell renewal are therefore vital for the repair of these tissues following insult, yet they are limited in adult mammals. As healing in peripheral tissues is highly dependent on monocyte-derived macrophages, we hypothesized that these cells are required following an insult to CNS tissues as well. In the present work we focused on the retina.

Methods: Adult mice were subjected to retinal insult in a model of glutamate intoxication. Renewal of retinal

progenitor cells (RPCs), survival of retinal ganglion cell (RGCs), the recruitment of distinct myeloid populations and their contribution to the local retinal milieu were analyzed by immunohistochemistry, flow-cytometry and quantitative Real Time PCR. Bone-marrow chimeric mice were used to characterize these myeloid populations and specifically to identify the infiltrating monocyte-derived macrophages. Effects of monocyte depletion or augmentation were tested using the anti-CCR2 antibody, MC-21, or adoptive transfer of monocytes, respectively.

Results: Glutamate intoxication changed the relative contribution of distinct myeloid populations in the retina. Monocyte-derived macrophages were found to infiltrate the retina and localize mainly to the ganglion cell layer. These cells contributed to the immunosuppressive and neuroprotective milieu of the injured retina. Enhancement of the monocytic population resulted in higher numbers of proliferating RPCs and increased the survival of RGCs, whereas depletion of monocytes in the blood resulted in diminished RGC survival and RPC renewal.

Conclusions: Recruitment of monocyte-derived macrophages is suggested in this study as one of the body's mechanisms for promoting neuroprotection and cell renewal in the eye, with potential implications to other tissues that were hitherto considered as sites of immune privilege.

The role of inflammation in the process of secondary damage occurring in the spinal-cord of fetuses with meningomyelocele – a developmental model of Rat-MMC

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Background: (MMC) is an important congenital malformation involving the CNS, occurring Meningomyelocele in 1-2/2000 live-births. Most babies will survive with paralysis, urinary incontinence, leg-deformities and brain abnormalities such as hydrocephalus, which are not prevented by fetal surgery. The 2-hit-hypothesis suggests (1) non-closure of neural-tube and(2) chronic exposure of the cord to the amniotic fluid (AF) as causes of the final morbidity. This study looked at pro-inflammatory cytokines in the AF, as part of a project studying the role of inflammation in this pathology.

Methods: MMC was induced by feeding rat mothers with retinoic-acid at E10. Fetuses were removed at early (E14-15) and late (E19-20) gestation. AF was collected and fetuses were inspected. Levels of TNF-alfa and IL6 (pg/ml) were measured in the AF of fetuses with MMC and controls using commercial kits (Quantikine, R&D, Mineapolos, MN).

Results: Amniotic fluids (100-200 microliter) of 59 fetuses, 35 with MMC and 24 controls, were examined for cytokines. TNFalfa levels were very low in both groups at early phase (C: 3.64+1.24; MMC: 2.57+0.99), and slightly increased in MMC group at late gestation (C: 0.62+0.22, MMC: 11.20+2.66, $p=0.006$ study versus controls, 0.001 early versus late MMC groups). IL6 levels were much higher in the MMC group (110.65+10.99 and 202.91+18.36 in controls and MMC respectively, $p=0.0001$), did not change at late stage in controls yet somewhat decreased in MMC group (C: 121.55+4.53, MMC 156.59+7.89, $p=0.005$).

Conclusions: Abnormally elevated levels of pro-inflammatory cytokines in the AF of fetuses with MMC may represent processes of inflammation potentially injuring the exposed spinal cord in MMC fetuses. In theory, anti-inflammatory treatment may be administered before irreversible damage occurs to the CNS. Even though further studies are needed to establish the role of inflammation in MMC, this study may open new frontiers of Fetal treatment for these children.

Can Trpc2 deficient mice sex-discriminate?

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To ensure survival and reproduction, animals must recognize their conspecifics and engage in gender- and species-specific social and reproductive interactions. In the mouse, as in other species, social communication relies on the discharge and detection of specific chemical cues, the pheromones. The Trpc2 channel is exclusively expressed in the vomeronasal organ (VNO), which is thought to mediate social behaviors elicited by pheromonal cues suggesting a direct role of the channel in the pheromone-evoked response. Trpc2-/- fails to display the pheromone-evoked aggression toward male intruders which is normally observed in wild-type males. Moreover, they display courtship and mounting behavior indiscriminately toward both males and females. These findings raise the inevitable question: can Trpc2-/- sex-discriminate? In order to illuminate this issue, we apply the conditioned olfactory aversion (COA) paradigm. Similar to conditioned taste aversion (CTA), the subjects learn to associate particular smell, in this case, female urine (the conditioned stimulus, CS) with delayed lithium-chloride (LiCl) toxicosis (an unconditioned stimulus, UCS) to yield olfactory aversion. We postulate that a non-discriminating Trpc2-/- mouse will not learn the association or will even generalize the aversion to male urine as well. First, we decided to examine whether the COA paradigm applies to C57BL/6 J mice. Preliminary results show that mice which received LiCl

injection immediately after a five-minute exposure to female urine, acquired an aversion to this smell but not to male urine. Remarkably, these results indicate that although innate factors are strongly involved, male selectiveness toward female odor is also influenced by past experience. In the future, we intend to apply the COA paradigm on mice deficient in Trpc2 in order to address this question and by doing so, gain a better understanding of the functional role of Trpc2 in the vomeronasal pathway.

Alternative splicing modulations in neurodegenerative disease

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Neurodegenerative diseases such as Alzheimer's and Parkinson's diseases (AD, PD), involve failed synaptic functioning and premature death of cholinergic or dopaminergic neurons due to as yet unclear mechanism(s). Our whole genome microarray studies suggest modified alternative splicing of brain and leukocyte mRNA transcripts as an underlying mechanism. In the AD brain, we observed massive changes in alternative splicing profiles. When experimentally tested in primary neuronal cells, parallel manipulations caused synapse loss, preventable by cholinergic stimulation. In lentivirus-injected mice, such changes led to learning and memory impairments yet were independent of amyloid or Tau phenotypes. Leukocytes from PD patients compared to healthy controls, showed stimulus-induced changes in mRNA transcripts, with distinct alternative splicing profiles after sub-thalamic deep brain stimulation (DBS) neurosurgery and post-surgery with or without electrical stimulus (ON-and OFF-stimulus). The majority of these changes was reversed following both stimulation and reversed again 1 hour OFF-stimulus, with the extent of changes correlated to the neurological efficacy of the DBS neurosurgery. Correspondingly, molecular signatures of 29 transcripts discriminated controls from PD patients, pre- from post-surgery patients and ON-from OFF-stimulus conditions; and 6 out of these transcripts also discriminated between controls and patients with early PD or other neurological diseases in an independent 3' leukocytes microarray dataset. Alternative splicing impairments thus emerge as a key mechanism in both AD and PD, suggesting new surrogate markers for early blood test diagnostics and proposing novel target transcripts for intervention early in the process of neuroinflammation-associated and/or DBS-treatable neurological diseases.

Estrogen synthase (aromatase) availability in the human brain in relation to cognitive function and gender: in vivo PET studies in healthy volunteers

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Aromatase is the final enzyme catalyzing estrogen biosynthesis. Recent PET studies have revealed that the regional distribution pattern of aromatase in the human brain is unique, with the highest levels found in the thalamus. In contrast, primate and rodent brain studies show low levels in thalamus and high levels in amygdala and preoptic area. To gain an insight into the possible functions subserved by estrogen synthesis in the human thalamus, we have examined the relationship between aromatase availability in the thalamus and amygdala and neuro-psychological assessment of higher brain function in healthy volunteers. Sixteen healthy volunteers (8 men and 8 women) were the California verbal learning test (CVLT) prior to a PET scan with the aromatase inhibitor [11 C]vorozole. Blood input data and brain regional time activity curves were collected from each subject and analyzed using the 2 compartment model to obtain the total distribution volume (VT) values in thalamus and amygdala, which where then correlated with CVLT performance traits control/constraint in the whole group as well as in men and women separately. Verbal learning and memory (CVLT1-5) showed a statistically significant negative correlation with thalamic VT ($R=-0.546$, $p<0.03$). However, this correlation originated exclusively from the women ($R=-0.73$, $p<0.04$); with no apparent contribution from the men ($R=-0.13$, $p=0.75$). Conversely, VT in amygdala was significantly and negatively correlated with CVLT performance in men ($R=-0.76$, $p<0.02$) but not in women ($R=-0.11$, $p=0.78$). These results suggest that estrogen synthesis in the human brain modulates cognitive function in a sex- and region specific manner.

MK801-induced disruption of latent inhibition is resistant to antipsychotic drugs

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Rationale: Schizophrenia (SCZ) patients are severely impaired in their ability to ignore irrelevant stimuli. Latent inhibition (LI), the poorer conditioning to a stimulus resulting from its non-reinforced pre-exposure, reflects animals' capacity to ignore irrelevant stimuli, and drug-induced alterations in LI are used to model SCZ-like

attentional deficits . Consistent with the glutamatergic hypofunction at the N-methyl-D-aspartic acid (NMDA) receptor implied in the pathophysiology of SCZ, we showed that the NMDA antagonist MK-801 produced disruption as well as abnormal persistence of LI at high and low doses, respectively. Abnormally persistent LI was reversed by atypical antipychotic drugs (APDs) and NMDA enhancers but not by typical APDs, lending the low MK801 LI model predictive validity for negative/cognitive symptoms. Objectives: To characterize pharmacologically the high MK-801 dose-induced disrupted LI.

Materials and Methods: LI was measured in a conditioned emotional response procedure in which rats were either preexposed or not preexposed to a tone stimulus prior to fear conditioning with the tone. MK801 (0.2 mg/kg), the typical APD haloperidol (1 mg/kg), the atypical APD clozapine (10 mg/kg) and the GlyT1 inhibitor SSR103800 (3, 10, 20 mg/kg) were administered in preexposure and/or conditioning.

Results: Rats treated with MK801 exhibited disrupted LI. This abnormality was not reversed by any of the drugs tested.

Conclusions: High dose MK801-induced disrupted LI exhibits distinct pharmacological profile from that of low dose MK801-induced persistent LI as well as from amphetamine-induced disrupted LI which is reversed by both typical and atypical APDs. We suggest that high MK-801-induced disrupted LI may serve as a model of treatment-resistant positive symptoms.

"So, do worms sleep?" and other questions that may have never crossed your mind

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Despite much progress in our understanding of C. elegans locomotion and navigation, little is known about the regulation of the absence of movement. Yet behavioral quiescent states are universal to the animal world, with the most famous and mysterious of these being sleep. In a famous example of studying a sleep-like behavior in a phylogenetically ancient model organism, Seymour Benzer – physicists, biologists and one of the founders of the field of molecular biology of behavior – studied the cycles of quiescence of the fruit fly Drosophila. He showed that the period gene was a key regulator of the circadian clock, which was found to have a role in regulating sleep in mammals. Recently, additional pathways were implicated in regulating sleeplike behavior in fruit flies and sleep in mice, rabbits and hamsters: Epidermal Growth Factor (EGF) signaling and cyclic-Adenosine MonoPhosphate (cAMP) signaling. The roundworm C. elegans is in many ways a simpler model organism than the fruit fly. It has only 302 neurons (the connections of which have been anatomically mapped), a short life cycle and an optically transparent body. The worm develops through four larval stages before it reaches adulthood. At the end of each of these stages it exhibits a quiescent behavior called lethargus. David Raizen et al. recently demonstrated that lethargus bears behavioral similarities to sleep, such as reversibility (the worms "wake up"), sensory gating (an elevated threshold for responding to sensory stimuli) and homeostatic control (following deprivation, lethargus is resumed faster and "deeper"). Curiously, lethargus is also phase-locked with cycles in the expression of the worm's period homologous gene. Moreover, EGF and cAMP signaling both appear to have roles in regulating lethargus that resemble their regulation of similar behaviors in flies and mammals. Taken together, these observations suggest a possible ~6×108 year-old genetic link between these phenomena.

The configuration of face-space is invariant under identity-preserving transformations

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According to the face-space framework, face representations are isomorphic to locations in a multidimensional psychological space, in which the distance separating these representations is proportional to the degree of dissimilarity between faces. Our aim was to test the extent to which similarity relations between faces, and thus the structure of the space, remained unchanged across identity-preserving transformations such as changes in viewpoint and lighting. In two experiments, perceived similarity was rated within different variants of a set of faces, differing either in illumination (Experiment 1) or viewpoint (Experiment 2). Based on these ratings, a separate face-space configuration was constructed for each variant using multidimensional scaling, so that each configuration represented the same faces under a different transformation. Procrustean analysis revealed that these configurations were highly correspondent in structure. In addition, the pattern of correspondence strongly correlated with performance in a sequential matching task: the better the matching of faces under two transformations was, the more correspondent were the configurations representing these transformations. While such correspondence of configurations serves as a face-space correlate of identity-invariant representation, we further present a theoretical model postulating a causal link between the structure of face-space and identity invariance. This model suggests that to attain an identity-invariant representation, it is possible that faces of the same identity

only share their similarity-pattern relative to other faces, perhaps rendering unnecessary a direct comparison of faces under different transformations based on inherent invariant features.

Probing functional brain mechanism of Schizophrenia Patients with Obsessive-Compulsive Symptoms, an fMRI study

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Background: A substantial proportion of schizophrenia patients also meet DSM-IV criteria for obsessive-compulsive disorder (OCD). Schizophrenia patients with OCD are characterized by a distinct course, poorer treatment response and prognosis. In the present study, as part of a project aimed to elucidate brain mechanisms underlying schizophrenia patients with OCD subgroup, we evaluated patterns of lateralization and functional connectivity in the domain of language and working memory processing in schizophrenia patients with OCD compared to "pure" schizophrenia and OCD patients.

Methods: We used functional magnetic resonance imaging (fMRI) to investigate language and working memory skills. Language-related activation in the IFG was used for regional estimation of brain asymmetry and for assessment of inter-hemispheric functional connectivity. In addition we examined the DLPFC function as well as inter-hemispheric coupling during the N-back task. Four groups of patients were recruited: schizophrenia patients with and without OCD, OCD patients and healthy controls.

Results: No between-group differences were found in the behavioral measurements of word generation. A reduced lateralization in the IFG and diminished functional coupling with left Broca was noted in the two schizophrenia groups as compared to OCD patients and healthy controls. In the N-back task both schizophrenia groups differed from OCD patients and controls in the behavioral measurements, DLPFC activity and functional coupling with the r-DLPFC.

Conclusions: This study demonstrated reduced functional coupling between homologue frontal regions with relation to language and WM tasks in SCH patients in comparison to OCD and controls. These findings possibly reflect a neuro-cognitive endophenotype of SCH disregarding a specific symptom cluster such as OC.

Interaction between ApoE genotype and environmental stimulation studied with diffusion tensor imaging

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Introduction: The causes of Alzheimer's disease are still unknown, however several risk factors has been identified including genetic factors and environmental. Recent imaging works indicates that brain function and morphology of subjects that carry the ApoE4 allele is different from subjects that carry ApoE3. Other imaging works showed that enriched environment causes significant morphological brain changes as studied in normal mice. In this work we used diffusion tensor imaging (DTI) to study the regional interaction between environmental factors and ApoE genotype.

Methods: 42 mice (20 ApoE3 and 22 ApoE4) were scanned in a 7 T MRI with or without exposure to enriched environment for duration of 2 months. The DTI-EPI data were analyzed using the DTI analysis framework to produce the fractional anisotropy (FA) and apparent diffusion coefficient (ADC) maps. ANOVA was performed to produce parametric maps of each factor main effects and the interaction between the two. Histology was performed with markers for astrocytes, synapses and neurons.

Results: The histology shows an interaction between genotype and environment both in synapses and astrocytes staining. The interaction of the DTI parametrs between genotype and enrichment was found in some parts of the dentate gyrus and medial septal nuclei. In these regions, the FA was found to decrease following enrichment in ApoE3 but to increase in ApoE4.

Conclusions: The main result of this study is that DTI can be used to measure the interaction between genotype and environmental stimulation. We found good correspondence between histological markers and DTI parameters, especially with GFAP, the astrocyte marker. Our results indicate that the effects of genotype and environmental stimulation are significant within the hippocampal complex. The present study shows that DTI can be used as a bio-marker to define early pathophysiological changes related to AD risk factors.

Membrane potential affects the rate constant of dissociation of acetylcholine from the m2 - muscarinic receptor

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G-protein coupled receptors (GPCRs) mediate most signal transduction processes. Recently it was shown in few studies that the first step in signal transduction, the binding of agonist to the GPCR, is voltage sensitive. In the case of the m2- muscarinic receptor (m2R) depolarization shifts the high

affinity receptor to a low affinity state. The biophysical meaning of this affinity change is not well understood. Here we attempt to address this issue directly by measuring the rate constant of dissociation (koff) of acetylcholine (ACh) from the voltage-sensitive m2R. We do so by using direct measurements of the dissociation of [3 H]ACh from m2R-expressing Xenopus oocytes, and by indirect measurements of the deactivation rate of m2R activated GIRK currents. We show that koff is higher under depolarization than at resting potential. To our knowledge, this is the first direct demonstration of voltage-sensitive rate constant of dissociation of any ligand from any receptor.

Effects of class-3 semaphorins on brain tumour progression

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Malignant brain tumors belong to the most frequent tumor encountered in childhood. Standard treatment modalities are neurosurgical resection, chemotherapy and irradiation. In contrast to the excellent results of well established treatment studies in pediatric patients suffering from leukaemia the cure rates of children with malignant brain tumors remained low. That is why the development of new antitumor strategies has become a major issue in experimental neurology. Class-3 semaphorins have been first identified as axon guidance factors and during the last years it was found that some are able to inhibit the angiogenesis and as a result they are candidates for the inhibition of tumor development. Goal of the project was to determine if class-3 semaphorins can be used for the treatment of brain cancer. Therefore class-3 semaphorin overexpressing U87MG glioma cells were implanted in the brain cortex of mice. We found that the semaphorin expression completely inhibits the development of tumors from these cells. The tumor inhibition was correlated with a dramatic effect on the survival of the mice, as in the groups after the implantation of semaphorin expressing cells was a very substantial increase in survival. Sadly, semaphorins do not pass the blood-brain-barrier efficiently so it is not possible to inject them intravenously for a treatment. Additionally the expression of recombinant semaphorin3D changes the migration and cell adhesion of those cells in comparison to control U87MG cells. This may be an explanation for the reduced invasiveness in the brain of the mice. Our main focus is now to circumvent the blood-brain-barrier to deliver semaphorins to the brain in order to treat cancer.

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Are whole bodies special? holistic neural representation of human bodies

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Recent evidence reveals specialized processing mechanisms for human bodies, including the discovery of body-selective areas in occipito-temporal cortex. Interestingly, bodies induce behavioral effects that are similar to faces and typically associated with holistic processing, such as impaired discrimination for inverted stimuli (i.e. body inversion effect). Therefore, it has been suggested that bodies, like faces, are processed holistically. Evidence for holistic body representation includes a behavioral Whole-Part effect, and a step-like response of the fusiform body area to large vs. small body parts. However, no study has directly examined whether body-selective mechanisms indeed prefer a whole body over the sum of its parts. Here we used fMRI to determine whether body-selective areas in occipito-temporal cortex discriminate intact vs. scrambled body configurations. Subjects were presented with blocks of intact (faceless) or headless bodies, in either whole or scrambled (part-based) configuration. For each subject we defined face, body and object-selective areas with a separate functional localizer scan. Body-selective areas showed highest response to whole intact bodies relative to headless intact or scrambled bodies. The response to scrambled bodies was similar regardless of the presence of the head. Face areas showed higher response to whole than headless bodies for both intact and scrambled bodies. In contrast to body and face areas showing higher response to whole than scrambled bodies, object-selective areas showed the opposite effect of higher response to scrambled than whole bodies. These findings suggest that holistic representation of human bodies uniquely exists in body-selective areas, but not in object general areas. The response of face-selective areas was more influenced by the presence of the head and may reflect mechanisms of face imagery, which are more likely to be generated by a whole intact faceless body than by headless or scrambled body.

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Individual differences in motivated behavior: Behavioral and genetic findings

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Individual differences in approach and avoidance motivation have been suggested to reflect differences in the relative reactivity of behavioral activation (BAS) versus

behavioral inhibition (BIS) systems (which mediate the sensitivity to stimuli associated with positive and negative reinforcement, respectively), and were reliably associated with asymmetric cortical activation patterns. Animal and human studies suggest that these patterns of activation reflect individual differences in asymmetry in dopaminergic signaling, which modulates aspects of appetitive and aversive behaviors. Orienting bias is known to reflect dopaminergic asymmetry in animals, and possibly in humans too. The present study investigated the association of approach and avoidance tendencies (measured by self report as well as behavioral task) with orienting bias and the COMT Val158Met polymorphism, in healthy individuals. 32 participants completed the BIS/BAS questionnaire and a probabilistic classification task, which required them to assign presented stimuli to one of two categories based on positive or negative feedback. They also performed the greyscales task, a reliable test of orienting bias. Carriers of the Met allele tended to rate themselves as having stronger approach (BAS score) relative to avoidance (BIS score) tendencies, whereas the opposite pattern was found for Val homozygotes. Greater rightward orienting bias was associated with better learning from positive reinforcement relative to negative reinforcement. Finally, rightward bias was associated with higher BAS (relative to BIS) scores, whereas the opposite pattern was found for subjects showing a leftward bias. These results support the hypothesis that asymmetric hemispheric activation reflects individual differences in approach and avoidance motivation, suggest a possible role for orienting bias as a neurobehavioral marker for motivational dispositions, and imply an association of the COMT gene with these traits.

Native and learned sources for expectations: exogenous and endogenous shifting of temporal attention

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Predicting the timing of upcoming events is crucial for both perception and action, as it has been shown that temporal preparation facilitates response time, accuracy and perception thresholds to a stimulus. The prevalent explanation for this effect is that it reflects increased allocation of attentional resources at the expected moment in time. There is evidence that this shifting of attention can be based on two levels of information. One level, 'low-level' expectation, is based on some regular temporal pattern preceding the target (e.g. stimuli at a fixed rhythm). Another, 'high-level' expectation, is based on abstract knowledge regarding target timing (e.g. association with a previous stimulus).

In the current work, we examined the interactions of high-level and low-level temporal expectation on performance in a visual detection task. Subjects responded to a target that appeared in either short or long SOA after a sequence of flickering stimuli. In alternate blocks, flicker frequency or sequence color were predictive of the ISI between the sequence and the target. Subjects were instructed to attend the predictive cue. In some trials (incongruent trials) the target appeared in the SOA which was unpredicted by the attended cue. Orthogonally, the unattended cue could be congruent with the target SOA.

We found an effect of congruity of the attended cue, which indicates facilitation by temporal expectation. This effect was modulated by the congruity of the unattended cue, with better performance in incongruent trials when the target SOA was congruent rather than incongruent with the unattended cue. Further, our results demonstrate the superiority of low-level expectations in these effects. Stronger automatic expectation by the low-level cue may result from it being more native to the observer, and not dependant on task-specific associations.

Spatial and temporal distributions of tic-related neuronal activity in the primate cortico-basal ganglia loop

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Motor tics are repetitive, involuntary brief muscle contractions, which appear as a symptom in several human movement disorders. Multiple lines of evidence suggest the involvement of the cortico-basal ganglia loop (CBG) in tic disorders, but the pathophysiology leading to tics is unknown. Theoretical models hypothesized an abnormal "action selection" process leading to tic generation in which an aberrant focus of striatal activation causes unwanted inhibition of a group of basal ganglia output neurons, which disinhibits a group of cortical neurons and thus leads to the expression of a tic. In this study, motor tics were induced in behaving monkeys by local microinjections of the GABA-A antagonist bicuculline to the putamen. Tic-related neuronal activity was recorded from multiple nodes along the CBG: motor cortex, putamen, globus pallidus external (GPe) and internal (GPi) segments. We characterized the temporal and spatial distribution of tic-related activity in each area and their relation to the spatial and temporal properties of the tics. While striatal tic-related activity displayed a localized spatial distribution, GPe and GPi responses to tics were detected in a very large fraction of neurons, and were widely spatially distributed in each

nucleus. While some neurons along the CBG displayed tic-related activity prior to the tic movement onset, the vast majority of neuronal responses were during or after the tic. Our results indicate that rather than selecting and initiating the abnormal movement the tic-related BG signal may have a more complex role in the modulation, maintenance or control of tics. The abnormal disinhibition from the GPi might be augmenting the tics expression, representing a failure of the behavior learning or control mechanism. The neuronal changes observed during tics in this model may provide valuable insights into the underlying mechanism of tic disorders as well as into basic information processing in the CBG loop

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A Bayesian model of dynamic image stabilization in the visual system

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Humans can resolve the fine details of visual stimuli although the image projected on the retina is constantly drifting relative to the photoreceptor array. Here we demonstrate that the brain must take this drift into account when performing high acuity visual tasks. Further, we propose a decoding strategy for interpreting the spikes emitted by the retina, which takes into account the ambiguity caused by retinal noise and the unknown trajectory of the projected image on the retina.

A main difficulty, addressed in our proposal, is the exponentially large number of possible stimuli which renders the ideal Bayesian solution to the problem computationally intractable. In contrast, the strategy that we propose suggests a realistic implementation in the visual cortex. The implementation involves two populations of cells, one that tracks the position of the image, and another that represents a stabilized estimate of the image itself. Spikes from the retina are dynamically routed to the two populations and are interpreted in a probabilistic manner.

We consider the architecture of neural circuitry that could implement this strategy, and its performance under measured statistics of human fixational eye motion. A salient prediction is that in high acuity tasks, fixed features within the visual scene are beneficial because they provide information about the drifting position of the image. Therefore, complete elimination of peripheral features in the visual scene should degrade performance on high acuity tasks involving very small stimuli.

The Swartz Foudnation (YB,UR), NEI (MM), ISF (HS), Ministry of Defense (HS)

An Information-Diffusion inequality for continuous-attractor networks

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How long can a continuous-attractor network maintain its persistent state? If a noise-free network is left to evolve on its own, without any sensory input, activity can persist in a given state indefinitely. In practice, activity will drift away from the initial state. The drift is an inevitable consequence of noise and the flatness of the attractor manifold. To maintain its state for times exceeding the synaptic and membrane time-constants, the network must use knowledge of its state in the past, as conveyed by its own spiking activity. Thus we hypothesize a basic relationship between the information conveyed by the action potentials about the network's state, and the drift of the network state. We derive the diffusion coefficient D, a dynamical quantity that quantifies the persistence of the network state for continuous attractor networks of Poisson-spiking neurons. We compute the corresponding Fisher information J conveyed by spikes about the attractor state, which is a static statistical measure of neural coding and has been considered more traditionally in the context of sensory encoding and decoding by downstream neurons. We show that a rigorous inequality relates diffusivity to the Fisher information: $2D \geq 1/(^{2}J)$ where is the intrinsic slow time-constant (membrane or synaptic) in the problem. Thus, the statistical bound on estimation in a continuous-attractor network is intimately related to the network's ability to maintain a persistent state. We discuss generalizations to other models of neural firing, and consequences for coding and dynamics in continuous attractor networks.

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An eye on the tongue: neural correlates of navigation in congenital

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Vision is a very important tool for navigation in general. Due to compensatory mechanisms people who are blind from birth are not handicapped in spatio-cognitive abilities, nor in the formation of novel spatial maps. Despite the growing volume of studies on brain plasticity and navigation in the early blind

(EB), the compensatory neural substrates or the preservation of this function remain unclear. How do EB form maps of their environment? To answer this question my doctoral thesis research exploited a sensory substitution device that could potentially serve EB to negotiate a path through an obstacle course. We demonstrated that despite a reduced right posterior hippocampus, and an atrophied visual system (Ptito et al., 2008) EB not only were able to accomplish this task, but had a better performance than the blindfolded sighted controls. To determine what the neural correlates of navigation in EB are, we devised an fMRI compatible virtual route task conveyed through the tongue. Participants had to learn to navigate the routes and recognize them. We showed that EB use another cortical network involved in cognitive mapping than the sighted when recognizing routes on the tongue. In the future we will continue to explore navigation in the blind using fMRI and virtual environments conveyed through various sensory substitution devices. We have emphasized neural networks connecting parietal and frontal cortices since they are re-enforced in EB. We show that SSD's can be used as a portal to the brain by transferring visual information from the visual environment of participants, allowing the elaboration of strategies to avoid obstacles and move around in their environment.

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Ventral horn clusters of sacral neurons are activated by α1 adrenoceptor agonists to produce"fast" rhythmic bursts in sacral and rostral lumbar motoneurons

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The axial and tail muscles in rodents are controlled by rhythmogenic sacral networks whose entrainment by the hindlimb central pattern generators (CPGs) ensures a reliable stabilization of the body during automatic movements such as walking, running, and swimming. Our previous findings that a "fast" (0.25-1 Hz) alternating left-right rhythm can be produced in the sacral and rostral lumbar segments of the spinal cord by selective application of the a1-adrenoceptor agonist methoxamine to the sacral segments, suggest that the hindlimb and body stabilizing rhythmogenic networks might be coupled not only in the rostro-caudal, but also in the caudo-rostral direction. Using electrophysiological recordings, surgical manipulations of the spinal cord and confocal imaging, we show that the ability of methoxamine to produce the "fast" lumbar rhythm depends on intact connectivity between the thoracolumbar and the first two sacral segments (S1-S2) of the cord. Because the rhythm produced under these conditions (spinal cord transected at the S2/S3 border) persists after surgical removal of the S1-S2 dorsal horn, we suggest that the sacral CPGs activated by methoxamine and the sacral relay neurons required for activation of the rostral lumbar segments, reside mainly within the sacral ventral horn. Lesion studies of the white matter at the lumbosacral junction revealed that the methoxamine induced lumbar rhythm depends on sacral neurons whose axons project rostrally almost only through the ventral funiculi (VF). Fluorescent back loading of cut VF axon bundles, labeled heterogeneous population of sacral neurons mainly within the contralateral laminae VII, VIII and IX of the gray matter. Further studies are required to clarify the roles of the ventral sub-clusters of VF neurons in pattern generation and in caudo-rostral coupling between the sacral and lumbar networks.

Determinants of network bursts in micro cultures of central neurons

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Spontaneous synchronized activity of neuronal assemblies is an essential attribute of the brain. Yet, the cellular mechanisms that determine the triggering and maintenance of such neuronal network activity are not fully understood. To investigate neuronal network bursts, small scale networks consisting of 4-30 hippocampal neurons were created on small permissive islands. A third of these networks (26 out of 82) displayed spontaneous bursts encompassing the entire neuronal population. The bursts did not depend on the presence of inhibitory neurons or on network size. An 'early to fire' neuron was occasionally identified as the one who started to fire before all other members of the network. Surprisingly, these bursts were still present following the elimination of 'early to fire' neurons, indicating that 'leader neurons' are not indispensable for small scale network bursts. The duration of network bursts was dependent on the depletion of presynaptic resources and not on changes in postsynaptic properties. To conclude, while connectivity determines the ability to ignite widespread network bursts, the availability of presynaptic resources dictates the maintenance of such bursts.

Molecular determinants of nociceptor function in C. elegans

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PVD neurons are mutli-dendritic poly-modal nociceptors that mediate responses to harsh touch and to cold temperatures and that also regulate the animal's movement and posture. Thus, they combine the functions of multiple mammalian somatosensory neurons. To identify signaling molecules functioning within PVDs, we have used micro arrays to identify PVD-enriched genes. Among genes identified in this study are three members of the TRP family, trp-2, gtl-1,and gon-2 and two subunits of nicotinic acetylcholine receptor, deg-3 and des-2.
TRP family ion channels are known to mediate sensory transduction and are also implicated in guidance of neuronal processes. Our analysis of mutants affecting trp-2 and gtl-1 suggest a role for these proteins in the development and/or function of PVD neurons. Specifically, trp-2 mutants are defective in the organization of PVD processes and have movement defects similar to that of animals lacking PVDs and FLPs. gtl-1 mutants show a defective response to cooling, a phenotype that also depends on intact PVD and FLP neurons.
DEG-3 and DES-2 are highly expressed in PVD and FLP. DEG-3 staining and a functional DES-2: GFP fusion show that the DEG-3/DES-2 receptor decorates the entire sensory arbor of PVD. To understand the role of DEG-3 and DES-2 in the sensory dendrites of PVD neurons we examined phenotypes of mutations affecting these genes. Analysis of these mutants reveals similar phenotypes to these of animals lacking PVD and FLP suggesting an important role for the DEG-3/DES-2 receptor in PVD and FLP function. Moreover, calcium-imaging shows reduced responses of mutants to harsh touch. Thus the DEG-3/DES-2 receptor appears to affect the sensitivity of PVD to sensory stimulus. In addition analysis of PVD morphology shows a late onset defect in morphology of PVD arbors, suggesting a role for this receptor in maintaining PVD morphology.
Overall our work identifies ion channels that are important for PVD structure and function.

Maternal experience induces cortical cross modal interaction between pup calls and odors

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Maternal behaviors are associated with different forms of physiological alterations including transient hormonal changes and long term brain plasticity. The underlying impact of these changes on sensory coding within the mother's brain is largely unknown. Using in vivo cell-attached recordings we detected a novel form of cross-modal interaction between pup body odors and the processing of pup calls in the primary auditory cortex of female mice. This cross-modal interaction appears naturally in lactating mother shortly after parturition and is long lasting. Moreover, experience with pups is sufficient to trigger similar plastic changes in the auditory cortex of otherwise naïve females. Independent of cross-modal interaction, maternal experience induced a long lasting increase in representation of distress ultrasonic vocalization in the primary auditory cortex. These findings are in correlation with the pup retrieval performance of female mice. Our work indicates that parenting induces a set of plastic changes acting in concert to retune the primary auditory cortex into novel mode of processing pup distress calls. This regulation of sensory processing may strengthen the bond between mothers and other caregivers to their neonates by facilitating maternal care of offspring.

An informatics approach to studying incidence and treatment of Epilepsy at Soroka Hospital

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Introduction: The emergence of EHRs (Electronic Health Records),offer an abundance of data still mostly unexploited for large scale epidemiologic studies. EHRs may be used for studying the efficacy and safety of medications or identifying phenotypic traits for genome wide association studies. Such studies are especially interesting in Israel, for its unique populations and the advanced level of EHRs. Unfortunately, much of the information required for such studies is recorded as free text in Hebrew, and is intractable for computerized studies. Epilepsy may be recorded under multiple codes in the commonly used ICD9/10 coding system (International Classification of Diseases) ,some of which may be very broad (e.g. 'loss of consciousness'). Several solutions for English have been implemented (NY-Presbyterian' Medlee,Mayo Clinic' OHNLP and others), yet no such solution is available in Hebrew.
Methods: We use state of the art natural language processing (NLP) techniques for Hebrew, tailored for the medical domain , to automatically extract medical terms from notes of patients treated in the Children Neurology Clinic in Soroka Medical Center. Medications are identified in both Hebrew and English and mapped to UMLS (Unified Medical Language System), a controlled English medical dictionary. Our method automatically takes into account Hebrew prefixes and suffixes (for example:'מהטגרטול') and various Hebrew spellings of English medical terms.
Results: A basic Medications and medical terms identification system for Hebrew documents is now available. In 891 notes, comprising all out patients' visits in 2009, our program identifies 10,603 medical terms and 4,968 medications references. Specificity was 95%.
Discussion: Automatically identifying medications, phenotypes other medical terms can assist in finding and

recruiting relevant patients for epidemiology, drug and genetic studies.Medical text in Hebrew can be mined for such information using NLP tools tailored to the task.
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Studying mechanosensory tiling in the medicinal leech
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The nervous system of the medicinal leech is an ideal model for studying how sensory fields are innervated by the terminals of sensory neurons. The skin is innervated by four pressure-sensitive cells per segment, two ventral and two dorsal domains. Previous studies have shown that cell-cell interactions are critical for the establishment of tile boundaries between adjacent dorsal P (PD) neurons. A different mechanism appears to be required for establishing the boundary between the ventral and dorsal P tiles in each segment. Based on the distribution of the axon guidance factor Netrin in the leech, we hypothesize a role for Netrin in the establishment of the dorso-ventral boundary between P tiles. Netrin is expressed and released by ventral, but not dorsal, longitudinal muscles. The Netrin receptor UNC5 is expressed by the PD but not by the PV cells. We have recently identified a unique domain in the UNC5 leech homologue receptor. Moreover, we have cloned a Netrin receptor of a second type, a leech-DCC. To study the role of Netrin, we use microinjections as well as a pneumatic capillary gene gun that enables accurate manipulations of gene expression at early stages of development. We use RNA-interference (RNAi) and ectopic gene expression techniques to modulate the expression of Netrin and its receptors in selected segments and cells. Both techniques allow us to manipulate one side of a segment keeping the contra-lateral side as internal control. Preliminary results of Netrin-RNAi show significant abnormalities in the local pattern of skin innervation and in the boundary between ventral and dorsal areas. Overexpression of Netrin (using a potent core promoter) in ventral cells, which usually lack Netrin, affect Pv arborization. We therefore conclude that the establishment of the P cells involves both cell-cell interactions and target-derived molecular signals. Future applications towards directing neuronal growth will be discussed.
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Time course of synaptic potentiation and de-potentiation of the ascending synaptic inputs to the piriform cortex during complex olfactory learning.
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Learning of a particularly difficult olfactory-discrimination (OD) task results with acquisition of rule-learning. Such rule learning is manifested in a dramatic enhancement of learning capability; while learning to discriminate between the first pair of odors required 7-8 days of training, discrimination between subsequent pairs of odors is achieved almost immediately. This remarkable enhancement in learning capability, termed 'rule learning', suggests that profound changes should occur in the relevant brain areas. OD learning is accompanied by a series of wide-spread physiological and morphological synaptic modifications in pyramidal neurons of the piriform cortex (PC). The purpose of the present study was to describe quantitatively the dynamics of modulation of synaptic connectivity during learning in the ascending synaptic inputs to PC. To that end, we used in-vivo recordings of field excitatory postsynaptic potential (fEPSPs) from different location in the PC, throughout the learning period. Recordings were obtained by implanted electrodes: two recording electrodes in anterior PC and two in posterior PC. An electrical stimulation in the olfactory bulb (OB) was delivered before learning for and every day during learning until rule learning was completed. The amplitudes of the fEPSPs response to the direct afferent input (monosynaptic) from the OB was modified gradually during the learning period in an initial amplitude dependent-manner; persistent potentiation was observed only for responses which were smaller than 0.9 mV prior to learning. On the day of rule learning completion, a dramatic reduction of the responses was always apparent. We suggest that transient synaptic plasticity of the ascending OB-PC pathway enables the PC network to enter into a learning mode. The beginning of learning depends on the bottom-up circuit to the point when the input is effective enough to activate intrinsic circuits, which are much less dependent on the environmental inputs.

Predicting individual learning dynamics using maximum entropy models
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Learning to classify patterns is a common task for many different animals' species, under various conditions. Understanding how such learning occurs is of central interest in neuroscience and psychology, as well as machine learning and statistics. Importantly, the possible complexity of classification rules grows exponentially with the number of possible patterns, which makes generic classification learning a hard computational task. Previous attempts to characterize the kind of rules that humans can learn were only partially successful.

We conducted a set of psychophysical experiments in which subjects had to learn binary classification rules of visual patterns of black and white checkers. Our testing method overcomes the shortcomings and biases of many frequently used paradigms by keeping a uniform appearance frequency of all stimuli, refraining from biasing subjects in any way, and by testing rules of different complexity.

Recently, we presented a theoretical framework that relies on the Maximum Entropy principle and Bayesian Inference, which enabled us to model the learning process from examples at the individual level. Here we demonstrate these models' ability to reproduce the full breadth of behavior, exhibited by human subjects. In particular, we show that using our model, we can fit each individual learning session with high accuracy. We further show that by fitting our model to the early stages of the learning sessions we are able to predict subjects' future learning curve and even single answers with high accuracy. We suggest that this modeling approach can be used to manipulate the learning processes.

Brain stimulation to the parietal and dorsolateral prefrontal cortices to affect learning and numerical competence

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Background: How do we learn to encode and represent numerical information? What are the necessary brain mechanisms underlying such abilities? Automatic retrieval of numerical quantity and mapping of numbers into space seem to both correlate and be causally related to arithmetic learning. We examined how non-invasive brain stimulation of the dorsolateral prefrontal (DLPFC) and the posterior parietal (PPC) cortices over six days of numerical learning affects: 1) the efficiency of learning a new numerical system, 2) the development of its automaticity, and 3) the interaction between newly learnt numbers and space.

Method: We trained subjects for six days with artificial numerical symbols during which we applied concurrent transcranial direct current stimulation (TDCS) to the PPC or the DLPFC. Animal studies have shown that the long-lasting effects are protein synthesis-dependent and accompanied by modifications of intracellular cAMP and calcium levels, and therefore share some features with long-term potentiation (LTP) and long-term depression (LTD). Magnetic resonance spectroscopy in humans found that depending on the type of stimulation, the molecular changes involved reduction in spontaneous neural activity of GABAergic and glutamatergic activity after motor cortex stimulation.

Results: Depending on the laterality of the stimulation, and its location (PPC, DLPFC), TDCS affected numerical competences or the learning process. These effects were specific to the learning of a new numerical system as brain stimulation did not affect other cognitive functions. Moreover, the improvement of numerical abilities was still present six months after the training.

Conclusions: The current results demonstrate the potential of TDCS to affect learning and high-level cognitive functions. More specifically, the long-term TDCS effect on numerical abilities makes its use attractive for the rehabilitation of developmental and acquired disorders in numerical cognition.

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The networks underlying auditory discriminations are determined by sound statistics: evidence from fMRI

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The auditory system automatically tracks regularities in sound sequences. Successful detection sharpens perception and facilitates performance in a range of complex auditory tasks. For example, in 2-tone frequency discrimination tasks thresholds are markedly improved when one of the tones is repeated across trials ("reference") at a fixed temporal position (either 1^{st} or 2^{nd} in each trial). We recently showed that this benefit concurs with switching from an online retain-and-compare strategy to stimulus categorization (Nahum et al, J Neurosci, 2010).

We now asked: 1. whether the implicit strategic switch concurs with a reduction in activation of the explicit working-memory networks; 2. whether overlapping networks implement this switch for verbal and non-verbal stimuli.

We tested 2-tone frequency discrimination of 18 participants under the Reference 1^{st} and No-Reference protocols and contrasted the BOLD signal measured under these 2 protocols. We applied series of 3 consecutive blocks (12 trials each) of one protocol followed by 3 blocks of the other for 5 times. The No-reference protocol activated networks of explicit working memory (prefrontal-BA6,44; intra-parietal-BA7) stronger, even though the levels of difficulty were equated across conditions and participants were not aware of any difference between the tasks. To assess the overlap between areas activated for verbal information with a similar contrast, 7 participants were also administered a phonological awareness task, with and without item repetition across blocks. We used the areas activated by the non-verbal contrast as ROIs for the verbal contrast. We found that the working memory areas

described above were also significantly more activated by the No-reference verbal protocol.

We conclude that when sound regularities are detected by the auditory system, perception sharpens. In parallel, the activation of the working memory networks decreases as the load on the explicit working memory is reduced.

Multi neuron activity monitoring using high-rate temporal focusing microscopy

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Two-photon dynamic calcium imaging of neural populations enables optical monitoring of spiking activity *in-vivo* and *in-vitro*. However, standard laser scanners are too slow for monitoring large neural population with sufficient temporal resolution. Temporal focusing is a simple approach for achieving optically sectioned wide-field excitation in nonlinear microscopy and multiphoton photo-manipulation. Temporal focusing based systems enhance data acquisition rate significantly and are also used for photo-stimulation of neural cells. By combining a detailed new geometrical optics model with Monte-Carlo scattering simulations, we theoretically analyze the dependence of the temporal focus and its broadening on the microscope's and the media's parameters. Theoretical predictions are validated using light-scattering phantoms and *ex-vivo* brain tissue.

By combining an amplified laser source with temporal focusing based imaging system we constructed a fast imaging system, with frame rates of up to 200 Hz, which is suitable for two and three dimensional imaging of large neural population. Initial physiological results from *in-vitro* rat retinas and neural cell cultures will be presented, and the potential advantages this approach could have for *in-vivo* imaging

Attentional modulation in human visual cortex: a combined intracranial EEG & fMRI study

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One of the puzzling aspects in the visual attention literature is the discrepancy between electrophysiological and fMRI findings. While single-unit and local field potential (LFP) studies in monkeys suggest that attention predominantly modulates high-order visual areas, human fMRI studies exhibit strong attentional modulation of early visual cortex. This discrepancy is intriguing because of the tight coupling between the BOLD signal and local field potentials which is typically reported both in human and animal studies. Here we used intracranial EEG (iEEG) recordings in epileptic patients and fMRI in healthy volunteers in order to address this issue. The participants were presented with a small object (line drawing of either a face or a house) superimposed on a large object (face or house). In separate blocks the participants were asked to attend the small or the large object while maintaining fixation and performing a target detection task. This paradigm allows simultaneous measurement of both spatial-based attention and object-based attention. Early visual cortex electrodes exhibited mainly spatial-based attention effects. These effects were manifested in changes of the ERP and gamma (30-150 Hz) power. The magnitude of the effect was correlated with the spatial selectivity of each electrode. A sub population of these electrodes showed also attentional modulation of the baseline activity. Electrodes placed over high-order visual areas (e.g. Fusiform Gyrus, FFA) showed robust effects of object-based attention, which were correlated with the selectivity of the electrode to a certain category. In addition, these electrodes showed spatial-based attention effects. Preliminary fMRI results are compatible with these findings and shed light on the coupling between fMRI and electrophysiological data.

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Experience-dependent changes in stimulus specific adaptation in auditory cortex

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Stimulus specific adaptation (SSA) is the reduction in responses to a frequency stimulus which does not (or only partially) generalize to other stimuli. We study here whether SSA is affected by experience.

Mice were trained in a two-tone discrimination task using a paradigm that elicited different levels of latent inhibition. The training was performed in an Intellicage, a modified mouse cage where animals live while their behaviour is monitored automatically, by means of a reporter transponder inserted into each mouse. Water is available in a specialized corner upon nose-poke. All visits to the specialized corner were accompanied with the presentation of a train of tone pips (30 ms, every 333 ms). There were two key tone frequencies: the neutral 7 KHz (neutral visits), and the conditioned 13 KHz (conditioned visits, 17% of

visits). In conditioned visits, nose-pokes were followed by an air-puff and no water was available. Before conditioning begun, mice were presented in 17% of the visits to a pre-exposure frequency without any aversive outcome. Pre-exposure to frequencies between 9 KHz and 14 KHz, elicited latent inhibition of the subsequent conditioning to the 13 KHz tone, but frequencies above and below this range did not.

We recorded from the auditory cortex of the anaesthetized mice before (baseline) or after conditioning. Two pure tones pips (30 ms) were presented to the mouse in an oddball sequence every 300 ms. We found that responses in animals that showed latent inhibition were larger than responses in baseline animals to all frequencies tested, while in animals that showed no latent inhibition, only responses to the 13 KHz tone were enhanced. Thus, subtle changes in behaviour can be correlated with large electrophysiological effects. SSA was increased in all conditioned animals with respect to baseline.

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Depolarization induces a conformational change in the m2 muscarinic receptor

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G-protein coupled receptors (GPCRs) controls most signal transduction processes. Although spanning the cell membrane, GPCRs were not considered to be voltage sensitive. Remarkably, it was recently found that the agonist binding affinity of several GPCRs is modulated by the voltage across the cell membrane.

For example, in the m2 muscarinic receptor (m2R), depolarization shifts the receptor from a high to a low affinity state. Moreover, it was shown that the m2R displays charge-movement-associated-currents, analogous to "gating currents" of voltage gated channels. A tight correlation was found between the voltage dependence of the charge that moves and the voltage dependence of the agonist binding affinity.

Here we show that the charge movement is likely to cause a conformational change in the m2R, which in turn leads to a shift in the binding affinity.

Conformational changes were measured by fluorescence measurements from site-directed fluorescence labeled m2R, using tetramethylrhodamine maleimide (TMRM), conjugated to cysteine residues, simultaneously with gating currents measurements using the cut-open oocyte voltage clamp technique. A cysteine residue at position 416, on the third extracellular loop, which is known to be part of the allosteric binding site and in close proximity to the orthosteric binding site, was labeled. Upon depolarization, a voltage dependent fluorescence signal with a time course that correlated with the time course of the charge movement was observed.

Acetylcholine reduced both the charge movement and the fluorescence signal, to a similar extent.

Furthermore, treatments or mutations that abolished the voltage dependent binding also reduced the fluorescence signal.

Finally, by mutating specific quenching residues we located the position of the fluorophore to be in the region of the orthosteric and allosteric binding sites, strengthening the notion that TMRM attached to Cys416 can indeed report on conformational changes in this region.

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A brain full of maps

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Since the discovery of place cells in the hippocampus in the 70's, it has been hypothesized that the hippocampus contains a cognitive map which can assist the animal in naviagation, and is related to spatial perception. Recently, a second region in the brain, the medial entorhinal cortex, has been hypothesized to be related to spatial perception as well. It contains various types of cells, one of which is grid cells. These are neurons whose firing locations in a walking animal define a periodic triangular array covering the two-dimensional space in which the rat is moving. Grid cells can be used to calculate the position of the rat in the environment, suggesting that they contribute to navigation. Two studies investigating the nature of the map are presented. In the first study, we were interested how complex multi-compartment environments could affect the nature of the grid cell maps. We found that the grids were fragmented; they were "reset" when the rat was moving from one compartment to another. Thus the environment is represented by a mosaic of interconnected spatial maps. In a second study, we investigated the connection between the place cells in the hippocampus and the grid cells in the entorhinal cortex. The hippocampus was inactivated transiently, using the GABA-A agonist muscimol and grid cells were recorded simultaneously. Although the grid structure disintegrated, grid cells did not lose their spatial specificity for a very long time. Furthermore, some grid cells turned into head direction cells during inactivation. All in all, it seems that the spatial representation in the brain is

performed by multiple dynamic interconnected regions, with a strong feedback component.
The Kavli Foundation; Norwegian Research Council

Persistent cognitive deficits in female mice with experimental allergic encephalomyelitis

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Multiple sclerosis (MS) is an autoimmune disease associated with a wide range of motor and sensory deficits. Recently it has been recognized that about half of MS patients also exhibit chronic neuropsychological deficits, although the mechanism linking MS pathology and cognitive deficits has not been established to date. Experimental autoimmune encephalomyelitis (EAE) is the most widely used animal model for studying the pathogenesis of MS, useful in developing new MS therapies. The purpose of this study was to explore cognitive deficits in MOG-induced EAE and their relationship to the disease course.

Female C57bl/B6 mice (8 weeks old) were immunized with MOG (n=60), adjuvant (n=40) or saline (n=40). Mice were then tested for cognitive performances in the novel object recognition test (NORT) at four different time points: before clinical symptoms appear, after clinical symptoms first appear, at the peak of clinical symptoms, and when partial remission starts (days 7, 12, 16 and 28 post disease induction, respectively).

The saline control group showed a clear preference for the novel object at all time points. Adjuvant immunized mice had a transient cognitive deficit, demonstrating no preference for the novel object on day 7 post immunization. However, on days 12, 16 and 28, adjuvant immunized mice showed intact object recognition memory. EAE mice showed a significant and persistent memory deficit, as they did not prefer the novel object at any time point.

These results demonstrate cognitive dysfunction in the EAE model which precede the clinical symptoms, persist through the acute stage of the disease, and extend into the chronic phase, when clinical symptoms are reduced. Therefore, it appears that EAE is an adequate model for the study of MS-related cognitive deficits and their possible modulation by experimental therapeutic agents.
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Active whisking: effects of touch

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The whisker system in rats serves as an excellent experimental model of active sensing and touch. Several behavioral experiments indicate the essential role of the whiskers, and their scanning movements ('whisking') in spatial object localization by rodents. It is believed that whisking is controlled by central pattern generators, which are under a strong influence of sensory feedback and internal control.

We studied the kinematics of whisking in free air with head-fixed rats. using a high temporal resolution video camera. We found that the whisk duration was narrowly distributed, and was weakly correlated with whisk amplitude. Whisking amplitude was widely distributed, and strongly correlated with maximum velocity. This suggests different control for whisking amplitude and duration.

We then studied the effect of contact with external objects. While the rat was whisking in free air, a single vertical pole was moved into either the left or right whisking field. We analyzed the effect of touch on whisking kinematics, on touching and not touching whiskers. The touching whisker often exhibited a brief pulse of significant velocity ("pump") change very soon (10-27 ms) after contact. The feedback pulses tended to cluster in time. This suggests a possible transition between two modes, referring to high and low probability for a feedback pulse. The whisking amplitude on the non-touching side increased significantly after contact, but starting only on the cycle following the contact cycle.

The contact therefore induces neuronal feedback effects on the contacting whisker as well as on non contacting whiskers. The fact that neighboring whiskers on the same side exhibit feedback effects within the contact cycle, while those on the contraleteral side only in the following cycle, suggests that bilateral feedback involve loops controlling bout variables whereas ipsilateral feedback involves loops controlling single cycle variables.

Exposure to methylphenidate during adolescence leads to long term increase in anxiety and testosterone

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Background: Attention-deficit/hyperactivity disorder (ADD/ADHD) emerges as a world-wide psychiatric disorder that mainly starts in childhood. Nowadays, individuals who do not meet the criteria for ADHD are prone to abuse stimulating drugs, specifically methylphenidate (MPH) which is the most common treatment for ADHD. However, the long term effects of MPH abuse are unknown. Thus, considering the common developmental path, we aimed to test whether pre-pubertal environmental enrichment, anteceding adolescence MPH abuse, can predispose individuals towards behavioral alterations following exposure to stress in adulthood.

Methods: We conducted a translational study by modeling the developmental trajectory (enriched environment during childhood followed by MPH abuse during adolescence, and coping with stress in adulthood) in male rats. At pre-puberty [post natal days (PND) 30-60] rats were reared in enriched environment and were treated with MPH (4 days per week/2.7 mg/Kg body weight/ intraperitoneally) during puberty (PND 60-90). Finally, in order to examine stress coping ability in adulthood, rats were exposed to stress (PND 90-92) and starting at PND 110, we assessed the behavioral and endocrine effects.
Results: We found a beneficial effect of environmental enrichment on attentive abilities, which was impaired by MPH consumption. Moreover, chronic exposure to MPH has led to an elevated anxiety and corticosterone level. Interestingly, MPH elevated testosterone level, which endocrinologicaly represents aggression.
Conclusions: In view of the marked increase in MPH consumption over the past decade, a vigilant perspective should be enforced in order to avoid potential drug abuse and its long term detrimental consequences

Brain substrates of memory conformity

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Our memories are often inaccurate. An intriguing and significant source for false recollection is social pressure which leads individuals to change their report of past events to match that reported by others. This phenomenon, dubbed "memory conformity" is of considerable personal and social importance and is encountered in a variety of contexts, including social interactions, mass media, and eyewitness testimony. The brain mechanisms mediating socially-induced memory errors are yet unknown. Here, we examined if the neural representation of memories are altered by social influence. Additionally, we differentiate the biological basis of socially induced transient memory errors from socially induced persistent memory errors. Transient errors are induced by normative influences and maintained only as long as the social influence is sustained. Persistent errors are long lasting alterations of memory that persist after the social influence itself ceases. 30 subjects participated in a novel subsequent memory paradigm based on Asch's classic conformity experiments in combination with functional resonance imaging. Our results show that social influence induces high rates of behavioral conformity, resulting in both transient and persistent memory errors. When subjects were presented with false recollections by others, enhanced activation was found in the medial temporal lobe when that information generated long lasting memory errors, but not when the errors were only transient, or when subjects maintained their accurate memories. In frontal areas heightened activation was found when subjects preserved their accurate memories and did not conform to the false information given by others. Connectivity analysis suggests a frontal-MTL network subserves memory conformity and that the amygdala may play an important role in mediating social effects on memory

MDMA administration alters Tyrosine Hydroxylase levels after minimal traumatic brain injury (mTBI) in mice

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Minimal traumatic brain injury (mTBI) is a common consequence of car accidents, especially among young adults. MTBI causes short and long term physical, cognitive and emotional impairments as well as apoptotic and cellular alterations. In mice, the administration of MDMA produces a rapid increase in the extracellular levels of dopamine. When a 10 mg/kg dose of MDMA was administered to mice before mTBI, the behavioral impairments disappeared and the cognitive abilities were restored to normal levels. The main goal of the present study was to asses the causes by which MDMA prior to mTBI preserve cognitive abilities. Previous studies have shown that TH levels are a useful marker for identifying dopaminergic alterations in a specific brain region.
MDMA was injected one hour prior to the induction of mTBI. Whole brains were removed 1, 24, 72 hrs 7 days and 30 days post-mTBI, and their striatum, hippocampus and cortex were immediately frozen in liquid nitrogen. Levels of Tyrosine Hydroxylase (TH) were measured by western blot analysis.
Changes in TH levels were significantly decreased in the cortex of mTBI mice evidence as soon as 24 h post injury. The decreased TH levels remained low even 30 days post injury. When MDMA was given prior to the brain injury the cortex TH levels stayed at sham mice level at all times tested. As oppose to the cortex, in the striatum and hippocampus no significant changes were seen regarding TH levels.
The results of the present study suggest that there are region specific alternations in TH levels following mTBI in mice. In addition the restoration of TH levels in the mice's cortex may be an explanation to the cognitive improvements seen after MDMA administration in mTBI mice. Further

research is needed, looking at the dopamine levels and it's down stream regulation in brain injured mice.

Early auditory experience alters the auditory spatial map of the barn owl

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The auditory map of space is based on the computation of auditory localization cues and their association with the appropriate location in space. In the barn owl, an auditory localization specialist, the main auditory cues are the interaural time difference (ITD) and the interaural level difference (ILD). Is normal experience with the auditory cues essential for the formation of the map? To answer this question, we raised barn owls in continuous omnidirectional broadband acoustic noise that minimized their experience with coherent localization cues, presenting a form of deprivation. The owls were exposed to noise from the age of ~1 week, before hearing onset, until the age of ~2 months, when they normally achieve adult appearance and leave the nest. We then studied the neural representations of ITD and ILD in the auditory map in the optic tectum (the homologue of the mammalian superior colliculus). The data from the noise-reared owls were compared to data from age-matched (juvenile) controls and from adult owls. We found that both ITD and ILD tuning were broader in the noise-reared owls. Furthermore, the ILD representation was asymmetrical, demonstrating a contralateral bias. A smaller bias was also found in the age-matched controls, but not in the adult owls. The abnormalities in the ITD and ILD representations in the noise-reared owls tended to gradually recover following the cessation of noise and exposure to normal acoustic environment. Thus, the auditory map of space in the OT of the barn owl relies on normal acoustic experience for its development. The effects of the deprivation recover with normal experience, demonstrating that the auditory map is capable of adaptive plasticity beyond the age of two months.

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EEG fMRI study: automatic localization of an epileptic focus based on parametric multi channel analysis and pattern recognition technologies

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Background: Epilepsy surgery requires precise localization of the epileptic source. To this end, the integration of electroencephalographic (EEG) and functional magnetic resonance imaging (fMRI) drew much attention due to their complementary properties. Nevertheless, methodological improvements are needed to increase sensitivity for localizing the epileptic zone. This study investigates whether the improvement of IED detection and classification increases the efficiency of combined EEG source localization and fMRI as complementary methods for non-invasive localization of the epileptic source. Specifically, we addressed three main issues: (1) the automated detection of IEDs, (2) source localization of the IEDs using sLORETA and (3) the statistical analysis of the fMRI data for localization of the hemodynamic response correlated to the IEDs.

Methods: EEG and fMRI were recorded simultaneously from 6 patients with focal epilepsy. The MRI-induced artifacts were removed off line using custom developed software (Micromed) and Optimal Basis Sets method developed by Niazy et al. (2005). The detection of IEDs was obtained using a two stage method: a multi channel screening stage based on the inverse filter principle followed by cluster analysis.

Results: The initial screening was found to be an efficient tool for the detection of fast and slow abnormal epileptoform activity. The cluster analysis procedure was able to distinguish between IEDs from different sources and non epileptic events. After identifying the IEDs, statistical analysis was performed to compare between the hemodynamic response in "high" and "low" occurring blocks to detect brain voxels which were sources for the IEDs. These brain regions were compared with sLORETA localization of the averaged IEDs of each cluster.

Conclusions: Automated IED classification can result in objective BOLD response models of IEDs and lead to improvement of non-invasive pre surgical localization of interictal epileptiform activity.

Resilience to social stress coincides with functional DNA methylation of the Crf gene in adult mice

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Recent studies have shown that changes in DNA methylation mediate long-term molecular changes and psychopathologies that develop following early-life trauma. However, there is little knowledge about the effects of adulthood stress on DNA methylation. In addition, a link between changes in DNA methylation and the different behavioral outcomes of traumatic events has not been deciphered. In our work, we have studied these questions by examining methylation at the genomic region encoding corticotrophin releasing factor (CRF), a key component of the neuroendocrine and behavioral response to stress. Increased CRF and cortisol levels, are often correlated with clinical depression. We detected a high amount of methylation at the CRF promoter region in the mouse hypothal-

amus, and relatively little methylation in the intronic region. Using two independent in vitro assays, we determined that methylation of the CRF promoter actively inhibits gene transcription. To determine the effects of adulthood stress on this genomic region, we subjected adult mice to social defeat. Social defeat induced a long-term increase in CRF mRNA levels, and decrease in CRF promoter methylation. Changes in DNA methylation were detected at numerous CpGs in the CRF promoter, including at the cAMP-responsive element. These changes were detected only in animals that displayed socially avoidant behavior following the stress protocol. Defeated animals that displayed normal social behavior had unchanged CRF mRNA levels and promoter methylation levels. Subsequent treatment with the anti-depressant imipramine attenuated the changes in CRF expression and promoter methylation. In addition, lentiviral-mediated knockdown of CRF in the hypothalamus attenuated social defeat-induced avoidance. These results suggest that the behavioral outcome of adulthood stress is mediated through changes in DNA methylation, and that the CRF system is a primary mediator of stress-induced social avoidance.

Investigating modular cortical connectivity with an optogenetic SLMscope

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The visual cortex of many mammals has a distinctively modular functional organization, where radial domains of neurons encoding similar visual properties form regular iterated patterns across the cortex. This regularly-structured architecture provides the foundation for a pattern of connectivity in which domains encoding similar properties are preferentially interconnected across medium- and long-range distances. However, the functional significance of this modular connectivity, as well as its contribution to the response properties of individual neurons within these domains remains unclear.

To address these questions, we designed a wide-field microscope that combines a spatial light modulator (SLM) and with an intrinsic optical imaging system. This design allows us to map the functional domains in an area of interest, and then deliver arbitrary spatio-temporal patterns of channelrhodopsin-excitation light into selected combinations of functional domains. We use this to drive responses in neurons expressing virally-delivered channelrhodopsin, and monitor the effects of this activation using single unit recordings or operating in the combined SLM-intrinsic imaging mode. The intrinsic responses to SLM-driven activation are spatially restricted to the excitation domains, allowing for tight control of the driven patterns. We were able to selectively modulate spiking responses to visual stimuli by activating channelrhodopsin in regions that do not directly drive the recorded cell, demonstrating the validity of our approach.

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Statistical functional model for single trials of LFP curves

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Local Field Potential (LFP) is the signal recorded from an extracellular electrode and then treated with a low-pass filter. LFP is assumed to represent the synchronized post-synaptic potentials induced by synaptic inputs for the neurons in the vicinity of the electrode. Similar to any neural response, LFP data can show a large variability in the trial-to-trial responses to the same stimulus. In order to extract information from the signal based on single trials and better understand the structure of the signal, this variability needs to be modeled in a compact fashion.

For this purpose, we regard the LFP as functional data and adopt a simple statistical model of the data of the form: $y(t)=G(t,a,b,c)=af(bt+c)$ where f is constant 'shape' function for all trials and {a,b,c} are parameters representing correspondingly the scale, speed and shift parameters of each trial. Estimation of the parameters can be done by using straight forward Least Squares optimization. The disadvantage of such a method is that it requires some initial approximation of the underlining constant function f, usually by taking the empirical global average. Depending on the distribution of the parameters {a,b,c} and on the function f, the empirical average can be quite different than f, and from any one of the single trials. Thus, I suggest an alternative approach based on local estimation of the parameters and linearization of the function G which produces better estimation of the parameters under some conditions and at a lower computational price.

I will present two variations of local parameters estimation and compare them and the global approach on simulated data. I will also present the results of fitting the model to real LFP data recorded in the context of an experimental setup designed to examine the Stimulus Specific Adaptation phenomena in the auditory cortex of a rat. I will demonstrate how the model provides strong tools for analysis and interpretation of the data.

Data was collected by Livia De-Hoz and Nevo Taaseh

Photoactivation of spinal neuronal circuits expressing Channelrhodopsin 2 ionic channels by fiber-coupled light emitting diodes.

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Our ability to improve the motor function of spinal cord injury patients depends on the exact site of the spinal lesion, the severity of the damage to ascending and descending pathways, and on the possibility to control the excitability of spinal neuronal networks below the lesion. The use of electrical stimulation for controlling the neuronal excitability of spinal circuits is problematic due to the limited ability of implanted extracellular electrodes to target the desired populations of spinal neurons, and to the damage that may be caused to the spinal circuitry by the inserted wires. Partial relief from these problems is offered by optogenetic tools that have been developed recently for detecting and controlling genetically targeted neurons in intact neuronal networks.

The present work exploits fiber-coupled light emitting diodes (LED) for specific photo activation of white matter tracts in isolated spinal cords of transgenic mice expressing the light-activated ion channel, Channelrhodopsin-2, fused to YFP under the control of the mouse thymus cell antigen 1 promoter (Thy1-COP4/EYFP). Sub- and supra-threshold responses could be elicited in populations of lumbar motoneurons by 2 ms light flashes emitted through small diameter fiber optic guide coupled to 460 nm LED, onto restricted regions of either the ventral, ventrolateral, lateral, dorsolateral or dorsal funiculi of the white matter at the upper or middle cervical, mid thoracic, and different lumbar and sacral levels of the spinal cord. Moreover, supra-threshold activation of descending pathways could be demonstrated by photo-stimulation of the ventromedial medulla. Our successful attempts to increase the motor output of the spinal cord by focal photo-activation of specific white matter tracts opens the possibility for future use of high-resolution cell-targeted light stimulation to control the activity of specific spinal circuits in spinal cord injury patients.

Photo-absorber induced neural thermal stimulation

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Thermal transients resulting from low power IR pulses have recently been introduced as a safe, minimally intrusive method for direct optical stimulation of neurons. Here we present and characterize a novel physical method for thermally induced neural stimulation. This method relies on introducing micron scale photo-absorbers in the vicinity of the cells and directing focused laser beams onto the particles to induce thermal transients. Towards this end, we dispersed micron-scale carbon particles in various acute and cultured neuronal preparations. To induce thermal transients, a focused laser beam (several microns in diameter) was directed onto the particles and pulsed for periods ranging from 100 μs to 10 msec. To characterize the properties of the induced thermal transients, experiments using the temperature sensitive dye RU were performed and complemented by theoretical analysis. The resulting neural activity was recorded using fluorescent calcium sensitive dyes imaging (OGB-AM and Fluo-4-AM).

Focused illumination pulses absorbed by the carbon-based photo-absorbers, led to rapid (milliseconds timescale) thermal transients with a well-defined and highly-localized dynamics which was visualized using temperature-sensitive dyes, and matched theoretical predictions. Using calcium sensitive dye imaging, we observed that the thermal transients repeatedly excited neurons in the close vicinity of the absorbers, when the pulse power exceeded a certain threshold.

Photo-absorber induced neural-thermal stimulation (PAINTS) introduced here is capable of repeatedly stimulating neurons in a highly specific manner in both space and time. Because it is physical, and can potentially interface with a diverse set of display devices, photo-absorbers and different laser wavelengths, it has properties that make it a powerful technology towards the development of optical neuro-prosthetics.

Gamma-secretase is required for microglia Alzheimer's beta amyloid clearance

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Background: Alzheimer's disease (AD) is the most common type of dementia affecting more than 18 million people worldwide. The cleavage of amyloid precursor protein by gamma-secretase, plays an important role in the pathogenesis of Alzheimer's disease. Gamma-secretase also cleaves other membrane proteins such as Notch, which control cell development and homeostasis. Presenilin 1 and 2 are considered important determinants of the gamma-secretase catalytic site. Our aim was to investigate whether gamma-secretase can be important for microglial phagocytosis of Alzheimer's disease beta-amyloid.

Methods: We investigated the role of gamma-secretase in microglia activity towards beta-amyloid phagocytosis in cell culture using gamma-secretase inhibitors and shRNA, and by using presenilin deficient mice.

Results and conclusions: We have demonstrated that gamma-secretase inhibitors impair microglial activity as measured in genes expression, protein levels and

migration ability which resulted in a reduction of soluble beta-amyloid 1-42 phagocytosis. Moreover, microglia deficient in presenilin 1 and 2 showed impairment in phagocytosis of soluble beta-amyloid. We further showed that dysfunction in gamma-secretase catalytic site led to an impairment in clearing insoluble beta-amyloid from brain sections taken from an Alzheimer's disease mouse model when compared to microglia from wild-type mice. In this work, we suggest for the first time, a dual role for gamma-secretase in Alzheimer's disease. One role is the cleavage of the amyloid precursor protein for pathological beta-amyloid production and the other role is to regulate microglia activity that is important for clearing neurotoxic beta-amyloid deposits. Further studies of gamma-secretase mediates cellular pathways in microglia may provide useful insights into the development of Alzheimer's disease and other neurodegenerative diseases providing future avenues for therapeutic intervention.

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Cell specific gene targeting to the CNS using engineered lentiviruses

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Viral-mediated gene targeting to specific cells and organs is a major challenge for establishment of an attractive gene therapy regimen. We have developed successfully a gene delivery platform into cells using lentiviral vectors that are pseudotyped with a sindbis mutated envelope and a single chain variable fragment (scFv). Incorporation of scFv onto the surface of viral particles was obtained either via interaction of scFv fused to human Fc antibody domain (scFvFc) with a protein A moiety, inserted to the sindbis E2 envelope protein, or through transient surface display of scFvFc fused with a transmembrane domain of cd28. A third approach facilitated stable surface expression of scFvFc fused with a transmembrane domain of cd28 by expressing it in a lentivector along with an Internal Ribosome Entry Site reporter gene (IRES), thus enhancing the incorporation of scFv to engineered particles. To demonstrate the feasibility of the targeting system, two versions of scFv that specifically target the receptor-binding region of the S1 spike glycoprotein of the Severe Acute Respiratory Syndrome Coronavirus (SARS CoV) strains were used. Despite high similarity of the two S1 antigens, gene transfer was obtained with low background of transduction levels (low levels of unspecific infection), indicating high affinity of the surface displayed scFv to their cognate antigen. Significantly, this delivery platform was exploited for in-vivo targeting of recombinant lentiviruses that incorporate an NG2 antibody to mice hippocampal cells. Colocalization of surface expressed NG2 and lentiviral mediated gene transfer of Zoanthus Green Fluorescent protein (ZsGreen) were detected. Overall, these results demonstrate efficacy of lentiviral vectors as a gene delivery platform. Furthermore, such a system could potentially be used to mark specific cells populations for studying their in-vivo biology under health and disease.

On the formation of the essential structural relationships for In-Cell recording and stimulation between cultured hippocampal cells and MEA of gold-mushroom shaped microelectrodes

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Using cultured Aplysia neurons as a model system our laboratory recently reported on the novel approach in which extracellular, non-invasive multi-electrode-array (MEA) system provides "In-Cell Recording" of sub-threshold synaptic potentials and action potentials, from individual neurons with signal to noise ratio matching conventional intracellular recordings (Hai et al., 2010a). This approach can be also used for intracellular stimulation (Hai et al., 2010b). Three principals converge to generate the In-Cell configuration: (a) the activation of endocytotic-like mechanisms in neurons to actively engulf gold-mushroom shaped microelectrodes (gMμE), (b) the generation of high seal resistance between the cell and the engulfed gMμE, (c) the localization of ionic channels (Ohmic conductance) in the plasma membrane that faces the gMμE.

Using electron and confocal microscopy we examined cultured rat hippocampal cells' (representing mammalian neurons) ability to engulf gMμE and thereby generate the physical configuration essential for In-Cell Recording and Stimulation. To that end hippocampal neurons were grown on matrixes of mushroom-shaped gold micro-protrusions (gMmP) functionalized by: (1) poly-D-lysine laminin (PDL/LAM). (2) Poly-ethilene-imine (PEI)-a highly positively charged polyamine. (3) A cysteine terminated engulfment-promoting peptide CKKKKKKKKK-PRGDMPRGDMPRGDMPRGDM.

Cultures formed on PDL/LAM and PEI where characterized by even distribution of the neurons and the glia. The cell bodies as well as extending neurites engulfed the gMmP. Neurons grown on the EPP clustered to form large aggregates. Nevertheless cells in physical contact with the gMmP revealed effective engulfments. Hippocampal cultures grown on matrixes of gMmPs could be maintained for weeks on all the examined substrates.

We conclude that the necessary structural relationships to enable the In-Cell Recording and Stimulation configuration are formed by cultured hippocampal cells grown on gMmP MEA.
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Modulation of lumbar spinal neuronal networks by sacral cholinergic circuitry activated by sacrocaudal afferents

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When the spinal cord is disconnected from supraspinal control, hindlimb locomotion can be elicited by stimulation of sacrocaudal afferents (SCA). The SCA-induced rhythm involves synaptic activation of sacral neurons projecting to lumbar segments, largely via the ventral funiculus (VF). We have demonstrated that elevation of intrinsic and/or extrinsic acetylcholine in the sacral segments enhanced the hindlimb locomotor rhythm in isolated spinal cords of neonatal rats. To reveal the sacral cellular elements and connections involved in the cholinergic modulation, sacral neurons projecting to the lumbar segments were filled by retrograde fluorescent labeling via the VF (VF-neurons), SCA were loaded by anterograde fluorescent labeling and immunofluorescence of vesicular glutamate transporter 1 (VGlut1) marked glutamatergic innervations. Cholinergic transmission components were identified by tracing choline acetyltransferase (ChAT), vesicular acetylcholine-transporter (VAChT) and acetylcholinesterase and confocal microscopy. Our studies revealed that a substantial fraction of the sacral VF-neurons received innervations by SCA and glutamatergic boutons. Almost 30% of the VF-neurons demonstrated AChE activity and about 11% were also capable of synthesizing acetylcholine (ChAT positive). A fraction of the VF-neurons received cholinergic inputs (VAChT positive boutons). Thus, we identified sacral VF-neurons which received glutamatergic afferent innervation and were cholinergic and others that received cholinergic innervations. Collectively, these findings provide numerous ways by which elevation of the intrinsic concentration of acetylcholine in the sacral segments of the spinal cord can increase the motor output during locomotor activity. This capacity may be used to improve the ability to reactivate the pattern generating circuitry in the absence of descending supraspinal control.

An extremely low dose of delta-9-tetrahydrocannabinol (THC) induces long-lasting cognitive effects and biochemical changes in the mouse brain

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A single administration of an ultra low dose (0.002 mg/kg, 3-4 orders of magnitude lower than doses that evoke the conventional acute effects) of THC (the psychoactive ingredient of marijuana) to mice induces a mild cognitive damage that begins 48 hours after the injection and lasts for at least 5 months. Since THC can affect the emotional state of the organism, we tested whether the cognitive deficits are secondary to possible effects of THC on depression or anxiety that are known to modify cognitive functions. THC affected neither depression (as measured by the forced swim test) nor anxiety (measured by the elevated plus maze). We also found no effect of THC on motor activity (another factor that may modify performance in behavioral assays) and so concluded that the mild cognitive deficits are a direct effect of the ultra low dose of THC.

Mild insults are known to activate adaptive mechanisms that protect against subsequent severe insults ("pre-conditioning"). Indeed, we have found that a single injection of the ultra low dose of THC protected against severe cognitive damage that was induced by subsequent treatment (1-7 days later) with PTZ (Pentylenetetrazol, an epileptogenic substance that induces cognitive deficits).

Next we tested whether this ultra low dose of THC has a long-lasting effect on signaling mechanisms in the brain. Seven weeks after the injection of the ultra low dose of THC we detected modifications in several proteins (pERK, pCREB, BDNF) in different brain areas (hippocampus, cerebellum, frontal cortex). Furthermore we observed biochemical interactions between THC and PTZ: although THC and PTZ, when injected separately, elevated pERK in the hippocampus, THC injected 24 hours before PTZ abolished this elevation. These interactions may provide a better understanding of the mechanism(s) of pre-conditioning by THC.

In conclusion, ultra low doses of THC can modify signaling mechanisms within the brain and induce long-lasting cognitive effects.

Placental mesenchymal stem cells are beneficial in an animal model of multiple sclerosis set in oral request poster

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Background: Numerous studies have shown that mesenchymal stem cells (MSCs) from adult and fetal tissues have the potential to differentiate into various cell types and may

be useful for clinical applications. Bone marrow derived MSCs have previously demonstrated beneficial effects in ours studies and others, in the animal model for Multiple Sclerosis the Experimental Autoimmune Encephalomyelitis (EAE). Another abundant source for MSCs is placental tissue (PL- MSCs) which is ethically acceptable, less immunogenic and easily accessible. These cells are also known for their immunomoladatory capabilities.

Methods: In the current study, we aimed to examine whether PL-MSC cells could beneficially affect the symptoms and survival of EAE animals. We intracerebroventricularly transplanted PL-MSC into the right ventricle of Myelin Oligodendrocyte Glycoprotein (MOG)-induced EAE mice and monitored them for 26 days, tracking their disease scores and survival rates.

Results: We showed that human PL-MSCs displayed typical MSCs membrane markers (positive for CD105, CD90, CD73, CD29, and negative for CD14, CD34, and CD45). These cells were also capable of differentiating into typical mesoderm lineages, osteoblasts and adipocytes.

We found that transplantation of PL-MSCs prior to the onset of symptoms reduced the animal disease score to 2.8 vs. 4.7 in the control mice group. Twenty six days post-transplantation the animals' survival rate was 84% in the treatment group and only 26% in the control group. Moreover, disease scores of mice transplanted after symptom onset, were significantly reduced to 3.2 vs. 4.7, and showed a higher survival rate of 73%.

In conclusion, our data indicate that PL-MSCs might be used as a safe and accessible cell source for the treatment of Multiple Sclerosis.

Regulation of microglial activity by neuropeptides in Alzheimer's disease

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Neuroinflammation has a prominent role during Alzheimer's disease which is expressed by activated microglial cells that migrate to sites of amyloid beta (A-beta) deposition, promote A-beta clearance by phagocytosis and release various biochemical markers (like cytokines, chemokines and nitric oxide). Several neuropeptides such as bradykinin (BK), endothelin (ET) and somatostatin (SST) are known to be important mediators of inflammation in the periphery. However, evidence of similar regulatory function in the brain is scarce. The aim of the present study was to examine the effects of these neuropeptides on various aspects of microglial activity such as chemotaxis, phagocytosis of amyloid-beta and the release of proinflammatory mediators. Using immunocytochemistry, we show expression of receptors for BK (B1, B2 subtypes), ET (ETA, ETB subtypes) and SST (SST 2, 3, 4 subtypes) in both microglial cell lines BV2 and N9. Our results also show that exposure of BV2 and N9, as well as primary neonatal rat microglial cells to BK or SST increased A-beta phagocytosis by the cells by more than two folds in a dose dependent manner. By contrast, ET decreased A-beta phagocytosis dose dependently. Pulse-chase experiments confirmed that all neuropeptides increased the overall phagocytosis of A-beta but did not affect A-beta degradation pathways. All neuropeptides increased chemotactic activity of microglia several folds. In addition, we show that amyloid-beta-induced expression of genes encoding the proinflammatory molecules iNOS and COX-2 in microglia was inhibited by 50% by BK. ET also significantly decreased the amyloid-beta-induced expression of monocyte chemoattractant protein 1 and interleukine-6. These results suggest that neuropeptides may play a role in chemotaxis and clearance of amyloid-beta and modulate the brain response to neuroinflammatory processes such as the release of inflammatory factors from microglial cells.

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On the mechanisms regulating synaptic vesicle release by endogenous amyloid beta peptides

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Accumulation of amyloid beta peptides (Abeta) is central to Alzheimer's disease pathogenesis. However, physiological functions of Abeta, a normal product of neuronal metabolism, remain largely unknown. Furthermore, the primary mechanisms by which endogenous Abeta initiates synaptic and cognitive impairments have not been identified. Our recent study demonstrates that endogenous Abeta peptides positively modulate release probability on a rapid timescale in hippocampal synapses (Abramov et al., 2009). To identify the cellular and molecular mechanisms underlying Abeta-mediated increase in release probability, we combine optical imaging of vesicle recycling by FM dyes and fluorescence resonance energy transfer (FRET) spectroscopy at the level of single synapses in cultured hippocampal neurons. Our results demonstrate that amyloid precursor protein (APP), in addition to being a source of Abeta, has a signaling function: it is essential for Abeta-induced enhancement of basal vesicle release. To further understand the mechanisms of this regulation, we explored the relationship between neuronal activity, APP structure and extracellular Abeta concentration at the level of presynaptic boutons. We observed FRET between CFP/YFP-tagged APP proteins, suggesting formation of APP homodimers in hippocampal presynaptic boutons. Nota-

bly, APP homodimerization depended on the level of neuronal and synaptic activity and exhibited high degree of variability among the boutons. Given a positive relationship between Abeta levels and neuronal activity, we are currently examining whether Abeta is the mediator transducing changes in membrane potential to APP homodimerization. Elucidating the mechanisms underlying the effect of Abeta on synaptic function may help to understand physiological Abeta signaling and to identify primary pathological events initiating synaptic dysfunction in Alzheimer's disease.

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The pathological effects of ApoE4 following activation of the amyloid cascade are associated with formation of annular protofibrillar amyloid beta oligomers

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Background. Aβ oligomers play a major role in AD. Aβ oligomerization proceeds via two pathways: a fibrillar pathway characterized by soluble fibrillar oligomers and a more toxic pathway in which Aβ forms soluble prefibrillar oligomers (PFO) which further oligomerize to form annular protofibrils (APFs) which permeabilize the membrane. Activation of the amyloid cascade in apoE4 and apoE3 targeted replacement mice revealed that apoE4 stimulates isoform specifically the degeneration of hippocampal CA1 neurons. This is preceded by the accumulation of intracellular Aβ and apoE in the affected neurons. Additional studies have shown that the presynaptic protein α-synuclein undergoes oligomerization similar to Aβ. Our objective is to examine the hypothesis that apoE4 stimulates the oligomerization of Aβ via the PFO pathway following activation of the amyloid cascade.

Methods. Immunohistochemistry and immunofluorescence stainings utilizing specific conformational Abs were employed to visualize and map distinct Aβ oligomers in apoE3 and apoE4 mice.

Results. Amyloid cascade activation in vivo by inhibition of the Aβ degrading enzyme neprilysin was accompanied by lysosomal and mitochondrial pathology and resulted in accumulation of Aβ and prefibrillar oligomerized Aβ (Ab I-11) within enlarged lysosomes and mitochondria. This was associated with the accumulation of annular protofibrils (Ab α-APF). In contrast, Aβ oligomerization via the fibrillar oligomer pathway (Ab OC) was not stimulated under these conditions. In addition, neprilysin inhibition triggers the accumulation of oligomerized α-synuclein (Ab Syn-33) in CA1 neurons faster and more pronounced in the apoE4 mice.

Conclusions. These findings show that the synergistic pathological effects of apoE4 and the amyloid cascade are specifically associated with activation of the prefibrillar pathway and suggest that annular protofibrillar Aβ oligomers and possibly α-synuclein may mediate the resulting neuropathology.

The neural correlates of object (im)possibility

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Impossible objects constitute a class of visual illusions that rely on erroneous perception of depth in which 2D line drawings seem to represent objects that could not exist in real 3D space. Previous studies have typically used long-term memory repetition priming to explore the cognitive and neural representations of impossible objects. Priming has been consistently found for structurally possible, but not for impossible object, which has been used to suggest that impossible objects cannot produce coherent 3D representations in long-term memory. Imaging studies support this conclusion, showing neural repetition effects for possible but not for impossible objects. In the present study we used short-lag fMRI adaptation to investigate whether equivalent differences between possible and impossible objects could also be detected at the perceptual level. Seventeen subjects performed same/different object judgments for pairs of possible and impossible objects. Contrary to our predictions, equivalent effects of fMRI adaptation were found for impossible compared to possible objects in the lateral occipital complex (LOC) as well as in other areas along the ventral visual stream. We suggest that these findings reflect the creation of 3D representations for (once) impossible objects. This assumption is supported by additional behavioral results, obtained in a separate experiment, showing that immediate repetition of impossible objects increased their likelihood to be perceived as possible. Overall, these findings suggest that qualitative differences may exist between perceptual and long-term memory representations of object (im)possibility in the visual cortex.

TSPO ligands of the quinazoline family protect against glutamate induced glial cell death

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Glial cells are important for neuronal survival in healthy and damaged brain. Thus protecting glial cells from cell death may help to prevent neuronal degenerative processes. Glial cells in the CNS are known to express the 18 kDa

mitochondrial Translocator Protein (TSPO). The TSPO exerts proapoptotic effects, thus blocking TSPO activity can prevent its pro-apoptotic effects. Recently, we have developed novel TSPO ligands of the quinazoline family, to study their capability to prevent glial cell death otherwise caused by glutamate overload. Affinity for the TSPO of our novel ligands was measured by binding assays. Promising novel TSPO ligands were applied to cells treated with glutamate. Previous studies have shown that glutamate (10 – 200 mM) is lethal for primary astrocytes and astrocytoma cell lines. For our study cells of the U118MG glioblastoma cell line were treated with glutamate (25 mM – 80 mM) for 24 hours. Induced cellular death was measured by trypan blue inclusion and release of lactate dehydrogenase. 7-Aminoactinomycin D (7-AAD) was applied to distinguish between late apoptotic and necrotic cells. Specific apoptotic features, such as mitochondrial membrane potential ($\Delta\Psi m$) collapse and cardiolipin oxidation, were assayed with 5,5',6,6'-tetrachloro-1,1',3,3'-tetraethyl- benzimidazolylcarbocyanine chloride (JC1) and 10-N-Nonyl-Acridine Orange (NAO) fluorescent staining, respectively. We found that our glutamate treatment caused cellular death, including apoptosis. Four of our novel TSPO ligands (tentatively named BD 42, BD 57, BD 66, and BD 108) protected against glutamate overload. Their protective effects were more pronounced than of the classical TSPO ligands, PK 11195 or Ro5-4864. In fact, the new TSPO ligands were able to reduce cell death down to control levels. Due to its relatively high affinity for the TSPO and robust anti cell death properties, BD 57 appears to present itself as our lead compound.

Fixational eye movements following stimulus onset reveal two types of microsaccades

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During attending a stationary visual target, our fixation is interrupted by involuntary low-amplitude saccadic eye movements, termed microsaccades. Recently, several studies have suggested that microsaccade execution is not random in time, but rather is correlated with the stimuli onset. It was also found that microsaccade suppression (intervals without microsaccades) is correlated with specific stimuli features, such as contrast.

We performed several experiments, with and without fixation point in the center of the display, and with varying stimulus onset intervals. Subjects were instructed to report whether or not they have detected the target or discriminated between target orientations. Eye movements of the subjects were tracked during the experiments and analyzed off-line for detection and categorization of microsaccades.

Following our experiments, we suggest that there are two types of microsaccades. The first type is for correcting fixation error. These microsaccades appear at about 200 msec after stimulus onset. The second type of microsaccades is associated with the "readiness" for attending the next stimulus. We show that the latency of the latter type of microsaccades is task-dependent and delayed to at least 300 msec after stimulus onset. We also show that, on a trial by trial basis, the latency of microsaccades is significantly correlated with the reaction time of the subject, thus supporting the suggestion that this type of microsaccades marks the end of processing and the "readiness" for processing new stimuli.

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Role for Reelin in stabilizing hippocampal architecture in the mature brain

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Reelin is known to control the migration of neurons during hippocampal development. However, recent studies have provided evidence that Reelin deficiency in the adult hippocampus induces repositioning of fully differentiated neurons, pointing to a role of Reelin in stabilizing the mature hippocampal network. Our recent studies have indeed shown that Reelin stabilizes the actin cytoskeleton by inducing the phosphorylation of cofilin, an actin-depolymerizing protein. Phosphorylation of cofilin renders the protein unable to disassemble F-actin. These findings have implications for brain diseases such as epilepsy and schizophrenia, known to be associated with decreased Reelin expression.

The neural generation and coordination of cockroach locomotion

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The cockroach is renowned for its remarkably stable, yet rapidly adaptable locomotion. This has been crucial for its evolutionary success. It is also a major inspiration for the development of mathematical models of multi-legged locomotion, as well as biologically-inspired robotics. This ability of both, stereotyped and adaptive locomotor behavior is largely dependent on the interplay between centrally-generated motor patterns and the sensory inputs that shape them. We utilized a combined experimental and theoretical approach to investigate the relative importance of central circuits interconnections vs. intersegmental afferents in cockroach locomotion. We simultaneously recorded motorneurons in the thoracic ganglia of a walking cockroach, while

sensory feedback was completely blocked, or allowed only from a specific intact stepping leg. We observed a default coordinated motor pattern with consistent phase relationship that shares similarities with a double tripod gait, suggesting central, feedforward control. This intersegmental coordination pattern was then reinforced in the presence of sensory feedback from a single stepping leg; we show transient stabilization of phase differences between the middle and hind thoracic motor neurons following individual steps of a front leg. Data was further analyzed using stochastic models of coupled oscillators and maximum likelihood techniques to estimate underlying physiological parameters, such as the uncoupled endogenous frequencies and strength and direction of coupling. Our findings indicate that descending ipsilateral coupling is stronger than ascending one while coupling between the left and right sides of the meso- and meta-thoracic ganglia appear symmetrical. A comparison with recent findings in stick-insects may indicate different inter-segmental coordination strategies in the two insects that exemplify opposite extremes of a fast-slow locomotion continuum, while sharing much of the neural and body architecture.

Identifying brain activity related to visual target detection in single trial EEG data

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Recent advances in Neuroscience have led to an emerging interest in Brain Computer Interface (BCI) applications for both disabled and healthy populations. These applications critically depend on online decoding of brain activity in single trials. The goal of the present study was to detect distinctive spatio-temporal brain patterns within a set of event related responses. Subjects were looking for targets (a given category out of five) within a rapid serial visual presentation (RSVP, 10 Hz). EEG data was collected from 64 channels at a high temporal resolution, yielding large spatio-temporal data matrices for the representation of single trial brain activity. These matrices are used to classify brain activity to several categories (or brain states), using machine learning, based on the statistical properties of the activity matrices.

We consider a linear algorithm in accordance with a framework introduced by Parra et al. (Neuroimage 2005). Our algorithm is based on a 2-step linear classification, using FLD classifier. We first classify time points independently to compute a spatio-temporal matrix of discriminating weights. We use this weighting matrix to amplify the original activity matrix by the discriminating weights at each spatio-temporal point. To perform dimensionality reduction we project the weighted data onto the first few PCA components computed separately in the temporal domain for each spatial channel location. The resulting matrix, representing the weighted activity at all spatial locations, is used for decision making by linear classification.

We compare the performance of our analysis with Parra's basic algorithm and find a systematic superiority of our classification algorithm in detection of infrequent visual targets within the RSVP. Moreover, we use our method to automatically extract maximally discriminating brain patterns, and thus extract both spatio- and temporal information about brain networks involved in visual target detection.

Cinnamon fraction reduces b-amyloid oligomerization and corrects cognitive impairment in Alzheimer's disease animal models

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An increasing body of evidence indicates that the accumulation of soluble oligomeric assemblies of the b-amyloid polypeptide (Ab) plays a key role in the pathology of Alzheimer's disease (AD). Specifically, the presence of a 56 kDa dodecameric oligomeric species was shown to be correlated with impaired cognitive function in AD model mice. Several reports have documented the inhibition of Ab plaque formation by compounds of natural source. Yet, evidence for the ability of common edible elements to modulate Ab oligomerization remains an unmet challenge. Here we identify natural substance, based on fraction of cinnamon extract (CEppt), which markedly inhibits the formation of toxic Ab oligomers and prevents the toxicity of Ab towards neuronal PC12 cells. When administered to AD fly model, CEppt rectified their reduced longevity and fully recovered their locomotion defects. Furthermore, oral administration of CEppt to aggressive AD transgenic mice model led to marked decrease in 56 kDa Ab oligomers, reduction of plaques and improvement in cognitive behavior. The conclusions of this study are:

CEppt inhibits SDS stable oligomers at very low concentration; this inhibition is dose dependent.

CEppt inhibits the fibrillization of Ab at low concentrations. Both ThT and TEM show that the inhibition is dose dependent.

CEppt rectified the Alzheimer's-related symptoms of 'AD' transgenic drosophila, which include defective locomotion and reduced life span, while having no effect on control flies.

CEppt is not toxic to pc12 cell line and reduces the toxicity of Ab oligomers towards the cells.

CEppt significantly improves the cognitive behavior of 5XFAD transgenic mice.

CEppt significantly alleviated 56 kDa toxic oligomer formation and plaque burden in 5XFAD transgenic mice.

A-to-I RNA editing as a putative mechanism of the transgenerational impact of adversity in rats

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Adversity to women can cause temperamental difficulties, neuro-developmental disorders, and childhood psychopathology in their infant offspring. Clinicians believe that adversity, even before pregnancy, impacts the future child's development, and research has suggested that this is due to the child developing in the same adverse environment. However, in a novel experimental paradigm in laboratory rats, we have previously shown (Shachar-Dadon, A. Schulkin, J. Leshem, M. Developmental Psychology, 45, 9-16, 2009) that stress to the mother before she becomes pregnant, impacts her future offspring behavior even where the environment is controlled. The offspring's emotional and social behavior is altered in complex ways that differ in males and females, and persist into their adulthood. Female offspring of dams stressed before conception were more fearful, anxious, depressed, impaired cognitively, and less sociable. Males were also less sociable, but were less fearful and more resilient. In search of a mechanism for these intriguing findings, we examined alterations in adenosine to inosine (A-to-I) RNA editing in the offspring of stressed and control dams immediately after birth (P0-P1) and in adulthood (P90-100). A-to-I RNA editing is an epigenetic process that entails site-specific modification in precursor mRNAs, catalyzed by members of the adenosine deaminase acting on RNA (ADAR) enzyme family, and impacts on neurotransmission at 5-HT, glutamate and GABA receptors. We found abnormal levels of A-to-I RNA editing in the progeny of stressed dams immediately after birth. These findings indicate that behavioral abnormalities observed in pups born to stressed dams may be due to changes in the epigenetic code that are transmitted across generations, rather than differences in early environment.

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Role of the sub-esophageal ganglion in the regulation of insect locomotion: lessons from predatory wasps and zombie cockroaches

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The parasitoid Jewel Wasp hunts cockroaches to serve as a live food supply for its offspring. The wasp stings the cockroach in the head and delivers a neurotoxic venom cocktail directly inside the prey's cerebral ganglia. Although not paralyzed, the stung cockroach becomes a living yet docile 'zombie' incapable of self-initiating walking or escape running. Our goal was to identify the neuronal substrate responsible for this venom-induced neuro-chemical manipulation of the cockroach locomotion. We show that the decrease in the drive for walking can be attributed to a decrease in neuronal activity in a small region of the cockroach cerebral nervous system, the sub-esophageal ganglion (SEG). Specifically, we have used behavioral, neuro-pharmacological and electrophysiological methods to show that: (1) Surgically removing the cockroach SEG prior to wasp stinging prolongs the duration of the sting 5-fold, suggesting that the wasp actively searches and targets the SEG during the stinging sequence; (2) injecting a sodium channel blocker into the SEG of non-stung cockroaches reversibly decreases spontaneous and evoked walking, suggesting that the SEG plays an important role in the up-regulation of locomotion; (3) artificial focal injection of crude milked venom into the SEG of non-stung cockroaches decreases spontaneous and evoked walking, as seen with naturally-stung cockroaches; and (4) spontaneous and evoked neuronal spiking activity in the SEG, recorded with an extracellular bipolar microelectrode, is markedly decreased in stung cockroaches as compared with non-stung controls. Our data strongly provides evidence for a critical and permissive role of the SEG in the regulation of locomotion in insects. By injecting a venom cocktail directly into the SEG, the parasitoid Jewel Wasp selectively manipulates the cockroach's motivation to initiate walking without interfering with other non-related behaviors.

On the role of IGF-I in regulation of presynaptic function in hippocampal circuits

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Insulin like growth factor 1 receptor (IGF-IR), a receptor tyrosine kinase, controls longevity in a wide range of species. In the brain, IGF-IR is abundant in various regions. Recent studies have shown that reduction in the IGF-IR expression levels prevents synapse loss and memory decline in Alzheimer's disease (AD) mice models (Cohen et al., 2009; Freude et al., 2009). In contrast, other studies have suggested improvement of cognitive function by IGF-1 injections. In order to understand the mechanisms underlying regulation of memory function by IGF-IR, we first aimed to explore

its role in normal synaptic transmission and plasticity. Here we examined the effects of endogenous IGF-I on basal synaptic vesicle recycling and presynaptic plasticity utilizing activity-dependent FM styryl dyes in primary hippocampal cultures. We found that both IGF-IR/IR antagonist AG1024 and antibody neutralizing IGF-IR activity (aIR3) induced presynaptic inhibition at functional boutons and reduction in the number of functional boutons during physiologically-relevant patterns of stimulation. These results suggest that the IGF-IR signaling positively regulates synaptic vesicle release and maintains the number of functional synapses in hippocampal networks. Based on these data, we hypothesize that reduction in the basal level of ongoing synaptic activity is the key trigger of synaptic and cognitive improvements in AD mice. We will further corroborate this conjecture by exploring the effect of IGF-IR knock-down in hippocampal circuits under physiological and pathological conditions.

Deep brain stimulation in the VTA increases gamma band synchronization in depressive rats

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Deep Brain Stimulation (DBS) has been shown to significantly reduce symptoms in multiple neurological disorders such as Parkinson's disease, epilepsy, Tourette's syndrome and depression. DBS treatment to the Ventral Tegmental Area (VTA), using a specific protocol of burst like activation, has been shown to reduce depressive symptoms in the Flinder Sensitive Line (FSL), a rat model for depression. In an attempt to understand the effect of the stimulations on the neural networks within the VTA, we studied Local Field Potentials (LFP) recordings and their synchronization patterns. For examining temporal shifts in spectral characterizations, a wavelet based synchronization measure (the Wavelet Phase Coherence) was used. We found that the synchronization between LFP recordings in distal parts of the VTA was increased in FSL rats following DBS treatment, in frequencies above 30 Hz (gamma frequency range), while there was no affect in the lower frequency bands. DBS treatment of the normal Sprague Dawley (SD) rats did not show any effect on LFP synchronization. We speculate that this increased high frequency synchronization may be a result of increased synchronization between GABAergic cells and networks within the VTA.

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Beyond the saccadic spike potential – scalp EEG manifestation of induced gamma band responses to visual stimuli

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High frequency (gamma-band) neural activity has been studied extensively as a possible correlate of cognitive processes such as object feature binding. Recently we showed that the analysis of induced gamma-band responses in scalp EEG recordings is seriously confounded by a myogenic saccade-related spike potential (SP), which manifests as a transient broadband induced response overlapping the gamma frequency band (iGBRtb). We further suggested an SP-guided artifact correction procedure based on Independent Component Analysis (ICA) to remove this confounding signal from EEG data, in order to unveil any neural signal in the gamma band present in the EEG. Here, we applied this method to analyze scalp EEG recorded from 14 subjects presented with short-duration visual stimuli. We then compared the induced gamma band responses in the corrected data and the uncorrected data, which was treated only with traditional artifact rejection methods. The results show that our method is effective in suppressing the SP artifact, allowing the investigation of neurogenic gamma-band activity thus far obscured by the higher-power myogenic iGBRtb. The results further suggest the existence of such an induced gamma-band response in the EEG, with a duration corresponding to the duration of stimulus presentation. We compare the spectro-temporal pattern of these results to previously reported intracranial recordings.

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Frequency-dependent effects of rTMS on markers for neuroplasticity: Differential outcomes in anaesthetized and awake animals

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Repetitive transcranial magnetic stimulation (rTMS) has become a widely used in basic neuroscience studies and clinical research. The long-term effects of rTMS on excitability or behavioral and clinical changes have been associated with neuroplasticity and mechanisms such as long term potentiation (LTP) or depression (LTD). High frequency stimulation can induce increases in excitability or thought to cause LTP-like effects while low frequency stimulation can reduce excitability or induce LTD-like

effects. The effect of frequency has not been consistent in all TMS experiments, and several studies indicate on a critical role of spontaneous neuronal activity on the neurophysiological and behavioral outcomes of the stimulation. Neurotrophic factors and glutamate transmission are critical mediators of synaptic plasticity and can be used as markers for studying long-term effects of rTMS. In this study we have measured the effects of 10 sessions of either high or low frequency rTMS on alterations of brain-derived neurotrophic factor (BDNF), which is one of the most prevalent neurotrophic factors in the adult. We have also measured alterations in the GluR1 subunit of the AMPA receptors, another marker for plasticity especially given its effect on calcium permeability. In order to test whether the long-term effects of stimulation on these markers for neuroplasticity depend on spontaneous neural activity, we have measured the effects of several rTMS sessions applied on either awake or anaesthetized rats. We found that high frequency rTMS in awake rats increased BDNF and GluR1 levels in the hippocampus (Hc) and BDNF levels in the prelimbic cortex (PLC). Conversely, in anaesthetized rats, the same stimulation decreased BDNF and GluR1 levels in the Hc and BDNF in the PLC. This study indicates how rTMS can affect neuroplasticity and emphasizes that the spontaneous neural activity during stimulation can dramatically affect the neurochemical outcome and thereby therapeutic effects.

Studying neuronal ensembles in bat hippocampus: towards uncovering the effects of sensory input on spatial representation

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Hippocampal neural recordings are an important model system for understanding cognition: The ensemble activity of hippocampal neurons has been shown to encode the location of an animal within its environment, along with contextual attributes associated with memories of that environment. However, little is known on how data from different sensory systems is embedded in the spatial "cognitive map" that these cells are thought to represent.

The project described in this poster aims to allow clean dissociation of the use of two long-range sensory systems – vision and echolocation. We study a unique animal model, the bat, which orients itself in the dark by emitting discrete sonar pulses. We intend to separate the use of the two sensory systems: Vision without sonar – in a lit environment, and Sonar without vision – in the dark. Through simultaneous recordings of multiple cells in the hippocampal CA1 region of flying bats, we plan to characterize the differences in the neural codes for space of individual cells, and in the ensemble activity, based on the two sensory systems. We will present theoretical analysis, using tools from radar theory, which along with existing behavioral data confirm that echolocation is comparable to vision in terms of the spatial resolution of distal information that it provides about the animal's surroundings. We will also present out first technical steps towards implementing large-scale ensemble recordings – including our first spikes recorded from a 12-tetrode microdrive – which in the long run will allow us to record up to ~50 single cells simultaneously in the behaving, flying bat.

The questions that we are asking are the following: Will the ensemble coding in the lit environment overlap with the ensemble coding at the same location in the dark? When switching between spatial representations in light\dark conditions – what are the dynamics of the cognitive-map buildup?

Mechanical manipulations of neuronal growth

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Dendrites and axons show extremely diverse complex structures which profoundly influence their ability to receive and transmit synaptic information and determine a neuron's role within neuronal circuitry. Elucidating mechanisms that control neural growth is therefore fundamental to understanding how individual neurons wire themselves into intricate functional networks and have important biomedical and bioengineering implications. Previous studies have identified processes that occur along neuronal growth and influence the geometry of the dendritic arbor, however, the question of how a single neuron gains a specific structure for a specific function remains unresolved.

Studies based on morphological measurements have shown that the pattern of growth is highly dictated by physical constraints such as adhesion and tensile forces along the neuronal branches. Furthermore, applying mechanical tension can facilitate neurites initiation and elongation.

We have developed the ability to manipulate and analyze specific single neurons from the leech central nervous system. We grow neurons in 2D and 3D cultures on different substrates, such as PDMS, gold, glass, gels and ConA coated dishes and can follow their growth for up to two weeks. Moreover, we plate the neurons on substrates with specific geometrical patterns, and examine the physical effects on the neuronal growth. In addition, we are using an emerging method of magnetic manipulation in which magnetic particles attached to neurons can be manipulated by magnetic field, generating tensile forces along the neuronal processes, thus affecting their growth pattern. We have tested these manipulations on primary neuronal culture obtained from the medicinal leech, as well as on mammalian cell lines. Experimental results from the different assays will be presented and discussed.

The Physical Mind: convergence of bottom-up and top-down full body multisensory representations.

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One of the characteristics of physical consciousness is awareness which enables us to perceive body and self, to project ourselves unto others, and to do simulations using for instance mental imagery of our own body. Different sensory systems permit body representations stemming from several sensory modalities: somatosensory body representations and visual body representations. Full body representation (FBR) must amalgamate congruent information from several different senses and from top down and bottom up influences in order to enable the experience of self. This central integration of both visual, tactile, bottom up with top down information is in the very basis of our ability to experience ourselves as an enduring entity that resides in the perceived human body. However very little is known about whole body integration across the senses and of bottom up vs. top down processes of the whole body.

This study focuses on the neural correlates of FBR using fMRI in humans. Specifically we focus on the integration of bottom-up and top-down somatosensory and visual information of the whole body. We used five different paradigms: tactile whole body perception, tactile whole body mental imagery, visual body perception and visual whole body imagery. To better compare our results to previous work related to the whole body multisensory perception we also used a mental projection of FBR.

Our results reveal a network of cortical areas activated throughout the different experimental conditions. This network seems to be involved in different aspects of FBR including the multi-sensory cross-modal representation of ourselves. Furthermore, there is the possibility that this network is used by us to project others upon ourselves to understand how they move and act physically, and possibly also mentally.

Protracted withdrawal following a single exposure to morphine

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Chronic drug use leads to persistent physiological changes that endure long after the end of drug exposure. This state of protracted withdrawal may contribute to the high rate of relapse in recovering drug addicts. We show for the first time that a single exposure to morphine is sufficient to cause protracted withdrawal – defined by increased anxiety following naloxone administration – for at least 80 days. This residual state of affective allostasis, caused by just one morphine exposure, may motivate further drug use during the earliest stages of addiction.

Design principles for inhibition in dendrites

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Inhibitory axons from distinct input sources typically target specific dendritic sub-domains. This domain-specific connectivity plays a key role in supporting different brain states. Our study presents a new framework for understanding the spatial integration of inhibition in dendrites and provides a functional definition for the notion of inhibitory "dendritic domain(s)" in analytical terms. We show that, for local control of dendritic excitability, "off path" inhibition is more effective than "on path" inhibition and that inhibition effectively spreads into regions more central to the inhibitory contacts, where it accumulates and might even exceed the inhibitory impact at the synaptic contact sites themselves. Hence, local morphological inhibitory domains may have a more global inhibitory impact on the tree. This holds for several reconstructed dendrites with known inhibitory loci, including Martinotti-to-pyramidal cell connection in rat neocortex. We thus highlight a new set of design principles for the operation of inhibition in dendrites.

PGW molecules are novel antipsychotics with NMDA modulation, and high efficacy against positive and negative symptoms of schizophrenia in mice models

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Background: Schizophrenia is a chronic disease associated with hypo function of glutamate transmission, manifested by psychosis symptoms induced by NMDA antagonists: phencyclidine (PCP) and MK801. NMDA positive modulators D-serine, D-cycloserine and sarcosine showed some improvement of negative symptoms.Yet, their efficacy is mild requireing huge amounts. We developed novel antipsychotics possessing an atypical neuroleptic moeity linked to positive modulator of NMDA. We hypothesize that such agents could be efficacious against positive and negative symptoms, and potentially improve cognitive and social tasks.

Methods: PGW4,5,6,7,8 possessing a moiety of olanzapine or clozapine linked through a spacer to a-glycinyl or, a-sarcosinyl were synthesized. Molecules were stable lipophyilic powder. Efficacy was evaluated in male mice

(Balb/c or C57bl). PGW molecules were administered PO alone or combined with MK801 or with PCP. Positive controls were olanzapine or clozapine. We performed acute open field and elevated plus maze (EPM) tests, and a subchoronic study (C57bl treated 14 days with PCP (10 mg/kg/d) with/without PGW5 (25 mg/kg/d). Social prefence test performed one week after PCP termination. Animal behavior was analyzed using the Noldus software.

Results: In the open field, PGW molecules were administered 90-360 min before MK801 (0.15 mg/kg ip) and evaluated for 20 min. PGW 5,7,8 at 25-50 mg/kg po effectively antagonized MK801-induced hyperactivity up to 6 hr. At variance from olanzapine and clozapine, the PGW molecules were not sedative, and demonstrated a significant anxiolytic activity. Anxiolytic effect was found also in the EPM for PGW 5,8. In the subchronic study, PCP mice showed impaired social preference which was antagonized by PGW5 but not by olanzapine.

Conclusions: PGW molecules are new class of neuroleptics efficacious against positve symptoms without sedation. The drugs show anxiolytic effect accompanied by normalization of impaired social performance.

Myelin inhibits myelin phagocytosis through CD47/SIRPα interactions in microglia and macrophages

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Traumatic injury to axons is followed by Wallerian degeneration distal to lesion where axons and myelin breakdown. The rapid removal of degenerated myelin by phagocytosis is advantageous since molecules in myelin inhibit axonal regeneration and thus repair. We presently test the hypothesis that myelin regulates its own phagocytosis by simultaneous activation and inhibition. Activation follows myelin binding receptors that mediate its phagocytosis. Inhibition, we hypothesize, follows CD47 on myelin binding immune inhibitory receptor SIRPα (signal regulatory protein-α) on macrophages and microglia, which was not studied before. We document here for the first time that CD47 but not SIRPα is expressed on Schwann cells, oligodendrocytes and myelin, and further confirm that CD47 and SIRPα are expressed on macrophages and microglia. We demonstrate also that phagocytosis is augmented after reducing SIRPα levels by lentiviral infection with SIRPα-shRNA and after blocking CD47-SIRPα binding with function blocking mAbs against CD47 and SIRPα. We further reveal faster in-vivo removal of degenerated myelin in CD47 knockout mice than in wild-type mice during Wallerian degeneration following peripheral nerve injury. Observations suggest altogether that myelin inhibits its own phagocytosis through CD47/SIRPα interactions. It may further be argued that CD47 functions normally as a marker of "self" that helps protect intact myelin and myelin forming Schwann cells and oligodendrocytes from activated macrophages and microglia. However, the very same mechanism may turn disadvantageous after traumatic injury to axons since it attenuates phagocytosis of degenerated myelin.

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Antidepressants elevate GDNF expression and release from C6 glioma cells in a beta-arrestin1-dependent, CREB interactive pathway

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Background: Glial cell line-derived neurotrophic factor (GDNF), essential for neuronal survival, plasticity and development, has been implicated in the mechanism of action of antidepressant drugs (ADs). Beta-arrestin1, a member of the arrestin protein family, was also found to play a role in ADs mechanism of action. The present study aims at evaluating whether the effect of ADs on GDNF in C6 rat glioma cells is exerted through a beta-arrestin1-dependent, CREB-interactive pathway.

Methods: Beta-arrestin1, GDNF, CREB protein levels were measured in fractions of C6 glioma cells chronically treated with different classes of ADs by immunoblot analysis. GDNF expression was also measured using confocal microscopy. GDNF release from control or beta-arrestin1 knock-down was measured by ELISA method. Beta-arrestin1/CREB interaction was detected by immunoprecipitation.

Results: Chronic treatment with ADs significantly elevated beta-arrestin1 levels in the cytosol, while reducing phospho-beta-arrestin1 levels in the cell nuclear fraction. ADs significantly increased both GDNF expression and release from the cells, but were unable to induce such effects in beta-arrestin1 knock-down cells. Chronic treatment with ADs significantly increased CREB phosphorylation without altering the level of total CREB in the nuclear fraction of the cells. Moreover treatment with ADs significantly increased beta-arrestin1/CREB interaction.

Conclusions: These findings support the involvement of beta-arrestin1 in ADs mechanism of action. We suggest that following ADs treatment, beta-arrestin1 generates a transcription complex involving CREB essential for GDNF expression and release, thus enhancing GDNF neuroprotective action that promotes cellular survival and plasticity when the survival and function of neurons is compromised as occurs in major depression.

LTS inhibitory interneurons reduce firing rate and may generate slow oscillations in models of cortical networks with short-term synaptic plasticity

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Excitatory synapses from regular-spiking (RS; pyramidal) neurons to low-threshold spiking (LTS; somatostatin-expressing inhibitory interneuron) cells strongly facilitate. Therefore, it has been suggested that LTS neurons protect cortical circuitry against overexcitation and epilepsy. We examine the dynamical roles of short-term synaptic plasticity in networks that include LTS neurons. We construct and analyze a rate model of the circuit that includes RS, LTS, and fast-spiking (FS; parvalbumin-expressing interneuron) cell types. Short-term plasticity is represented by the Tsodyks-Markram scheme. RS and FS neurons, but not LTS neurons, receive external thalamic input. In an RS-LTS circuit, activity of LTS neurons reduces the firing rate of the RS neurons. Well above the LTS firing threshold, this reduction is constant and independent of the firing rate of RS neurons. Surprisingly, the strongest impact of the LTS neuron on the shape of the firing rate-input curve is just above the LTS firing threshold. Like LTS-to-RS connections, FS-to-RS synapses reduce the firing rate of RS neurons by a constant amount at high firing rates. An RS-LTS-FS network may exhibit slow oscillations at the time scale of recovery from facilitation (~2 Hz); these oscillations persist even when all the synapses do not exhibit any synaptic depression. RS neurons oscillate between a more-active state and a less-active state; the firing rate in both states is larger than zero. FS neurons fire episodes of spikes in phase with the more-active state of the RS neurons, whereas LTS neurons fire in phase with the less-active state of RS neurons, i.e. they fire in anti-phase with FS neurons. We conclude that the short-term synaptic plasticity of synapses to and from LTS interneurons allows these cells to shape the dynamics of cortical circuits not only at high firing rates, but also just above their firing threshold.

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Neural representations of the human sensitivity to reinforcement cues: insights along an animal model

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Motivation is a widely investigated psycho-behavioral concept regarding the drive to facilitate or inhibit behavior in response to environmental incentives and threats (i.e. punishment and reward cues). Based on animal research, a neurobehavioral model named "Reinforcement Sensitivity Theory" (RST) was suggested, including 3 systems involved in motivation: 1) The "Behavioral Activation System" (BAS) mediates sensitivity to reward via e.g. Nucleus Accumbens (NAC) and dorso-medial Pre Frontal Cortex (dmPFC). 2) The "Fight Flight Freeze System" (FFFS) mediates sensitivity to punishment via e.g. the hypothalamus and amygdala. 3) The "Behavioral Inhibition System" (BIS) responds to goal-conflict represented by mixed or ambiguous cues via e.g. the hippocampus and ventro-medial PFC (vmPFC). Abnormal operation of these systems has been further proposed to underlie pathological reaction to cues, as manifested in anxiety and mood disorders. To date, however, the RST model has been established in animal studies while the evidence regarding the human brain are yet non conclusive. 24 healthy subjects participated in an fMRI study while playing an interactive modified Domino game encompassing distinct periods of response to punishments, rewards or goal-conflict. We found a typical brain signature for each interval of the game, corresponding to the motivation systems as proposed by the RST: Fitting with the FFFS; the amygdala and hypothalamus increased activation during the interval of response to punishment. Fitting with the BAS; the NAC and dmPFC increased activation during the interval of response to reward. Fitting with the BIS; the hippocampus and vmPFC increased activation during periods of conflict. Our initial analysis suggests that motivational processes in humans may be operating with accordance to the RST model. This understanding opens a new horizon for therapeutic interventions based on individual brain-profile of response to environmental cues.

The Levie-Edersheim-Gitter Institute for functional brain imaging

Beneficial treatments for visual dysfunction by short-acting anti-muscarinic drugs following ocular exposure of the nerve agent sarin in the rat

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Eye exposure to the organophosphorus irreversible acetylcholinesterase inhibitor sarin results in long-term miosis and reduction in visual function. Anti-cholinergic drugs, such as atropine, are used topically in order to counter these effects and obtain symptomatic relief. Unfortunately, such compounds attenuate ocular discomfort at the expense of producing mydriasis and partial cycloplegia symptoms,

which may worsen visual performance. This study was aimed to test short acting anti-cholinergic drugs against sarin-induced miosis and visual impairment, which will minimally affect vision.

Male Pigmented Long-Evans rats were topically exposed to sarin (0-10 μg) and 20 min later were topically treated with tropicamide, cyclopentolate, atropine or saline. Pupils were illuminated with an infrared spotlight and images were digitally recorded with a computerized infrared-capable video camera, thus measuring pupil width. Miosis was determined as a 50% reduction in pupil width. Pupil width was determined 15 min -72 h following each treatment. Visual function assessment was performed using the "Cued" Morris Water Maze task, 15-35 min, 2 h and 4 h following sarin exposure. The cue was a circular green rod (5 cm high) attached to the visible escape platform (1 cm above the surface of the water). Rats exposed topically to various sarin doses showed a dose-dependent miosis, which returned to pre-exposure levels within 24-48 h. Significant reduction in visual function was seen in animals 15 min following exposure to 0.2 sarin and above, opposed to animals examined 2 or 4 h following exposure. Finally, short-acting anti-cholinergic treatments differentially affected the sarin induced miosis and the resulting impairment in visual performance. The miosis, as well as the visual defects observed following topical sarin exposure are contradicted to various extent by different anti-cholinergic drugs.

Preclinical development of davunetide (NAP) as a peptide-drug candidate: microtubules, schizophrenia and cognitive behavior

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Background: NAP (davunetide) is an active fragment of activity-dependent neuroprotective protein (ADNP). ADNP and the homologous protein ADNP2 provide cell protection. ADNP is essential for brain formation, proper development and neuronal plasticity, all reported to be impaired in schizophrenia. ADNP haploinsufficiency inhibits social and cognitive functions, major hallmarks of schizophrenia. NAP treatment partly ameliorates ADNP haploinsufficiecy.

Aims and Methods: 1] To evaluate a possible involvement of ADNP and ADNP2 in the pathophysiology of schizophrenia in humans, we measured relative brain levels of mRNA transcripts of both proteins compared with control subjects. 2] Protection by NAP (davuentide) treatment was tested in the microtubule stable tubule-only polypeptide (STOP) deficient mice, modeling aspects of schizophrenia.

Results: Quantitative real time polymerase chain reaction in postmortem hippocampal specimens from normal control subjects exhibited a significant ADNP to ADNP2 transcript level correlation. In contrast, in the hippocampus of matched schizophrenia patients this correlation was significantly decreased, mirroring disease-associated increased ADNP2 transcripts (Eur Neuropsychopharmacol. 2010 [Epub ahead of print]). Daily intranasal NAP (davuentide) treatment significantly decreased hyperactivity in STOP-deficient mice and protected visual memory (Peptides 31:1368-73, 2010).

Conclusions: The imbalance in ADNP/ADNP2 expression in the schizophrenia brain may impact disease progression. Davunetide is currently under clinical development by Allon Therapeutic Inc. (www.allontherapeutics.com) and has shown cognitive protection in patients suffering from amnestic mild cognitive impairment as well as improved functional capacity in schizophrenia patients (Javitt, Schizophr. Res. 117, 118–119, 2010).

Gildor Chair, Adams Super Center, Elton Lab., AMN Foundation, Allon Therapeutics Inc.

Non channel function of KV2.1 to facilitate exocytosis; underlying molecular mechanism

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Classically, voltage-gated potassium channels are viewed as inhibitors of exocytosis by hyperpolarizing membrane potential which is potassium flux-dependent.

Recently, we identified a new role for Kv2.1 channels in facilitating vesicle release from neuroendocrine cells, as well as from soma of neurons.

Importantly, this Kv2.1-induced facilitation is potassium flux-independent and is mediated by direct association of Kv2.1 C1a domain with Syntaxin. Accordingly, the physical interaction of native Kv2.1 with Syntaxin was shown to be dynamic and enhanced during Ca2+- triggerring; impairment of the interaction attenuated release under conditions of no potassium flux. Further, it was shown that the facilitation of exocytosis was mediated by an increase in total number of exocytotic events due to enhanced rate of vesicle recruitment during high Ca2+. Hence, it was suggested that Kv2.1 belongs to a group of proteins that regulate vesicles recruitment by virtue of their direct interaction with Syntaxin.

Since Kv2.1 was shown by us to interact with both the open conformation of Syntaxin and the binary t-SNARE complex, but not with the ternary SNARE complex, we hypothesized that Kv2.1 stabilization of open Syntaxin and/or the t-SNARE complex underlies the Kv2.1-induced

recruitment of vesicles. To investigate this hypothesis,we now utilize a probe, constructed by us, that reports, through fluorescence resonance energy transfer (FRET), conformational changes of t-SNAREs with regard to induction of exocytosis via the opening of voltage gated calcium channels in intact PC12 cells.

A role of calcium stores in neuronal plasticity of dorsal and ventral hippocampus

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Previous studies have shown that synaptopodin – an actin – binding protein located at the base of some dendritic spines - is unequally distributed between dorsal (DH) and ventral (VH) hippocampus with significant predominance in the ventral part [1]. It has also been shown [2] that synaptopodin may be functionally associated with ryanodine-type calcium stores which are activated by caffeine. In the present study we examined electrophysiological properties of acute slices of the dorsal and ventral hippocampus in response to caffeine. In addition, the effect of caffeine on [Ca2+]i was measured in cultured hippocampal slices using 2-p microscopy. Population excitatory postsynaptic potentials (EPSPs) were recorded in stratum radiatum of CA1 region of the DH and VH slices taken from 30-day-old Wistar rats. Caffeine was applied at concentrations of 0.5 to 10 mM for 30 minutes. We found that VH is significantly more sensitive to caffeine at low concentrations (1 mM) than DH. LTP was induced by high frequency stimulation (100 Hz, 1 s). Caffeine (5 mM) was added after the second train of stimuli and led to the potentiation of the both pathways (stimulated and non-stimulated) in VH slices exclusively. In a parallel series of experiments, 2-3 weeks old cultured slices of VH and DH were preincubated with 10 μM Fluo-3 AM during 2 hours at room temperature. Administration of 10 mM Caffeine induced transient calcium responses lasting 1.35 times longer and being 1.87 times larger in the VH than in the DH slices. These results indicate that caffeine produces larger response in the VH than in the DH, which is congruent with the assumption that the role of calcium stores in modulating neuronal plasticity is more significant in VH than in DH.

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Fast visual processing based on retinal spike times

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Vision relies on the transmission of information from the eye to central brain regions via the activity of retinal ganglion cells (RGCs). The responses of RGCs are remarkably precise, raising the possibility that the timing of individual spikes could encode aspects of the visual scene. How the brain interprets these spike trains is still unclear. In particular, it is intriguing that humans can evaluate abstract features of a visual scene within mere tens of milliseconds. This suggests that the underlying neural computations can be performed with just one or two spikes per neuron.

To explore this issue, we used a biologically plausible model neuron (tempotron) to decode spike trains simultaneously recorded from RGCs in the isolated salamander retina. The model is based on an integrate-and-fire neuron, which receives the recorded spike trains as synaptic input. Its response is sensitive to the relative timing of spikes on different afferents. We asked the neuron to discriminate between stimulus conditions on the basis of the spatio-temporal spike patterns in the RGC cell population, and used the tempotron learning rule to adjust the synaptic weights appropriately. The visual stimuli consisted of briefly presented spatial gratings for which both spatial phase and contrast level were varied independently.

We found that the tempotron can successfully learn to discriminate between the spatial phases of the stimuli based on only the first spikes from each afferent RGC. This rapid mode of processing can be performed in a contrast-invariant manner. Furthermore, the tempotron accomplished certain difficult tasks – involving the polarity-invariant detection of an edge – that cannot be realized by comparable decoders based on firing rates. We quantified how the performance depends on decision time and spike correlations between different RGCs. Our results highlight the biological plausibility of spike-timing based population codes in early visual processing.

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Molecular mechanisms of neuronal remodeling: Plum - a novel pruning receptor

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Background: Neuronal remodeling by axon pruning is widely used during development of neural circuits. Although pruning has been observed in nervous systems ranging from nematodes to mammals, the molecular mechanisms regulating axon pruning remain mostly unknown. In particular, little is known of how axons receive extracellular signals that trigger their degeneration. Understanding the molecular mechanisms regulating developmental axon pruning should provide a broad insight into the mechanisms of axon fragmentation and elimination during development, disease and after injury

Results: Remodeling of Drosophila mushroom body (MB) gamma-neurons is an excellent model to investigate the molecular mechanisms of axon pruning due to its stereotypy and wide spectrum of genetic tools at hand. A mosaic forward genetic screen identified a novel immunoglobulin super family (IgSF) protein that we named Plum, as a key promoter of axon pruning in a cell-autonomous manner. By performing detailed structure function analyses we identified a sub-segment of the Plum extracellular domain that is both necessary and sufficient for its axon pruning promoting activity. In contrast, we demonstrated that the cytoplasmic domain is not required for Plums function in axon pruning, suggesting it functions as a co-receptor. In addition, in-vivo mosaic rescue experiments, combined with in-vitro aggregation assays suggest that Plum binds a heterophilic ligand that is present in limited amount. We finally show that plum's function is not only limited to elimination of larval gamma neurons but is also required for the elimination of ectopic axons at the fly NMJ.
Conclusions: Taken together, our observations indicate that plum is a pruning co-receptor well poised to provide spatial and temporal control of axon elimination during development.

Octopus vulgaris uses proprioception to direct a single arm in a two-ways choice maze

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Controlling eight flexible arms the octopus carries out many complex tasks, such as crawling, exploring, mating and swimming. With all their infinite options of movement researchers have found them disappointing, as they consistently failed in tasks requiring knowledge of the location of their arms. It was assumed that octopus were incapable of combining a peripheral feedback signal with central reward information to achieve such learning. To test proprioceptive single arm control in Octopus vulgaris we designed a Y shaped maze, which was opaque to the animal, was attached to the front glass of the home tank. Octopuses were trained to insert a single arm through the tube and into one of the two goal compartments to retrieve a food reward. Octopuses performed 10 trials a day each lasting 180 s. After testing side preference animals were assigned a target side (left or right). 5 of 6 Animals learned to reach through the maze to retrieve a food reward from their target side within 20-90 trials. With a lack of visual and chemical information on the location of their arm the only input octopus could utilize to direct the arm is from the arm itself. This simple bifurcation maze provides the first evidence for the utilization of proprioceptive information in a learning task.
This work was supported by the EU EP7 and ISF

Fn14-TRAIL, a novel fusion protein, and effective treatment of experimental autoimmune encephalomyelitis

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Fn14-TRAIL, a soluble protein designed to modulate signals between immune cells, and to act as anti-inflammatory agent. Fn14-TRAIL is combined of the extracellular domain of Fn14 (blocking the pro-inflammatory TWEAK ligand) fused to TRAIL ligand (inducing apoptotic signals through its receptors on activated inflammatory cells). The present study explores the anti-inflammatory efficacy of Fn14-TRAIL in experimental autoimmune encephalomyelitis (EAE). EAE was induced by immunization with myelin oligodendrocyte glycoprotein (MOG) 35-55 peptide in CFA in C57bl mice. Daily treatment with Fn14-TRAIL started on day 10 post immunization. Mice were followed daily for EAE clinical severity. T-cell reactivity towards the encephalitogenic peptide was tested by proliferation and by secretion of inflammatory cytokines, tested by ELISA. Fn14-TRAIL treatment markedly and significantly ameliorated EAE clinical signs by 40-50%. Clinical improvement was observed 6 days after treatment initiated, and lasted up to day 40 from disease induction. Decreased reactivity of encephalitogenic T-cells and production of pro-inflammatory cytokines were observed, with reduction in IFN-γ and IL-17 secretion as well as increase in IL-10. Hence, Fn14-TRAIL treatment induced a shift of the cytokine profile from Th1 and Th17 dominance to Th2. In-vitro assays established the ability of Fn14-TRAIL to induce apoptosis of target cells expressing TRAIL receptors and TWEAK. Fn14-TRAIL is unique fusion protein combining two potentially functional domains. Treatment with Fn14-TRAIL has immunomodulatory influence in EAE.

Differential effect of 'controllable vs. uncontrollable' stress on amygdala activation and gene expression in CA1 and DG

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Recent studies in our laboratory (Kavushanski et al., 2006; Vouimba et al., 2004) suggest that an exposure to Controllable vs. Uncontrollable stress conditions results in different levels of amygdala activation, and that different levels of amygdala activation lead to different patterns of synapse plasticity within the hippocampus formation. It is assumed that such distinct alterations may lead to differential gene transcription and protein expression (Silva et al., 1998; Kandel, 2001; Dudai, 2004). The current project examined alterations in gene expression in different hippocampal GABAergic interneurons (Freund and Buzsaki, 1996), following exposure to Controllable vs. Uncontrollable stress. To induce graded amygdala activation controllability over the situation in the Morris Water Maze varied using 'Control', 'Invisible platform' and 'No platform' groups, as was described before (Kavushanski et al., 2006; Vouimba et al., 2004). Blood CORT levels (assessed by ELIZA) and p-ERK expression levels in the amygdala (assessed by Western Blot) were measured following the behavioral training. Significant differences in blood CORT concentration levels were found between the stress groups and the 'Control' group. Additionally, 'No-platform' group differed significantly from the other two groups' in levels of amygdala p-ERK expression. Five hours following behavioral training, rats were perfused and potential alterations in gene expression were evaluated. We found hippocampal sub-region specific alterations in GABA interneuron related gene expression among the groups.

In-cell recording and stimulation by an array of extracellular microelectrodes

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Here we report on the development of a novel neuro-electronic interface consisting of an array of noninvasive gold-mushroom-shaped microelectrodes (gMμEs) that can provide intracellular recordings and stimulation from many individual neurons, while the electrodes maintain an extracellular position. The development of this interface allows simultaneous, multisite, long-term recordings of action-potentials and subthreshold excitatory and inhibitory synaptic potentials with matching quality and signal-to-noise ratio of conventional intracellular sharp glass microelectrodes or patch electrodes. The extracellularly gMμE-recorded action potentials reach up to 25 mV in amplitude, and synaptic potentials reach up to 3 mV. The key to the multi-electrode "in-cell recording" approach is the outcome of three converging cell biological principals: (a) the activation of phagocytotic-like mechanisms in which the cultured cells are induced to actively engulf gold-mushroom microelectrodes that protrude from a flat substrate, (b) the generation of high seal resistance (~100 MOhm - according to ultrastructural studies) between the cell's membrane and the engulfed gMμE, and (c) the localization of ionic channels (Ohmic conductance, 100-1000 picosiemens according to computer simulations) in the plasma membrane that faces the gMμE. We refer to the novel approach as "in-cell recording and stimulation by extracellular electrodes" to differentiate it from the classical intracellular recording and stimulation methods. This novel technique is expected to revolutionize the analysis of neuronal networks in relations to learning, information storage and can be used to develop novel drugs as well as high fidelity neural prosthetics and brain-machine systems.
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Anxiolytic properties for microRNA in the amygdala

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Background: Dysregulation of the stress response can have severe psychological and physiological consequences. The role of microRNA, in this highly synchronized homeostatic process, was not yet elucidated.

Methods and Results: Here, we inactivated microRNA processing by a lentivirally induced local ablation of the Dicer gene in the central amygdala (CeA) of adult mice. CeA Dicer ablation induced an increase in anxiety-like behavior, while manipulated neurons survive and exhibit normal gross morphology. We further observed differential microRNA expression profile in the amygdala of wild type mice following exposure to acute stress. One of these stress-induced microRNA, miR-34c had anxiolytic properties when lentivirally over-expressesed in the CeA. Furthermore, we show that miR-34c target the stress-linked corticotropin releasing factor receptor type 1 via a single evolutionary conserved seed complementary site on its 3'UTR.

Conclusions: Our results suggest a physiological role for microRNAs in regulating the central stress response, and position them as potential targets for treatment of stress-related disorders.

Network response to repetitive stimuli

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Responses of large-scale neuronal networks to repetitive stimuli are highly variable. We are studying this variability in networks of cortical neurons in-vitro. The 20 networks we studied presented a wide repertoire of response dynamics to repeating input. While several networks did exhibit "simple" dynamics, characterized

by a narrow distribution of response latencies and intensities throughout the range of stimulation frequency tested, the majority of networks presented more "complex" response dynamics. The latter are characterized by widely distributed latencies and intensities, sometimes with clear frequency dependent components. A subset of networks was also inspected under the effect of Bicuculline, an antagonist of GABAA receptors, exposing the impacts of the inhibitory sub-network on the dynamics of response. Initial results indicate that under a blockade of the inhibitory sub-network, the frequency dependent component of response dynamics becomes more pronounced.

Specificity in perceptual learning: is it all overfitting?

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Perceptual learning refers to long-term improvement in perception which is gained by practice. Previous studies showed that performance gains obtained at one retinal location do not generalize (transfer) to another location. A typical example is the texture discrimination task (Karni & Sagi, 1991). This result is taken to indicate learning at a processing stage where the two locations are encoded by separate neuronal networks, probably at the primary visual cortex. Alternatively, specificity could arise if the learning process considers detailed neuronal representations which may differ between locations, possibly due to random variations in anatomy (overfitting). The latter predicts learning generalization when practice is not constrained to a single location since now common features shared by the different locations are learned and overfitting is avoided. Here we used the backward-masked texture-discrimination task: 10 ms target followed by 100 ms mask with varied Stimulus Onset Asynchrony (SOA). In the experiments, one group practiced at a single location while another group at two locations (eccentricity of 5.3°, diagonally opposing from fixation). After 4 daily sessions, both groups improved their SOA threshold (x1.5). Surprisingly, while learning in the 1-location group was location specific, in the 2-location group it transferred to two new locations. The results support a view of perceptual learning as a statistical modeling process with locality explained by overfitting. However, this theory is challenged by (1) the finding of equal rates of learning in both groups, and (2) results showing no further learning in the 2-location group when given additional practice with target positioned at a fixed location, thus allowing for overfitting. The results are consistent with an account according to which each target location is represented by multiple neuronal states, with only one of the redundant cortical representations selected during the learning process.

A perimotor framework reveals functional segmentation in C. elegans locomotion network

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Seventy five motorneurons of eight classes innervate the body musculature that propels *Caenorhabditis elegans* dorsoventral undulations. These motorneurons receive input mostly from five pairs of interneurons and are synaptically interconnected to create a motorneuronal network. To date, only the anterior half of the motorneuronal network of one animal, spanning 42 motorneurons, has been reconstructed from electron micrographs to provide a connectivity data set that is unavailable for any other animal model. We analyzed this dataset by mapping each motorneuron in perimotor space (defined by the location of muscle fibers it innervates). We expressed all the connections made by each motorneuron according to their relative position with respect to other motorneurons of the same class and described a typical connectivity pattern for each class. We found that connections in the dataset are significantly more iterated (occur multiple times) compared to computer-generated shuffled networks. In fact, most (74 – 91%) connections made by each motorneuron iterate within its class.

We described a repeating segment that contains 12 motorneurons and iterated it six times along the body of a nematode to give a connectivity model. We are using this connectivity model of the motorneuronal network to give context to the recorded activity of motorneurons during locomotion. We expressed a calcium sensor in subsets of motorneurons to record their activity and correlate it to locomotion behavior. We found that some classes of motorneurons are dedicated to either forward or backward locomotion, forming two overlapping motorneuronal networks. A neuronal network comprised of direction-specific classes of motorneurons, might be an ancestral form of locomotor control to which dedicated and multifunctional interneurons were subsequently added.

Weighted averaging determines amplitudes of binocular saccades

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Humans constantly shift their gaze between targets of interest in their environment. These gaze shifts are primarily achieved by extremely rapid eye movements called saccades. Here we present a fundamental finding concerning the saccadic system: when the eyes are moved to a new target, each eye's saccadic amplitude results from a weighted average of the target's two angular demands. This replaces the classic scheme where saccadic amplitudes were thought to result from the arithmetic mean of the two

angular demands. By analyzing the left and right eye weights within and between individuals, we show the following: (1) the two eyes' saccadic amplitudes are inherently unequal; consequently, the smooth movement complementing the saccade must also be inherently asymmetric; (2) separate neuronal circuits generate convergent and divergent saccades; (3) there is a strong indication that left and right eye weights arise through interocular competition during development; (4) the ocular weights may serve as individual physiological markers. Finally, we argue that our results provide an explanatory framework for recent neurophysiological findings and derive a testable prediction on the discharge pattern of saccadic burst neurons.

Are 'blindsighted' subjects cheaters? The neural correlates of 'blindsight' performance in normal observers studied with continuous flash suppression

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'Blindsight' refers to the observation that, after a lesion to primary visual cortex, patients can exhibit a residual or recovered ability to localize, detect and discriminate between visual stimuli, despite a lack of subjective perceptual awareness for these stimuli. Here, we examined a similar dissociation of behavioral performance and visual consciousness in a group of healthy subjects (N=18), using the method of continuous flash suppression (CFS) in a functional magnetic resonance imaging (fMRI) experiment. Subjects had to detect images of faces and tools in four quadrants relative to fixation (4-alternative forced choice, 4AFC) and report the subjective stimulus visibility. The contrast of the flashed Mondrian masks was adjusted individually for each subject to achieve comparable numbers of 'visible' and 'invisible' trials. Activity in regions-of-interest in early and high order visual cortex showed a strong effect of subjective visibility, while the activity was not modulated significantly by the objective 4AFC performance. We found similar results when separately analyzing two groups of 'blindsight' and 'non-blindsight' subjects, based on a median split of 4AFC performance in 'invisible' trials. Using multi-voxel pattern analysis (MVPA) of retinotopic activity in early visual cortex, we found that 'invisible' trials with correct 4AFC performance result in significantly higher prediction accuracies than 'invisible' trials with incorrect 4AFC performance. Taken together, our findings point to a tight link between fMRI activity and subjective reports rather than objective performance. These findings pose a challenge for criterion-based models of 'blindsight' performance in normal observers.

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Is corticosterone involved in the attenuating effect of DHEA at the acquisition and extinction stages of cocaine addiction in the self-administration rat model?

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DHEA is a neurosteroid, synthesized in the brain, which modulates different behavioral disorders. In previous studies using rat models of self-administration, we found that DHEA attenuates cocaine-seeking behavior. In view of the fact that publications have shown that rats do not become addicted unless their corticosterone (Cort) level is above the minimum and that DHEA decreases the levels of Cort, we decided to investigate whether the DHEA's attenuating effect is due to the decrease in Cort concentration below the threshold level. We divided the rats into 3 groups: control, DHEA-treated and DHEA+Cort. Cort was administered continuously through s.c. micro-pumps to achieve the Cort basal level. We found that DHEA and DHEA+Cort treated rats did not become addicted, suggesting that DHEA, not the decrease in Cort level, causes the attenuating effect of cocaine-seeking-behavior. In addition to the attenuating effect during the acquisition phase, we observed that DHEA treated rats did not demonstrate cocaine-seeking behavior during extinction. To investigate whether the effect in the extinction phase is modulated by the Cort level, we divided addicted rats in to 2 groups, one treated by DHEA 90 min prior and during the extinction phase, while the other served as a control. The Cort blood levels of both groups were the same. Despite the similar Cort levels, the DHEA-treated group did not express a desire for cocaine, pressing the active lever significantly less than controls. These findings indicate that the Cort level is not involved in DHEA's attenuating effect on the different stages of cocaine addiction in the self-administration rat model, and that DHEA effect is maybe modulated by other mechanisms.

Cephalopods as a ‘simpler model’ for investigating the neurophysiological basis of ‘complex brain’ function

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The work pioneered by JZ Young and MJ Wells confirmed the involvement of the vertical lobe (VL) in the highly sophisticated behaviors of the modern cephalopods. Like the mushroom bodies of insects, the cephalopod (VL) reveals an architecture characterized by millions of small interneurons, which are innervated en passant by the incoming input axons. Interestingly, the large divergence from the input neurons to the amacrine interneurons and the consequent convergence to a fewer large efferent cells, is

reminiscent of simple two layered computational networks like that for pattern discrimination in machine learning. We therefore believe that understanding the neurophysiological properties of the yet simpler than vertebrates' brain, will advance understanding of the biological principles of complex brain functions. Results from our research on VL connectivity, synaptic plasticity and neuromodulation, and implementation of these properties in behavioral learning and memory, demonstrate the fruitfulness of this approach. We will further describe striking differences between the organization of short- and long-term synaptic plasticity in the VLs of Octopus vulgaris and Sepia officinalis. These differences show how adaptive homologous neural networks can be and inspire discussion on possible rationalization.

The Charles E. Smith Family and Prof. J Elkes Laboratory, the Hebrew University and BSF

Exploring the physiological roles of placental stress-related genes in mediating the central stress response of dams and their pups using placental-specific lentiviral-based system

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The corticotropin-releasing-factor (CRF) neuropeptide and its related family members, the urocortins, play an essential role in regulating the hypothalamic-pituitary-adrenal (HPA) axis and the behavioral response to stress. In addition to their expression in the brain, these peptides were also identified in several peripheral tissues, in particular, in the placenta during human pregnancy. It has been suggested that placental CRF influences embryo implantation, as well as mechanisms leading to the onset of labor and fetus delivery. Placental CRF is secreted into the maternal blood and its levels increase exponentially through pregnancy and peak during labor. A recent study in humans has shown a strong correlation between placental CRF levels during gestation and the subsequent development of postpartum depression in the mothers. Moreover, placental CRF also enters the fetal circulation, can reach the fetal brain and affect the embryo development and the subsequent behavior and physiology in adulthood.

We are using a placental-specific lentiviral-based system to functionally knockdown or overexpress our genes of interest specifically in the placenta.

In this ongoing study, we have established a variety of lentiviral constructs that knockdown or over-express the different members of the CRF/urocortin family. We then used these viruses to infect mouse blastocysts to generate placental-specific transgenic embryos. Current studies focus on morphological, physiological and behavioral characterization of the dams and their offspring under basal and stressful conditions.

Establishment of CRF/urocortin mice models, which express modified levels of these peptides restricted to the placenta, provide us with a powerful in-vivo model to explore the contribution of these stress-linked placental peptides to the normal stress response of the offspring and the ability of the dams and her mature offspring to cope with homoeostatic challenge.

How do we react to stress? possibility for differential activation of primal emotional circuits in the brain

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Different emotional tendencies might be of relevance when dealing with affective disorders and their stress responsiveness systems of the central nervous system (Panksepp, 2006; Taylor et al., 2006). Two primal emotional circuits were proposed by their ability to evoke coherent emotional displays among experimental animals in response to aversive stimuli: 'FEAR' system which is designed to help an animal to reduce pain and to avoid the possibility of destruction and 'PANIC' system which mediates subtle feeling of social presence (Panksepp, 1982). Both systems have considerable overlap and probably interactions in certain parts of the brain, especially in "lower" areas such as the Periaquducatal grey, Thalamus, Hypothalamus and Amygdala. We tested for potential differential activation and involvement of the 'FEAR' and 'PANIC' systems in the consequences of exposure to stress (i.e. in juvenility, in adulthood, or both). Following exposure to the stressors, activation levels of c-fos protein were assessed within brain regions devoted to the 'FEAR' and 'PANIC', in male rats. Prior to stress in adulthood, exploration was assessed and immediately following it, avoidance task was introduced for two purposes: I) assessment of the rats' ability to learn under stressful conditions; II) exposure of rats to a stressful experience in adulthood . Rats exposed to 'Juvenile stress' exhibited a significant reduction in exploration prior to exposure to the adult stress. Further, only 'Juvenile stress' rats' failed to escape the shock while learning the two-way shuttle task. Finally, compared to all groups, rats exposed to adult stress following previous exposure to stress in juvenility, exhibited the highest c-fos activation in the PAG together with a decrease in c-fos activation in the BLA. We also found similar pattern of c-fos activation in the thalamus and hypothalamus of all exposed groups, compared to controls.

HDRF - Hope for Depression Research Foundation

The effects of long-term ovariectomy on latent inhibition and anxiety-like behavior in rats

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In schizophrenia (SCZ), women have later onset and better response to antipsychotic drugs (APDs) than men, but this favorable course of the disease is restricted to reproductive years, whereas at around menopause, reports show worsening of symptoms, reduced response to treatment and an additional onset peak in women ('late-onset SCZ'). Little is known about the effects of long-term ovarian hormone withdrawal on SCZ women, although recent studies report that chronic absence of gonadal hormones in rodents induces anxiolytic-like behaviors. Latent inhibition (LI), the capacity to ignore irrelevant stimuli, is a measure of selective attention that is disrupted in acute SCZ patients and in rats and humans treated with amphetamine and can be reversed by typical and atypical APDs. We have recently shown in female rats that ovariectomy (OVX) led to LI disruption, which was reversed by 17β-estradiol or the atypical APD clozapine. The current study aimed to characterize the long-term effects of OVX on LI expression and on anxiety-like behavior and to further test whether administration of the anxiolytic drug midazolam would normalize these effects. Adult female rats underwent OVX or sham procedures and behavior was assessed at short (1 month) and long (3 and 6 months) time intervals post-surgery. OVX induced a long-lasting excessive behavioral switching, manifested in loss of LI and in abnormally rapid reversal learning. In the elevated plus-maze (EPM), a significant reduction in the time spent in open arms and in number of entries to open arms was observed in the long-, but not short-term OVX group, as compared with sham-operated age-matched controls. Systemic administration of the benzodiazepine midazolam normalized LI expression, reversal learning in the wet T maze and EPM activity. In conclusion, prolonged absence of ovarian hormones in rats produces an anxiolytic-like effect that can be reversed by administration of the anxiolytic compound midazolam.

Perceptual re-learning in V1-damaged humans - challenging the dogma of visual perception and plasticity in a blind population

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Damage to the adult primary visual cortex (V1) deprives the visual cortical hierarchy of its main source of visual information, causing a loss of conscious vision over the same part of the visual field in both eyes. Cortical blindness represents an increasingly common and significant cause of permanent disability in older humans, hindering every aspect of an individual's daily life, including reading, navigation, and driving. Though visual rehabilitation remains controversial for this condition, the presence of residual visual processing abilities in cortically blind fields (commonly known as 'blindsight') suggests a possibility of visual recovery though perceptual retraining. Part of our research aims to understand whether and how visual training may improve visual perception in cortical blindness. To date, we have shown that the discrimination of both simple and complex moving stimuli can be retrained back to normal levels in cortically blind fields. Preliminary data suggest that this is associated with a localized decrease in the strength of center-surround antagonism for motion stimuli at retrained locations. While this result and the bulk of the blindsight literature may imply an important role of hMT+in training-induced recovery of motion perception in cortically blind fields, it does not eliminate a putative contribution from other brain areas in re-learning. Indeed, we recently found that training-induced improvements in cortically blind fields generalize to stimulus conditions that do not normally invoke blindsight. fMRI results on the same subjects show these blind field improvements to be associated with changes in activity of multiple areas at both lower and higher levels of the visual cortical hierarchy. Thus, training-induced perceptual re-learning is possible following V1 damage. It occurs over a very broad range of stimulus characteristics and may be mediated by, among other factors, decreased inhibition in stimulated visual circuitries. Finally, our data suggest that the circuitries recruited by visual training in cortically blind fields may not be limited to pathways mediating blindsight. Instead, they appear to involve a more canonical route of visual information transfer that includes spared early as well as higher-level visual areas.

NAP (davunetide) treatment ameliorates central nerve system pathology in diabetes mellitus animal model: behavior, brain imaging and immunohistochemistry

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Background: Streptozotocin (STZ) injected rats is a diabetes animal model commonly used to study diabetes related neuropathologies. This model exhibits learning deficits, brain structural changes such as reduction in grey matter density and white matter lesions, reduced expression of synaptic proteins and a mild increase in apoptotic markers. The neuroprotective drug candidate NAP (NAPV-

SIPQ, generic name, davunetide) has been shown before to protect against various neurotoxins, which are also related to diabetes.

Aim: The current study was set out to evaluate the effect of chronic treatment with NAP on the above-mentioned central nervous system complications.

Results: Our data showed that daily NAP treatment alleviated memory deficits caused by STZ injection, as indicated by the Morris water maze paradigm. Magnetic resonance T2 scans revealed a significant lower density in the prefrontal cortex area of the STZ injected rat group when compared either to the control- or to the STZ+NAP-treated group. Synaptic plasticity and apoptosis were evaluated in the cortex (prefrontal cortex area included) and the hippocampus using immunohistochemical markers. A major reduction in synaptic markers including synaptophysin was detected in the STZ rat group in all areas tested and was completely absent in the STZ+NAP-treated group. A small, though significant increase in the apoptotic marker active caspase 3 detected in the brains of the STZ- compared to the control-group, was significantly diminished following NAP treatment.

Conclusions: These results correlate brain structural and cellular protection to cognitive behavior and indicate a significant protective effect of NAP (davunetide) against one of the most severe complications of diabetes.

Gildor Chair, Adams Super Center, Elton Lab., AMN Foundation, Allon Therapeutics Inc.

Involuntary strategy dependent dual task performance

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Simultaneous performance of two tasks typically show costs relative to single task performance. There is good evidence that strategic processes play an important role in this phenomenon, but very little research has been dedicated in recent decades to this issue. In this study I focus on the influence of task context on dual task performance. Previous experiments in our lab have demonstrated that task context plays an important role in dual task performance. Participants had to name a word (task 1) and to discriminate between colors (task 2). When the input to the two tasks was always presented simultaneously (Experiment 1, fixed 0 SOA) there was no dual task cost. However, when the input to the two tasks were manipulated unpredictably (Experiment 2, SOAs of 0,50,150,800), costs were observed even in the 0 SOA condition even though this condition in and by itself was identical to that of Experiment 1. The costs in the 0 SOA of the mixed SOA study must be strategic, and yet they were observed even after extensive practice in the task. To further examine the nature of this strategic cost, I initially extensively trained subjects for 8 sessions on the 0 SOA condition (as in Experiment 1). Like Experiment 1, participants performed the two tasks in parallel and no dual task costs were observed. Following this training participants were shifted to the mixed SOA conditions (as in Experiment 2) without any change in the task instructions. The performance of the subjects in the 0 SOA condition of the transfer blocks changed dramatically to a serial performance of the two tasks, and resembled the performance of Experiment 2. These findings demonstrate that task context is a powerful factor in dual task performance and may lead participants to exhibit costs even in condition where they can perform the tasks without any costs. I will discuss the importance of these findings for theories of task performance.

Arit Glicksohn, Maya Zuckerman, Noam Schleisner, Tali Arad, Tal Goldman, Anat Hornik

MicroRNAs as endogenous modulators of serotonergic activity

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The link between disregulated serotonergic activity and psychiatric disorders such as anxiety and depression is well established, yet the molecular mechanisms are not fully understood. MicroRNAs (miRs) are a subset of small RNA molecules that regulate gene expression post-transcriptionally and are abundant in the brain. The current study aim to explore the endogenous role of miRs in regulating the activity of serotonin (5HT) expressing neurons, under normal and pathological conditions. To this end, we determined the miRs expression pattern of 5HT neurons, obtained from the raphe nucleus (RN) of 5HT reporter mice (ePET-YFP), using miRs microarray. The unique miRs expression profile of serotonergic neurons obtained from the array was bioinformaticly analyzed to indentify miRs that putatively target important genes in the serotonin circuitry, such as serotonin transporter (SERT) and serotonin auto receptor (Htr1a). Targeting predictions of these genes 3'UTRs were further tested by in-vitro luciferase assays and mutation studies. Furthermore, miRs expression levels at the mouse RN, the main source of 5HT in the brain, were altered following antidepressant administration, and not following acute or chronic stress. In vivo manipulation of a specific miR in the RN is currently performed using site-specific over-expression or knocking down of specific miR using lentiviruses in adult mice. Following these genetic manipulation, mice will be behaviorally examined for changes in anxiety and depression-like behaviors. Reviling novel endogenous regulatory compo-

nents of the serotonin circuitry, may pave the way for better understating abnormalities of 5-HT in psychopathologies.

Inhibition and facilitation of cognitive functions

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Background: Response inhibition refers to the ability to inhibit an action once initiated and has been localized to right inferior frontal gyrus (rIFG) based on functional imaging and brain lesion data. Transcranial magnetic stimulation (TMS) over rIFG is known to impair response inhibition. To date, however, no physiological manipulations have been shown to improve response inhibition performance. In order to explore whether cognitive control can be improved, we stimulated the rIFG with transcranial direct current stimulation (tDCS)

Methods: In a single-blind within-subjects design, we compared subject's performances following stimulation in the Stop Signal Task (SST) which is a valid test to measure response inhibition. There were five stimulation conditions (anodal unilateral, cathodal unilateral, anodal bilateral, cathodal bilateral and a sham).

Results: Remarkably, activation of the rIFG by unilateral anodal stimulation significantly improved response inhibition. The same tDCS protocol did not affect a control task, and, complementary, the SST task was not affected by tDCS in a control site, the right angular gyrus.

Conclusions: Our results confirm the rIFG involvement in responses inhibition and imply that the specific coupling of stimulation condition (anodal/cathodal) and reference electrode (unilateral/bilateral) may support the treatment of cognitive control impairments. I will discuss a broader perspective of tDCS mechanisms of facilitation and inhibition of various cognitive functions in light of the results.

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Preliminary results with an action perception model of sensory motor synchronization

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Sensory motor synchronization (SMS) experiments in the form of tapping along with a metronome are an important case study of the interaction between action and perception. The challenge of modeling SMS is to accurately predict the action (the next tap) from the perceptual information (recent stimuli and responses) available to the brain.

The Perception Action Loop framework (PAL) developed by Tisby and others (Tishby & Polani 2011) is a framework that enables mathematical modeling of the entire action perception model.This framework describes the "action" taken by the subject as a solution to an information theory problem in which the subject is trying to optimize a goal function ("reward") based on predictions of the stimuli.

We administered a simple tapping paradigm-each block of the experiment included a single type of perturbation: either using the typical step change, where the tempo of stimuli alternates between two fixed values(2-tempo conditions),or using random step changes (random condition), where the tempo changes to a new fixed value every random number of beats.

The main experimental findings are that, the asynchrony one beat after the perturbation is non-linearly dependent on the perturbation size and is similar in the 2 tempi and the random conditions.This is surprising because it means that the fact that the next tempo was less predicted on the random condition did not significantly affect the performance implying that information about potential step changes is not utilized.

We will show preliminary results, based on a simplified version of the PAL framework that predicts the main experimental findings better than four other linear models from the literature(Michon 1967; Hary & Moore, 1985; Mates 1994; Schulze et. al. 2005).The ability to explain novel conditions without introducing novel parameters suggests that the PAL model is a promising framework for understanding sensory-motor loops.

Neural correlates of anchoring deficit: different patterns of correlation between auditory ERP and behavior among Dyslexics and controls

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In discrimination tasks subjects' performance quickly improves when one of the stimuli repeats itself across trials. The implicit learning of the repeated reference leads to switching from explicit working memory mechanisms to implicit ones, underlying comparisons with internal references. We previously found that dyslexic individuals do not gain as much as controls from cross trial repetition, i.e. their anchoring abilities are impaired. The anchoring deficit hypothesis of dyslexia proposes that this is a core deficit underlying dyslexics' major difficulties. Anchoring is best exhibited in a two-tone frequency discrimination task with a reference tone (Ahissar et al, 2006). A previous ERP study with control participants (Cohen & Ahissar, ISFN, 2009) found that when participants passively listen to the protocol of 2-tone discrimination with a reference tone, the delay to their automatically produced P2 component

(~200 ms after tone onset) is correlated with their subsequently measured behavior. Poor performers had later P2 than good performers.

We now asked whether Dyslexic subjects exhibit the same pattern of correlation between performance and delay to P2. We administered the same protocol of cognitive tests and ERP sessions to dyslexic university students. As expected, their overall performance was poorer than controls', though it greatly varied across individuals. When passively listening to the same protocol, dyslexic participants did not show the same correlation as controls. The delays to P2 among poor performers were not larger than among good performers. On the other hand, poor dyslexic performers had lower N1-P2 peak-to-peak amplitudes compared with good performers.

This different pattern of correlations between performance and ERP measures suggests that dyslexics use a compensating mechanism to overcome their anchoring deficit. Rather than shortening tones' processing time by detecting their repetition, dyslexics enhance their responses to these tones.

Sensitivity to tone frequency and aptitude for foreign language acquisition

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One of the prominent characteristics of dyslexic individuals is lower aptitude for acquiring foreign languages. Ahissar et al. (2006) proposed that dyslexics' reading difficulties stem from impaired ability to implicitly learn ("anchor to") regularities of sound sequences. We now asked whether variability in auditory anchoring abilities, measured with 2 tone frequency discrimination (FD) tasks, can account for variability in aptitude for foreign language acquisition in the general population. We recruited native-English speakers (N=47; age=22.43±4.37 years), who came to the Hebrew University's Ulpan for an intensive Hebrew course. We used tasks measuring 2-tone FD abilities, spatial reasoning, word reading and phonological awareness abilities in subjects' native language (English – L1). We found that, in line with previous reports (Ahissar et al., 2000), subjects' performance in FD tasks was correlated with L1 proficiency measures of reading accuracy, verbal memory and phonological awareness. These findings indicate relations between sensitivity to frequency of simple sounds and L1 proficiency. In addition, a subgroup of 23 subjects, who had no prior knowledge of Hebrew, was tested with a standard Hebrew exam at the end of an intensive 5 week Hebrew course. We found that their final grade in the Hebrew exam was correlated with 3 types of measures: general cognitive abilities ($r(21)=.57$, $p=.005$), 2-tone frequency discrimination ($r(21)=-.51$, $p=.012$) and single-word reading rates in L1 ($r(21)=.45$, $p=.033$). Specifically, to better assess which aspect of sensitivity to sound is relevant to Hebrew acquisition, we used four FD protocols which varied in anchoring difficulty to repeated frequencies. The correlation with the Hebrew grade was attained only for the difficult anchoring protocol, suggesting that anchoring to sound statistics (frequency regularity in our assessments) is indeed a relevant parameter for predicting aptitude for Hebrew acquisition.

NAP treatment selectively increases life span in ALS mice in correlation with protection against brain damage as observed by MRI

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NAP (NAPVSIPQ, davunetide), a peptide derived from activity-dependent neuroprotective protein (ADNP), is a neuroprotective drug candidate (CNS Drug Rev. 2005; 11:353). SOD1G93A transgenic mice serve as a standard model for ALS. Here, we compared the survival rates of SOD1G93A transgenic mice treated at 11 weeks of age with NAP (either, twice daily with 2 microgram/mouse/one daily injection – n=10, or once daily with 10 micrograms/mouse/day, n=23). The control saline-treated ALS mice included 37 mice. The NAP-treated ALS mice showed an apparent increase in the mean life span of 3.5 days as compared to the saline control. Hanging wire test performed at the age of 16 weeks showed motor improvement in the NAP-treated mice. Magnetic resonance imaging (MRI) evaluation of brain changes showed that NAP treatment reduced T2 value of the trigeminal nucleus, nigrostriatal bundle and regions of the lateral ventricles. When T2 values of motor nuclei were correlated with the life span of the respective mice, no correlations were found, however survival time showed a very strong correlation with the T2 value of the brain lateral ventricles. Thus, motor improvement after NAP treatment can be explained by decreased damage of the trigeminal nucleus and the nigrostriatal bundle and the extended life span by reduced damaged in the lateral ventricles. Statistical analysis of the control group indicated that the group can be divided into two subpopulations, one living up to 130 days (n=16) and one living for longer time periods (n=21), this division resulted in increased homogeneity within the two groups and a ~2-fold reduction in the standard deviation of the respective average life spans. When the results were further analyzed for the NAP-treatment group, a significant prolonged life span was observed with a mean of 142+2.1 days (n=15) vs. 136+1.3 in the controls (n=10). This increase in life span is attributed to the reduced damage to lateral ventricles in the NAP-treated group.

Adams Super Center for Brain Studies; Gildor Chair; IsrALS; Elton Lab.; AMN, Allon Therapeutics.

Changes in brain electrical activity under the influence of anesthetic drugs

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The mechanisms underlying loss of consciousness and amnesia created by various anesthetics drugs are not fully understood. Different anesthetics create different sates of unconsciousness: Midazolam is a GABA agonist with a potent amnesic effect; and Ketamine is an NMDA antagonist which creates a state of dissociative anesthesia.

A state of awareness during anesthesia is a well known complication, and was found to be related to postoperative PTSD. The amygdala, a set of nuclei in the medial-temporal-lobe, is involved in the acquisition and consolidation of emotional memories. We hypothesized that it has a major role in memory formation during anesthesia and awareness episodes. In order to learn more about the mechanisms, we recorded extracellular electrical activity in the amygdala of a Macaque monkey during delivery of aversive odors and under the influence of Midazolam (IM 0.1 mg/kg) or Ketamine(IM 6 mg/kg). We used odors because they have a direct anatomical route into the primate amygdala and underlie intense emotional states. We used a pressure sensor and a nasal mask to monitor the respiratory rate and its modulations that measure implicit valence. Local field potentials (LFP) that reflect synaptic activity were recorded from 11 electrodes located in the amygdala (anatomical location was pre-established by individual MRI scans): 6 sessions under the effect of Midazolam and 5 under Ketamine. We observed a radical change after Ketamine injection: Beta waves disappeared, and alpha waves were diminished. A gamma band (40-60 Hz) appeared, and theta became dominant.

The changes in LFP oscillations under the influence of Midazolam were less prominent: alpha remained, but delta (3-4 Hz) became dominant. On top of these, picks of higher frequency oscillations in the beta and low gamma range appeared during odor release. We suggest that differential activity occurs after Midazolam vs. Ketamine and explains the different states of anesthesia induced with these drugs.

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Interaction between stop-signal inhibition and task conflict in the Stroop task: evidence for two separate control mechanisms

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Performance in the Stroop task reflects effects of two conflicts: the informational conflict (between the information provided by the incongruent word and ink color) and the task conflict (between the relevant color naming task and the irrelevant word reading task). Neuroimaging studies imply that congruent as well as incongruent trials cause a conflict, which Goldfarb and Henik (2007) argued is due to the task conflict. They found that when task control was damaged, there was a Stroop reverse facilitation (reaction times for congruent trials were slower than for neutral trials), which is the behavioral indication for task conflict. Task conflict requires certain control processes that may be different from those involved in the informational conflict. Here we suggest that the stop-signal and Stroop task conflicts can be conceptualized as inhibition of prepotent responses, and share the same control mechanism. In the current study, we combined the stop-signal and the Stroop tasks, and found that when participants' control failed during the stop-signal task (i.e., the response did not stop), a reverse facilitation emerged in the Stroop task (Experiment 1). This reverse Stroop facilitation was restricted to the condition in which no task conflict existed in the neutral condition (Experiment 2). In addition, when participants failed in the stop-signal task the informational conflict was not affected. This suggests that task conflict and stop-signal inhibition share a common mechanism of prepotent response inhibition and that a different control mechanism exists in the Stroop informational conflict.

A Multi-Model Unbiased Algorithm for Reliable Detection of Seizures

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Epilepsy is one of the most common neurological disorders and is characterized by recurrent spontaneous seizures, often monitored using electroencephalography (EEG) or intracranial electrocorticography (iEEG).We propose an unbiased and reliable system for detection of seizures, designed to replace manual inspection of iEEG recordings and to be potentially coupled with automatically triggered treatments.Cortical activity was continuously recorded in three different mouse models of epilepsy (genetic, status epilepticus-induced and albumin-induced), through two epidural electrodes connected to an implanted telemetry transmitter. The acquired signals were filtered, segmented and underwent extraction of features, to be classified by an

artificial neural network (ANN). For classifier training, a dataset of seizure and non-seizure recordings was comprised and represented by 22 extracted features. Forward selection analysis led to the identification of a 5 feature subset, allowing optimal tradeoff between robust ANN classification and reduced computational time. Classification output was post-processed using sliding-window thresholding, applying a persistence rule for positive detection. A graphical user interface was created for simple execution of data analysis and seizure detection. System performance was assessed by analyzing over 2,800 hours of raw iEEG recordings from 15 animals (12 epileptic and 3 controls). Performance evaluation revealed overall sensitivity and positive predictive value above 98% in unedited signals containing noise, artifacts and interictal discharges. The system also successfully detected seizures in an iEEG recording of an epilepsy patient, suggesting the human applicability of the proposed approach.

Mesenchymal stem cells promote the proliferation and maturation of neural stem cells in the subventricular zone

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Mammalian neurogenesis has been demonstrated in the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the dentate gyrus in the hippocampus. However, the low rate and the restricted long term survival of newborn cells limit the restorative ability of this process. Adult bone marrow derived mesenchymal stem cells (MSCs) have been extensively studied due to their wide therapeutic potential. The aim of this study was to determine if MSC transplantation to the normally restrictive SVZ of mice housed in an enriched environment stimulates endogenous neurogenesis. In the presented study thirty C57BL/6 female mice were divided into 3 groups: standard environment injected with phosphate buffered saline (PBS) and enriched environment injected with either PBS or MSCs. Bromodeoxyuridine was injected for 6 days, and 3 weeks later the mice were killed and the brain tissue analyzed immunohistochemically. PBS-treated mice housed in enriched cages showed augmented neurogenesis in the SGZ but not the SVZ. MSC transplantation was associated with increased proliferation and neuronal differentiation of neural progenitors within the SVZ and an increase in the proportion of the newborn neurons out of the total proliferating cells. Histological analysis confirmed the survival of a significant amount of the transplanted cells at least three weeks after transplantation, and the presence of brain-derived neurotrophic factor expression. To our knowledge, this is the first study to show that MSCs might interfere with the tight regulation of the SVZ, independent of the induced brain lesion.

Does neurogenesis blockade affect lithium-induced behavior in the Porsolt forced swim test of antidepressant activity

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Lithium, used to treat mood disorders, was demonstrated to increase dentate gyrus neurogenesis in adult rodents. Chronic lithium reduces mice immobility in the Porsolt forced-swim test (FST). Bessa et al showed that antidepressants retain their therapeutic effect on immobility in the FST even when neurogenesis is blocked by the cytostatic agent methylazoxymethanol (MAM).

The study examines whether lithium-induced decreased immobility in the FST remains under neurogenesis-arrest conditions. Mice were treated as follows: I. regular powder food (RF); II. lithium-supplemented RF according to the O'Brien et al protocol; III. RF and daily MAM subcutaneous injections (14 days); IV. lithium-supplemented RF and daily MAM subcutaneous injections. On the last day mice were injected with BrdU. On day 15 FST was tested and the level of neurogenesis blockade examined.

A preliminary experiment indicates that 1 and 3 mg/kg/day MAM for 14 days do not significantly affect general activity of the mice.

We hypothesized that blockade of neurogenesis will not affect the behavioral impact of lithium. Lithium treatment reduced, as expected, immobility in the FST but MAM pretreatment did not block this effect. This suggests that lithium's effect on neurogenesis is not involved in the mechanism of action of lithium in FST. Neurogenesis level is currently being studied.

The effects of cholesterol and fish oil diets on ApoE4 mice following environmental enrichment

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Background: ApoE4, the most prevalent genetic risk factor for AD, is an important brain lipoprotein. We have previously demonstrated that the neuronal and cognitive

impairments of ApoE4 following environmental stimulation are associated with accumulation of Abeta in the affected neurons. The main objective of our research is to examine the effects of the ApoE4 genotype and cholesterol or fish oil diets on brain Abeta levels in mice subjected to environmental stimulation.

Methods: 4 weeks old ApoE4 and ApoE3 transgenic mice were maintained on cholesterol, fish oil and control diets for 4 months after which they were subjected to object recognition testing and immunohistochemical analysis.

Results: Abeta levels of mice which were maintained in a regular environment on cholesterol and control diets were higher in the ApoE4 mice than in ApoE3 mice. Exposure of these mice to an enriched environment increased the levels of Abeta in the ApoE3 mice and decreased it in the ApoE4 mice. In contrast, neither the ApoE genotype nor environmental stimulation had an effect on brain Abeta of mice which were maintained on fish oil diet. Object recognition experiments revealed improved performance, following exposure to the enriched environment of ApoE3 mice that were maintained on control diet but not of the corresponding ApoE4 mice. Further examination revealed that the cholesterol diet impaired the performance of both mice groups whereas the fish oil diet improved the performance of the ApoE4 mice.

Conclusions: The effects of ApoE4 on Abeta levels and cognition are ameliorated by fish oil diet.

NLGN3 knock-out mice as a model for Autism- behavioral phenotype.

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Autism spectrum disorders (ASD) are severe neurodevelopmental disorders characterized by abnormalities in three functional domains: reciprocal social interactions, communication, and restrictive interests and/or repetitive behaviors. Etiologically, ASD is thought to involve an interaction between genetic and environmental factors. In order to advance our understanding of the genetics and biological mechanisms underlying autistic behavior, several mutant mouse models with an autistic-like phenotype were developed, including Neuroligin-3 (NLGN3) knock out mice. Neuroligin-3 is a member of the postsynaptic cell-adhesion molecules family that has been found in human ASD patients and plays a role in synaptic function. Since examination of the behavioral phenotype in NLGN3 KO mice led to controversial results in different labs, in this project we focus on systematically examining autistic-like aspects of the behavior of this strain. To this end, we set a battery of tasks for the defining features of autism and additional related symptoms. This array includes well validated tests as plus-maze, T-maze, open field exploration, food-find, sociability and social novelty. In addition, we develop novel examinations especially for this aim; Olfaction discrimination test to examine non-verbal communication, "Running-Wheel" test to examine rigidity to change in habit and 4-chamber-exploration test to examine olfactory memory for care-giver.

Preliminary results show subtle tendency towards autistic like behavior in some tests (food find, olfaction discrimination), while other showed no difference (exploration) or even in some cases have contradicted our initial hypothesis (plus-maze). In the current phase of the project settling the controversy is not yet possible. Nonetheless, future validation and implementation of the above mentioned tests should lead us to better understanding of the behavioral phenotype of mouse-model for ASD.

MgSO4 treatment for sarin-induced convulsions causes dissociation between overt convulsions and seizure activity

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Exposure to sarin, a potent cholinesterase inhibitor, induces an array of toxic effects including convulsions. Anticonvulsant drugs are included in most of the antidotal treatments, aimed to impede seizure activity and subsequent brain damage. Since Magnesium sulfate ($MgSO_4$) is the treatment of choice in cases of eclamptic seizures in pregnant women with hypertension, we evaluated its neuroprotective efficacy against sarin-induced convulsions. Rats were exposed to convulsant dose of sarin (96 μg/kg, i.m). One minute later, all animals were treated with TMB-4 (T, 7.5 mg/kg, i.m) and atropine (A, 5 mg/kg, i.m.) (TA mixture). Five minutes subsequent to initiation of convulsions, $MgSO_4$ [i.p. Loading dose (600 mg/kg)+maintenance dose (300 mg/kg/q30min.)] or caramiphen (CRM, 20 mg/kg, i.m) or midazolam (MDZ, 1 mg/kg, i.m) were administered. In all three groups the tonic-clonic convulsions were attenuated or abolished shortly after the anticonvulsant treatment; however, differ from the CRM and MDZ-treated groups, the $MgSO_4$-treated group exhibited sustained seizure activity as monitored by radiotelemetric elecectro-cortico-graphy. Analysis for brain translocator protein (TSPO) and GFAP labeling corroborated these findings and demonstrated marked neuroinflammation in the $MgSO_4$-treated group. Interestingly, histological staining for Cresyl Violet and for MAP-2 labeling, revealed that in the $MgSO_4$-treated group the susceptible pyramidal cells of the hippocampus area were protected in contrast to the piriform cortex and other brain areas which were extensively damaged. These findings exemplify that $MgSO_4$, as a single anticonvulsant drug, offers incomplete protection against sarin-induced convulsions and the presence, or lack of convulsions following OP

exposure are an unreliable indicator of seizure activity and ensuing brain damage. Nevertheless, further research is warranted to explain the differential protection of $MgSO_4$ to the hippocampus over other brain areas.

In vivo IgG deposition in interneurons of experimental antiphospholipid syndrome mice brains correlates with clinical manifestations and serological tests

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Mice immunized with β2-glycoprotein I (β2GPI), develop all the major systemic manifestations of antiphospholipid syndrome (APS) including elevated titers of circulating antiphospholipid antibodies (aPL). We hypothesized that penetration of specific neuronal-binding IgG into the brains of these mice plays a role in causing brain dysfunction. eAPS was induced by immunization of Balb/c mice with β2GPI and control mice by adjuvant alone. aPL levels in the mouse sera were measured by enzyme linked immuno assays and behavior was assessed by the staircase test. Immunofluorescence staining was used to evaluate accumulation of IgG in brain parenchyma in vivo and in vitro binding of eAPS serum IgG. The integrity of the blood brain barrier (BBB) was evaluated by injection of Evans blue (EB). We found a significant correlation between serum aPL levels, total IgG accumulated in the brain homogenates and behavioral hyperactivity. EB levels retained by the brain parenchyma in eAPS mice were higher compared to naïve mice. In vivo immunofluorescence for IgG significantly stained neurons and especially inhibitory interneurons (Basket cells) in the hippocampus of eAPS mice. A similar pattern was found with eAPS IgG by in vitro immunofluorescence staining of normal brain sections. Penetration into the brain and direct interaction of eAPS IgG with inhibitory interneurons in the hippocampus may explain the hyperactive behavior of the mice. A direct role of aPL in causing CNS dysfunction points to aPL as an important therapeutic target in APS.

The gender of face stimuli is represented in multiple regions in the human brain

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Face perception is mediated by a distributed neural system in the human brain, however conventional univariate fMRI data analysis failed to localize differential responses to male as compared with female faces. We used fMRI and multivariate pattern decoding to test whether we can detect gender-specific neural responses in forty hetero- and homosexual men and women, who viewed male and female faces and rated their attractiveness. Face stimuli evoked activation in the inferior occipital gyrus, fusiform gyrus, superior temporal sulcus, amygdala, inferior frontal gyrus, insula, and orbitofrontal cortex. Pattern classification with a sparse logistic regression algorithm revealed successful decoding of gender information with above chance accuracies in the IOG, FG, STS, IFG, INS and OFC. We did not find any differences in decoding the gender of face stimuli (male vs. female) as a function of the subject's gender (men vs. women) or their sexual orientation (hetero- vs. homosexual). Our findings suggest that gender information is widely distributed and is represented in the "core" regions that process invariant facial features, as well as the "extended" regions that process changeable aspects of faces. The lack of gender-specific information in the amygdala is consistent with its role in threat detection and emotional processing.

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Impairment of aversive memories associated with cocaine addiction by inhibition of PKM zeta in the Nucleus Accumbens shell

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Rationale: Drug addiction is accompanied by long-term neuronal adaptations and synaptic plasticity mostly in reward-related brain areas such as the Nucleus Accumbens (NAc). The atypical protein kinase C isoform, PKM zeta, is essential for the maintenance of such long-term adaptations, and therefore might serve as a pharmacological target in the treatment of addiction, by interfering with drug-related associations.

Objectives: We tested the effect of local PKM zeta inhibition in the medial shell of the NAc (msNAc) on relapse to cocaine seeking, using two different Self-Administration (SA) procedures.

Methods: Rats were implanted with intravenous catheters and bilateral guide cannulas in the msNAc, and underwent cocaine SA training followed by conflict or extinction procedures. In the 'conflict model', an Electric Barrier (EB) is incorporated within the SA environment, leading to reduced drug SA with increasing intensities of the electrical current. In the widely used extinction procedure cocaine is replaced by saline, thus leading to reduced SA behavior. Cocaine-seeking and relapse behavior were examined following administration of The Zeta Inhibitor Peptide (ZIP) into the msNAc.

Results: In both procedures, ZIP administration led to higher expression of relapse parameters, compared to controls.

Conclusions: These results imply that inhibition of PKM zeta in the msNAc impairs aversive memories related to drug addiction, thus leading to increased relapse behavior in spite of the last aversive experience in each procedure. That is, inhibition of PKM zeta in the msNAc impairs negative associations, but has no effect on positive

reinforcement. These results indicate that the msNAc plays a key role in the persistence of aversive memories associated with drug addiction.

Conditions for unbiased localization of multiple EEG and MEG sources by linear estimators

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Reconstructing cerebral sources of EEG and MEG is an ill-posed problem, as the number of possible sources exceeds the number of sensors. Linear source localization methods, such as minimum norm, sLORETA and beamformer, apply different optimization criteria to obtain a single solution. The prominent peaks of the reconstructed neural activity image are commonly considered as the estimated activity foci. Unfortunately, these estimated foci are generally biased or spurious.

In this work we introduced a general framework for linear estimators, and employed it to mathematically analyze the conditions for unbiased localization. We validated and demonstrated the theoretical results by simulations.

We found that unbiased localization of a single source can be obtained by some of the adaptive beamformer solutions, as well as by all of the solutions of a standardized form, such as the standardized lead field (SLF), sLORETA and a standardized version of the minimum variance beamformer. Depending on the spatial and temporal distribution of the sources and sensors, unbiased localization of multiple sources can be obtained by some of the adaptive beamformers as well as by the SLF. Such particular cases are when the signal-to-noise ratio (SNR) approaches infinity, when the sources are uncorrelated and have orthogonal lead fields, or when the temporal correlations counteract the lead fields' inner products.

We conclude that unbiased localization can be achieved by some of the linear estimators, however only in particular cases of source distributions.

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Saccadic spike potentials in gamma-band EEG and MEG: characterization, detection and suppression

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Non-invasive recording of high frequency (gamma) neural activity in EEG and MEG is gaining increasing importance as oscillations in this range are believed to have a major role in neural integration. However, we have recently shown that a saccade-related Spike Potential (SP) resulting from extraocular muscle contractions, associated with microsaccades, seriously confounds the analysis of induced Gamma-Band Responses (iGBR) in EEG. It is unclear whether this artifact also affects MEG recordings, which are increasingly used in analysis of the iGBR, and whether the impact of the SP can be effectively diminished using analytical methods. In the first part of the study we recorded simultaneous EEG and eye movements of subjects performing an object recognition task. We analyzed thousands of saccades of five subjects, characterized the SP spatial, temporal and spectral signature, and evaluated methods for detecting SPs at the absence of an eye-tracker and for suppressing their effect. In the second part, we measured MEG and EOG while subjects performed a visual search within complex colored images. We detected SPs in the EOG traces using methods developed in the first phase and used these to assess the presence of SP effects in saccade-related magnetic fields.

We found the SP to appear both in EEG and in MEG as a transient biphasic deflection of about 22 ms starting at the saccade onset, with a frequency spectrum maximal between 20-90 Hz. The SP amplitude gradually changes from the extra-ocular channels towards posterior sites with the steepest gradients around the eyes. While in EEG the SP effect has a posterior-anterior bipolar topography, in MEG it has a double bipolar field topography, n congruence with two dipoles along the muscles of the left and right eyes.

We conclude that the SP affects MEG as well, though to a lesser extent than EEG, and that its effect in EEG can be effectively attenuated by both ICA and CSD.

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The phenotype characterization of laboratory and wild-backcrossed TRPC2 mutant mice

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TRPC2 (transient receptor potential cation channel) is expressed in neurons of the vomeronasal organ (VNO) and is essential for mediating the response to pheromone stimuli. In laboratory mice, genetic ablation of the TRPC2 gene results in changes in sexual and social behaviors. However, the phenotype of the mutant mice may reflect interactions of the targeted gene with background genes. Therefore, we wanted to test the influence of genetic background on phenotype of TRPC2-KO (knockout) mice.

In order to do so we ran social and sexual behavioral tests with male, female, and pups stimulus mice, and measure morphology, physiology, and genetic parameters on TRPC2-KO and control (TRPC2+/-) mice of laboratory or wild genetic backgrounds. The wild background TRPC2-KO mice were produced by backcrossing TRPC2-KO laboratory mice with wild-caught mice for 10 generations. The following significant differences were found: 1. Behavior: In four-choice chamber test (stimulus animals chambers and empty chamber), the laboratory KO mice spent equal time in all chambers while the wild KO mice showed preference to chambers with stimulus animals. In resident-intruder test, the control laboratory mice spent more time in sexual behavior with male and female intruder, and in sniffing behavior with male intruder compared to control wild mice. 2. Morphology: The laboratory background mice were found bigger (in length and weight) compared with wild background mice. 3. Physiology: The corticosterone level was lower in the laboratory background mice than in wild background mice. Within the groups with same background, the levels were almost equal. 4. Genetic: Real-time PCR analysis of VNO, MOE, and Hypothalamus, revealed that genes expression levels are largely depended on the mice genetic background and the genotype.

In conclusion, we can say that the genetic background has major effects on the morphology, physiology, and behavioral phenotype of the TRPC2-mutant mice.

The impact of behavior on RNA at the GluR2 in rats

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Adenosine (A)-to-inosine (I) RNA editing is an epigenetic process that entails site-specific modification in precursor mRNAs, catalyzed by members of the adenosine deaminase acting on RNA (ADAR) enzyme family, and impacts on aspects of neurotransmission and RNA stability. One of the best characterized examples of A-to-I RNA editing is the Q/R site of the GluR-B subunit of the AMPA glutamate receptor, where A is converted to I at nearly 100% by ADAR2. This editing site is highly conserved between species, and rodent studies have shown decreased editing at this site results in a lethal epileptic-like phenotype, arising from altered conformation of the GluR-B that leads to excessive Ca2+ influx. Rapid changes in Ca2+ concentrations often accompany periods of learning (siqiong et al., 2006), and are an integral component of cellular plasticity phenomena such as LTP. Alterations in A-to-I RNA editing impact on LTP (ingo et al., 2006) and editing is decreased in the brain during early developmental stages. We hypothesized that decreases in A-to-I RNA editing also occur transiently in adult animals, following periods of intense learning. We exposed rats to a protocol of contextual fear conditioning, a hippocampus-dependent task, and measured the rate of RNA editing and ADAR expression levels in the hippocampus. The results of this study shed light on the role played by AMPA receptor plasticity in hippocampus-dependent learning.

Impaired temporal selectivity in the auditory midbrain of aged mongolian gerbils

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Studies on auditory perception report that aged humans show a decrease in speech recognition under adverse listening conditions, decreased temporal auditory resolution and increased minimal resolvable angles in sound localization tasks. An age-related degradation of auditory temporal processing has also been reported in experimental animals. To investigate age-related changes in auditory temporal processing, we recorded extra-cellular responses to temporally variable noise pulse trains and human speech in the inferior colliculus of young adult (3 month) and aged (3 years) Mongolian gerbils. When we compared receptive fields for pulse trains, we observed a significant decrease of selectivity in neuronal responses from aged animals. This decrease in selectivity led, on the population level, to an increase in signal correlations and a decreased efficiency in encoding of speech signals. Our results are in line with the reported down regulation of the inhibitory transmitter system in aged animals. The alterations in temporal processing described in this study may be causal to declines in auditory function unrelated to peripheral hearing loss and may therefore not be compensated by traditional hearing aids.

Impact of glioma cell gene expression due to semaphorin expression

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Glioblastoma multiforme belongs to the most common and aggressive subtype of high grade gliomas. Unfortunately, even with optimal therapy, consisting of surgical resection and radiotherapy, a glioblastoma multiforme is essentially incurable. Therefore new agents for the treatment of glioblastomas are needed. Class-3 semaphorins were first identified as glycoproteins that negatively mediate neuronal guidance by binding to neuropilin. The discovery of more widespread expression of class-3 semaphorins in different tumour cell types implicates a role in tumour biology.

The overexpression of class-3 semaphorins in breast cancer cells leads to inhibition of tumour growth. We overexpressed class-3 semaphorins in the human glioma cell line U87MG and monitored a reduction of tumour growth after

intracerebral implantation into mice, too. We were also able to detect changes in adhesion and migration. To determine the variation of tumour cell behaviour we analysed the gene expression profile of class-3 overexpressing cells via microarray analysis. We validated changes in transcription levels with the help of realtime-PCR. Changes in the gene expression levels of cell adhesion molecule 2 and Integrin alpha 7 confirmed the changes in adhesion and migration of class-3 semaphorin expressing glioma cells. Further investigations of changes in gene expression levels of different genes are needed to determine the effect of semaphorins on adhesion and migration and the determine the use of class-3 semaphorins as anti-tumour agent.

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"I'm scared" brain network: individually guided clique clustering approach

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Subjective emotional experience to stimuli is a crucial component of stimulus response in humans. Real-time self-report of subjective emotional experience is required in order to identify brain structures that mediate such a response. However, the use of real-time emotional rating in neuroimaging studies is still scarce due to the possibility that the measurement itself might affect the brain representation of the experience.

We used free viewing of horror movie clips to elicit intense fear in healthy volunteers while recording their subjective conscious feeling of "I'm scared". Behavioral reports confirmed that minimally intrusive cues for real-time emotional rating enabled the detection of authentic variability in the reported individual experience of fear.

Individual data-driven clustering of voxel-based functional cliques in the amygdala was validated by corresponding self-reported periods of high fear during the movie viewing. These cliques thus depicted the conscious subjective experience of "I'm scared". Individually-tailored functions derived from the time course of the amygdala's emotional cliques were used for whole brain GLM analysis. Two distinct networks were revealed with relation to the 'I'm scared' time periods: one showed amygdala co-activation including bi-lateral amygdala, dmPFC, dorsolateral prefrontal, brainstem (i.e. dorsal raphe nucleus & periaqueductal grey matter), hippocampus and cerebellum while the other showed amygdala co-deactivation including the subgenual cortex, ventral striatum and insula. Interestingly, these networks correspond inversely to previously shown spontaneous co-activation and co-deactivation with the amygdala during rest. Our results contribute to the idea that networks of spontaneous and evoked activity might involve similar brain areas in an opposite fashion, thus pointing to an "amygdala-related emotional default network".

Cognitive status, hippocampal volume and cortisol in stroke patients - preliminary results from the TABASCO study

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Background: Patients with ischemic stroke are at risk for developing cognitive impairment. Neuro-anatomical markers such as brain atrophy, infract number and location, hippocampus size and white matter lesions have all been mentioned as possible contributors to post-stroke cognitive impairment. Stress-related biochemical and psychological reactions following stroke could have additional profound implications for subsequent cognitive and neurological deterioration. We present preliminary results regarding the correlations between stress assessments (cortisol levels), MRI volumetric data, and cognition in patients following first ischemic stroke event.

Method: Data from preliminary cohort of 62 patients with first-ever stroke or transient ischemic attack (TIA) from the Tel-Aviv Brain Stroke cohort (TABASCO) was analyzed using FreeSurfer image analysis suite. All patients were cognitively assessed with a computerized neuropsychological battery (NeuroTrax®) and with the Montreal Cognitive Assessment test (MoCA) within 3 days from symptoms onset and after 6 months. Stroke severity was evaluated using the NIH stroke scale (NIHSS). Wakening and bedtime saliva cortisol measurements were preformed 1-7 days from symptoms onset and after 6 months.

Results: Sixty two patients (mean age 65.7+10.6 years) were evaluated. The mean MoCA score was 24.8+3.3. Significant inverse correlation exists between the cognitive and the neurological scores ($r=-0.3$, $p<0.001$; $r=-0.413$, $p<0.001$). Hippocampal volume correlated with the MoCA ($p=0.005$). Patients with higher bedtime cortisol levels had smaller hippocampi ($r=-0.272$, $p=0.05$ for left and right hippocampi).

Conclusions: These data confirm the inverse relationship between stroke severity and cognitive function, but add important information as to the possible neurotoxic effects of cortisol on the hippocampus.

Changes to neurochemical features of interneurons in cerebellar molecular layer may contribute to tremor in Parkinson's disease

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Background: The classical basal ganglia model of Parkinson's disease (PD) accounts for akinesia but not for tremor. Neuroimaging suggests that cerebellar (CBL) function is affected in PD and correlates with manifestation of tremor. Since neuroimaging does not provide cellular detail the present study explores changes to cerebellar cells in PD.
Methods: Cresyl violet general stain and immunohistochemistry of calcium binding proteins (parvalbumin, calbindin, calretinin), neuronal nitric oxide synthase (nNOS), tyrosine kinase receptor (c-Kit), and neurofilament 200 (NF200) in postmortem CBL of PD cases (n=8) and age-matched controls (n=10).
Results: In PD, no changes were detected in CBL by Cresyl violet stain. Immunostaining did not reveal changes in packing density of Purkinje (PC), Lugaro or granule cells. However, in PD there was decrease of 45% in packing density of parvalbumin immunoreactive (ir) interneurons in the upper molecular layer, and decrease of packing density of nNOS-ir interneurons by 49% in upper molecular layer and 63% in deep molecular layer. At the contact of interneurons with Purkinje cells (pinceau), parvalbumin-ir density decreased by 36% and cKit-ir by 70%. Density of NF200 profiles decreased by 45% in the upper molecular layer.
Conclusions: The present data, combined with neuroimaging evidence of cerebellar hyperactivity in PD suggests that abnormal interneuron regulation of PC activity may result in excess PC inhibition of deep cerebellar nuclei resulting in abnormal cerebellar output to thalamic nuclei and to striatum and hence result in abnormal coordination of basal ganglia and cerebellar oscillating networks contributing to tremor.

Overlooked early CT signs of cortical venous thrombosis with lethal outcome

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Introduction: Thrombosis of the cerebral veins and sinuses (TCVS) is an emergency condition resulting from venous congestion that may lead to regional ischemia and cortical infarction. Distinction between two mechanisms of this disorder is important: cortical vein thrombosis (CVT) which detection appears appears to be much more difficult on imaging studies and thrombosis of the major dural sinuses (DST).
Purpose: The aim of this report is to emphasize the consequences of overlooked initial CT signs of CVT.
Methods: Brain CT was ordered in an afebrile patient with neck pain and occipital headache. Since no abnormalities were noted on non-contrast CT study, the patient was discharged. However, right hemiparesis developed the next day with persistent headache and the patient was sent back to Neurology Clinic where he developed myoclonic seizure compatible with focal motor status epilepticus.
Results: Imaging study, performed two days later, revealed huge hemorrhagic venous infarcts in the left cerebral hemisphere associated with the typical signs of dural sinus thrombosis. The presence of subtle curvilinear hyperdensity was detected within the left parietal cortical-subcortical border during the reevaluation of initial brain CT, most compatible with developing venous infarct, associated with the ill-defined hyperattenuation of superior sagittal sinus and the presence of two hyperdense foci, most compatible with CVT. No improvement was noted after administration of anticoagulant treatment and the lethal outcome appeared 11 days after initial CT scanning.
Conclusion: Detection of early CT signs of TCVS, especially CVT, is usually rather difficult, but extremely important, since the delay of adequate treatment may have catastrophic consequences. Education of both radiology and neurology residents in detecting both direct and indirect CT signs of TCVS is extremely needed in order to decrease the rate of fatal outcome.

The implementation and use of a virtual acoustic space algorithm to study the responses of auditory neurons to moving stimuli

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Moving auditory stimuli are an important part of the sensory environment, particularly for a nocturnal predator such as the barn owl. Yet most studies of auditory spatial processing use static stimuli. This is mainly due to the difficulties of producing well controlled acoustic motion. Here we aim to overcome this difficulty by implementing an accurate off-line algorithm to simulate acoustic motion at any desired direction and velocity. We used a set of head related transfer functions (HRTFs) measured from the barn owl to present, through earphones, static as well as moving acoustic stimuli that are spatially defined in virtual acoustic space (VAS). Motion in VAS was obtained using an algorithm developed by Jacobson, Poganiatz and Nelken (Journal of neuroscience Methods, 2001) in which the measured HRTFs are linearly interpolated in space and time. Using this setup we characterized the responses of auditory space specific neurons from the barn owl's optic tectum. The VAS responses were compared with responses of the same neurons to stimuli in binaural space (ITD/ILD)

and to stimuli in visual space. First, we report that the acoustic receptive fields (ARFs) obtained with static stimuli are correlated with those obtained in binaural and visual space, similar to the correlations reported in free field experiments. We also show a general correspondence between the positions of the motion and static ARFs. These results validate our technique. Second, we compared between ARFs obtained by left to right motion with those obtained by right to left motion. Interestingly, the horizontal position of the ARF depended on the direction of motion; the receptive field shifted towards the origin of the movement. It has been suggested in the literature that such directional shifts towards moving stimuli may underlie the behavioral ability to predict the location of a moving stimulus. To our knowledge, this work is the first to show this effect with fully cued auditory motion.
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Getting proof of concept in Parkinson's disease assessing cognitive functions as a new measurable translational clinical relevant end-point

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Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopamine neurons in the substantia nigra, culminating in severe motor symptoms, and a variety of non-motor symptoms associated with PD, like cognitive impairments. However, there is a paucity of animal studies focused on cognitive impairments in PD. Among the various toxic models of PD, the MPTP (1-methyl-4-phenyl-1,2,3,6- tetrahydropyridine) model has become the most commonly used. The mouse MPTP model with marked depletion of dopamine (DA) in striatum is defined with behavioural impairments, that are usually only of motor origin. In the present study we were able to show cognitive impairments, as well as motor impairments following MPTP lesion in mice. Mice were injected with MPTP (IP, 40 mg/kg MPTP), daily for 5 days. Rota Rod, (RR); Passive avoidance (PA); and social recognition (SR) test were all performed on day 11. Rota od: A statistically significant reduction in time spent on the RR, a motor test, was observed in MPTP-treated compared to control group. This observation was also supported by a similarly statistically significant reduction in distance travelled on the RR. Social recognition test: The SR test measures memory on the basis of olfactory cues. MPTP lesion animals showed a social memory effect by spending significantly more time investigating the same juvenile animal following subsequent exposure, compared to the control. Passive avoidance test. Single-trial (step-through) PA test measures short and long-term memory process for aversive stimuli. Retention latency to enter the dark compartment in MPTP mice was significantly lower than the control animals . Our study reveals cognitive deficits as a result of MPTP lesion, along with the usual motor deficits. Thus, we have tailored a battery of tests that predict whether tested item can reverse or protect against motor as well as cognitive deficits in a mouse model of PD.

Measuring neuroinflammation by TSPO autoradiography in Alzheimer's disease brains postmortem

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Alzheimer's disease (AD) pathology appears earlier and is more pronounced in temporal cortex and hippocampus than in the striatum. Neuroinflammation is known to vary across brain regions. Translocator protein 18 kDa (TSPO) is an established biomarker of glial activation and therefore suitable for measuring neuroinflammation. The goal of the present study was to test the regional distribution of neuroinflammation in AD.

Frozen samples of hippocampus and striatum from 22 AD brains (10 male and 12 female) and 16 age- and sex-matched controls were obtained from the Netherlands Brain Bank. Cryostat sections were used for autoradiography with [3 H] PK11195, a selective TSPO antagonist. Non-specific binding was assessed on consecutive sections in the presence of excess unlabeled PK11195. Washed and dried sections were apposed to film with calibrated tritium micro scales. Quantitative image analysis was performed using ImageJ program. Two way ANOVA of TSPO density displayed a highly significant increase in AD patients compared to controls (154%, $p< 0.001$, "diagnosis" main effect). TSPO density also displayed significant regional variation, with higher protein density in the hippocampus (especially in the dentate gyrus) compared to the striatum ($p<0.0001$, "region" main effect). In all of the tested regions, the increases were also linearly associated with the progression of the pathology (measured as Braak stages; all p values<0.01, linear regression). In most regions, the increased TSPO density was associated with the presence of ApoE4 allele ($p<0.05$, Student's t-test). There were no sex differences, and no "region x diagnosis" interactions.

These results suggest TSPO is a reliable biomarker for AD progression, and therefore may be used for in-vivo diagnosis by PET imaging.
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The role of AKT phosphorylation in acquisition and extinction of conditioned fear

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Impairments in extinction of fear memory are implicated in different anxiety disorders. While the acquisition of fear

memory is mainly dependent on the amygdala, the medial prefrontal cortex (mPFC) plays a critical role in the consolidation of extinction memories. AKT (also known as PKB), is one of the kinases that form the PI3 kinase cascade which has been found vital in cell proliferation and prevention of apoptosis. In the brain, activation of AKT via phosphorylation has been implicated in formation of long-term memory and synaptic plasticity. This study aimed to investigate in the adult rat, the role of the AKT in the mPFC and the amygdala during acquisition and extinction of conditioned fear memory. The AKT inhibitor LY294004 was injected into either the basolateral amygdala (BLA) or the mPFC at different time points. Microinjection of the AKT phosphorylation inhibitor into the mPFC 15 minutes after fear conditioning or before retrieval of extinction memory did not affect the behavioral output. However, the microinjection of the AKT inhibitor into the mPFC immediately after the first extinction session resulted in impairment in consolidation of long-term extinction memory, suggesting a role of AKT phosphorylation in the mPFC in extinction consolidation, but not in acquisition or consolidation of conditioned fear. In contrast, the LY294004 microinjection into the BLA after fear conditioning resulted in increased freezing levels but not after the first extinction day, suggesting that AKT phosphorylation in the amygdala is required for consolidation of fear memory but not for the consolidation of extinction of conditioned fear. These results point to differential involvement of AKT during acquisition and extinction of fear conditioning in the mPFC-amygdala circuit and potentially contribute to understanding and treatment of anxiety disorders.

Correlation-based identification of retinal ganglion cells' spike train models

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The correlation structure of neural activity is believed to play a major role in the encoding of information in neural populations. In previous work, we showed that the correlation distortion induced by the Linear-Nonlinear-Poisson (LNP) model family can be used for controlling the correlation structure of synthetic spike trains, for performing the multivariate causality analysis of populations of neurons, and potentially for 'blindly' identifying the parameters of the LNP model. Recently, we extended this feed-forward-only framework to a more powerful multivariate self- and mutually-exciting Hawkes model class that can fit spike trains with more complex multi-correlation structure. Here, we apply this novel approach to retinal ganglion cells' spiking activity and perform 'blind' correlation-based identification of the model's parameters.

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Understanding the alien, deciphering the behavior of the octopus

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Living in a sensory world very different from our own, octopuses provide a challenge and inspiration for generations of researchers. Not only are their bodies boneless and flexible but they come with a unique advanced visual system for an invertebrate, analogous to the vertebrate model. For years research on octopuses has focused on simple learning tests, relying on an innate attack response animals were trained to either attack or not attack a seemingly endless variety of shapes and patterns, combined with surgical lesion experiments researchers were able to identify some of the most important neural pathways in the octopus nervous system. However one major question remains unanswered – to what extent and how does this soft bodied animal control its' body and specifically its arms. So how can we try to understand and decipher the behaviors and abilities of the octopus?

To do so we forced our animals to perform tasks challenging their standard repertoire of arm movements. Using a variety of mazes and similar experimental devices we were able to show that octopuses posses more control of their bodies then previously thought. They can complete tasks requiring them to have knowledge of the position of their arms and they can reshape some motor primitives to meet physical constrains to their arms.

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Corticotropin-releasing factor receptor type 2 activation in the ventromedial hypothalamus is required for energy balance regulation following metabolic challenges

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Corticotropin-releasing factor (CRF) and its related Urocortins are key regulators of energy balance. Stressful stimuli, food deprivation and leptin administration remarkably alter hypothalamic CRFR2 expression, suggesting an important role for this receptor in regulating energy homeostasis during challenge. To examine the role of CRFR2, expressed by the ventromedial hypothalamus (VMH), in modulating energy balance, a lentiviral-based system for site-specific knockdown (KD) of CRFR2 was established and VMH-specific CRFR2 KD mice were

generated. Mice were tested both on basal conditions and following exposure to physiological perturbations to homeostasis. Reduced expression of VMH-CRFR2 did not affect basal metabolic parameters suggesting that under basal state VMH-CRFR2 does not play a crucial role in maintaining energy homeostasis. However, exposure to stressors reveals its regulatory physiological significance. In the 24 h period following food deprivation challenge, in order to regain energy homeostasis, control mice increased their food intake and reduced their physical activity. In contrast, CRFR2 KD mice increased their food intake only up to 75% of the control mice, did not reduce their activity level, and showed reduced respiratory exchange ratio (RER) during the light phase compared to control group. This maladaptive recovery suggests that hypothalamic CRFR2 signaling is essential for re-establishing homeostasis following metabolic challenge. Glucose tolerance test profile of CRFR2-KD mice was similar to that of the control mice while insulin tolerance test profile revealed reduced insulin sensitivity in these mice compared to control. The reduced insulin sensitivity may be a consequence of reduced suppression of the counterregulatory responses. Our results support an important role for VMH-CRFR2 neurons in the control of food intake and energy expenditure in response to homeostatic challenge and suggest a role for these neurons in glucose sensing

Neuroprotective activity of novel multimodal iron chelating drug M30 in an Alzheimer's disease transgenic mouse model

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#,$ share equal recognition
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The concept of iron chelators for clinical use in neurological disorders lead our group to develop non-toxic, lipophilic, brain permeable multifunctional compounds with iron chelation properties for neurodegenerative diseases. The aim of the present study was to evaluate the therapeutic effect of novel multimodal iron chelating drug, M30 on the neuropathology and deficits of spatial learning and memory in amyloid precursor protein (APP) and presenilin 1 (PS1) double-transgenic mice, a well established Alzheimer's disease (AD) mouse model. Here, we report that treatment of APP/PS1 transgenic mice with M30 (1 and 5 mg/kg PO; three times weekly) for 5 months, significantly attenuated cognitive impairments in a variety of tasks of spatial learning and memory retention, working memory, learning abilities, anxiety levels, and memory for novel food and nesting behavior. These were accompanied by a marked decrease in several AD-like phenotypes, including cerebral levels of amyloidogenic Aβ peptide (APP), number of Aβ plaques, and tau hyperphosphorylation levels. The activities of cyclin-dependent kinase (cdk) 5 and glycogen synthase kinase (GSK)-3β, major kinases involved in both APP and tau phosphorylation, were markedly downregulated by M30 treatment. These findings suggest that M30 is a potential therapeutic agent for the prevention and treatment of AD.

Metallocorroles as cytoprotective agents against oxidative and nitrative stress in cellular models of neurodegeneration

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Water-soluble iron, and manganese(III) complexes of corroles and porphyrins were examined with regard to their neuroprotective/neurorescue activities by using various neuronal cytotoxic models of oxidative and nitrative stress. The present study demonstrates that the metallocorroles significantly protect human neuroblastoma SH-SY5Y and mouse motor neuron-neuroblastoma fusion NSC-34 cell lines against neurotoxicity induced by either the peroxynitrite donor 3-morpholinosydnonimine or the parkinsonism-related neurotoxin 6-hydroxydopamine. The neuronal survival effect is further reflected by the prevention of 3-morpholinosydnonimine-induced protein nitration, inhibition of caspase 3 activation, as well as attenuation of 6-hydroxydopamine-mediated decrease in growth associated protein-43 levels. The iron(III) corrole, but not manganese (III) corrole, also significantly promotes neuronal survival of hydrogen peroxide (H(2)O(2))-impaired SH-SY5Y and NSC-34 cells. A substantial superiority of the metallocorroles relative to the corresponding porphyrin complexes is revealed in all examined aspects. These results highlight the large potential of corrole complexes as novel agents for therapeutic approaches in degenerative disorders of the central and peripheral nervous systems, where oxidative and nitrative stresses are involved

The human olfactory epithelium is functionally tuned to odor percept

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The principal axis of human olfactory perception, odorant pleasantness, has been linked to the principal physicochemical axis of odorant structure (Khan et al., 2007). We set out to ask whether electro-olfactograms (EOlfG) recorded directly from the human olfactory epithelium are

tuned to this axis (odorant pleasantness), or in turn better reflect the chemistry the stimulating odorant. We chose eighteen odorants that mutually span pleasantness as well as the principal physico-chemical axis. Due to experimental time constraints within subjects, EOlfGs were recorded in three sets of six odorants each. In each set, the odorants were diluted with heated (36°C) humidified (80%) air inside the olfactometer to obtain equated perceived intensities. An overall flow of $5.5_{l/min}$ and maximum partial odorant flow of $3_{l/min}$ were kept. ISI=45 s, Stim. Dur.=0.5 s, 4-5 events per condition, Sampling rate=1 kHz. Subjects held their breath 1.5 s before stimulus onset and 3 s thereafter. Following each trial subjects rated pleasantness and intensity. We found that EOlfGs distances better correlated with distances in the perceived pleasantness ($r=0.405$, $p<E-9$) than with the stimuli chemical euclidean distance ($r=0.141$, $p=.034$). Our findings imply that the OE is functionally tuned to higher level of processing than to naiive chemical variation.

From neuron to network: the role of doc2b in late-burst activity

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The plasticity of the brain plays a key role in shaping our behavior, learning and memory. It is well known that plasticity is associated with alteration in synaptic strength and efficacy. Some of these effects correlate with changes in the levels of synaptic proteins (Jaaskelainen et al. 2007; Martin et al. 2000). However, the implications of genetic alteration in synaptic proteins on the network activity of neurons are not known. We examine the effect of DOC2B, a synaptic neuronal Ca2+ sensor that is known for its ability to enhance synaptic transmission, on neuronal network activity (Friedrich et al. 2008). For that purpose we use MicroElectrode Array (MEA) technology to simultaneously record action potentials from multiple neurons in ex vivo neuronal network. Proteins overexpression is achieved by viral infection and fluorescent-microscopy combined with long-term time-lapse imaging is employed to study the kinetics of the overexpression. Overexpression of DOC2B leads to a distinctive increase in the durations of neuronal network spikes bursting activities and noticeable change in the spiking order within the bursts. Furthermore, it changes the distribution of the spikes in the burst, leading to an increased spiking activity mainly after the burst peaks. Moreover, electrical stimulation of DOC2B-enhanced neuronal culture unveils its role in facilitating synaptic replenishment. This unique combination of genetic manipulation on the neuronal network level complements and extends our understandings of the role of DOC2B in synaptic transmission. It has been previously suggested that synchronized bursting activities may be templates for modifications of network-wide neuronal plasticity (Baruchi and Ben-Jacob 2007). Together, we suggest a novel role for DOC2B – tuning of synaptic plasticity to allow imprint of activity patterns.

Beginning to elucidate on the role of pheromonal detection in social reward: NAc DA and 5-HT levels in TRPC2 heterozygouts exposed to females

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Innate social behaviors in mammals, including sexual and aggressive behaviors, are rewarding and largely mediated by pheromone communication. TRPC2 (transient receptor potential channel) mutant mice, are unable to detect pheromonal cues via the vomeronasal organ, and thus, both males and females knockouts (KO) express unique behavioral profile towards conspecifics. Specifically, males show increased sexual behavior towards other males and very low inter-male aggression; females show increased sexual behavior towards both males and females. Using microdialysis technique we aim to characterize changes in brain monoamine levels of both TRPC2 KO and control mice, while exposed to either male/female social stimuli. Focusing on the nucleus accumbens (NAc) as part of the reward brain system, we propose to elucidate the role of pheromonal detection in the rewarding properties of both sexual and aggressive behaviors. Based on a previous work (Chengjie et al., 2008), we developed a protocol for detecting DA, 5-HT and 5-HIAA in small CSF volumes of 12 microlitter and less, using UPLC- MS/MS. Here we will present preliminary results of the monoamine changes in the CSF within the NAc of TRPC2 heterozygouts (control) male mice while exposed to females and manifest sexual behaviors. As expected, we observed a rise in DA levels while the female is presented and then a decline. Also 5-HT levels increase moderately throughout the exposure. These results support the efficiency of our new protocol for UPLC-MS/MS analysis of small CSF volumes, and promote our ongoing research. On further steps, we will continue characterizing the rewarding aspects (neurobiochemically and behaviorally) of both TRPC2 mutant and control mice exposed to either pheromonal or social stimuli of males and females.

Neuropathological symptoms without cognitive impairments following sub-chronic low-dose VX exposure in rats

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VX, a persistent nerve agent, may remain absorbed to environmental elements even after intensive decontamina-

tion. Therefore, it was of interest to study the effect of chronic exposure of minute doses of VX on rat brain biomarkers. The present study was aimed toward examining possible correlation of histopathology with putative cognitive deficits following chronic VX exposure in rats. Rats were exposed using osmotic mini-pumps either at asymptomatic dose (13.5 μg/kg/day) or symptomatic dose (18 μg/kg/day) of VX for a period of one month. Cresyl Violet staining was uncapable of detecting any cellular damage, although space enlargement between the nuclei at the hippocampus CA2 region was noted. These findings were further supported by using confocal analysis for NeuN labeling. MAP2 immunolabeling, presenting the neuron-specific cytoskeletal proteins in the brain, demonstrated a decreased immunoreactivity in dendrites processes and increased immunreactivity in cell bodies of CA2 pyramidal cells, thalamus and pyriform cortex neurons. GFAP labeling of astrocytes revealed activated astrocytes in all brain regions. We have further examined the possible implications of these histopathological abnormalities on cognitive function. We demonstrate no difference in both Passive Avoidance (PA) and Morris Water Maze (MWM) tests, between control, sham operated and VX-treated rats (13.5 μg/kg/day). These findings indicate no deficits in reference and working memory despite the observed neuropathology. In contrast, VX-treated rats at 18 μg/kg/day exhibited motor/emotional deficits. In summary, our data suggest that further studies are required for elucidating the role of cellular and cytoskeletal proteins involved in mediating VX neurotoxicity especially at low doses. Such studies will help in understanding the physiological effects of brain pathology following chronic VX exposure.

Novel functions of nerve growth factor on brain microcapillary endothelial cells

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Nerve growth factor (NGF) promotes survival, differentiation and neuroprotection of sympathetic and sensory neurons in the periphery and frontal cortical neurons in the brain. Recent studies have indicated direct effects of NGF on blood vessels however the mechanism of action of NGF on blood vessel endothelium was poorly investigated and is the aim of the present study.

To understand NGF signaling in endothelial cells (ECs) we compared NGF-induced phosphorylation of Erk1/2, Akt and PLCγ signaling pathways in brain microcapillary ECs and sympathetic PC12 neurons. NGF-induced phosphorylation of these pathways in ECs had transient effect compared with prolonged effect in neurons. These results propose that NGF-induced signaling in ECs supports pro-angiogenic activity, as opposed to differentiation in neurons. Furthermore, using an oxygen-glucose deprivation, ischemia-like model, it was shown that NGF-induced protection of ECs was dose-dependent and that this effect was inhibited by K252a, a NGF-TrkA receptor antagonist. Attenuation of ischemia-induced Erk1/2 phosphorylation was correlated with NGF-induced protection. These results emphasize the importance of NGF in the survival of brain microcapillary ECs in response to ischemic injury. In another set of experiments, the secretion patterns of NGF from brain and heart vascular beds were measured. In normoxic conditions NGF was released by brain and by heart ECs. In ischemic conditions the NGF secretion from ECs derived from both organs was blocked. This response of brain microcapillary ECs implies that under ischemic insult the major source of NGF for endogenous neuroprotection are neurons and glia but not ECs.

In conclusion, NGF maybe considered as a neurotrophin with dual protective activities on both cardiovascular and nervous systems. These activities are relevant for the understanding of the endogenous protective mechanisms of the brain during ischemic insults.

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Light stimulation of synaptic input to Inferior Olive cells in-vitro

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The modular organization of the cerebellar system is well documented. The olivo-cerebellar loop, the fundamental component of the cerebellar module, is comprised of inhibitory connections between the Purkinje cells (PCs) and the cerebellar nuclei (CN); inhibitory connections between the CN and the inferior olive (IO) and excitatory input from the olivary neurons onto PCs. In this study, optogenetic approach was used to investigate the functional role of the inhibitory connections between the CN and the IO using specific stimulation of olivary inputs. Immunocytochemistry of the Thy1-COP4 transgenic mice revealed expression of the light-gated cation channel, channel rhodopsin2 (ChR2), in GABAergic cells of the CN. IO neurons were devoid of ChR2, although great amount of labeled fibers were seen in the nucleus. Indeed, light stimulation of CN cells during whole cell patch recordings in acute slices, resulted in a depolarizing event which was modulated according to the duration and intensity of the light. Whole cell patch recordings from IO cells, combined with light stimulations, also resulted in significant responses. As oppose to the responses in CN neurons, the responses of olivary neurons was clearly synaptic responses, namely the light activated presynaptic axons. Both excitatory and inhibitory responses were recorded.

The inhibitory response, that had a reversal potential of about -60 mV, markedly affected the subthreshold oscillations; Persistent subthreshold oscillations were readily and reversibly annihilated. On other occasions quiescent neurons had started oscillating upon light activation. EPSPs could also be evoked by light stimulation. These potentials, although failed to affect the subthreshold oscillations could easily derive the cells to fire. In conclusion, these findings indicate that GABAergic CN cells can modulate the subthreshold oscillations in IO cells, enabling us to study the role of the CN input on the functional organization of IO network.

Forward masking recovers the temporal mismatch in internal response

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Collinear facilitation is an enhancement in the visibility of a target by laterally placed collinear flankers (COL). Non-collinear configuration (parallel, side-by-side, SBS) produces less facilitation. Surprisingly, presentation of COL and SBS configurations simultaneously (CROSS) abolishes the facilitation rather than increases it - a phenomenon that has not been well understood. In our previous study we explored the effect of cancelled facilitation using ERP recording and found that the latency of SBS is delayed by about 10 ms compared to COL, suggesting that the facilitatory process is selectively cancelled due to a backward masking effect by the delayed signal from the SBS. Here we report results from study (behaviour and ERP) in which we presented the flankers before (20, 40, 60 ms) the other configurations (forward masking). We found that the presentation of the SBS flankers 20 ms before the CROSS, recovered the facilitation. Moreover, forward presentation of 20 ms, (but not 40 or 60) enhanced the response speed (shorter latency) by about 10 ms. The results support the idea that propagation of COL signal is faster than of the SBS signal, consistent with our earlier findings that training on collinear facilitation shortens the latency. They also confirm our suggestion that SBS produce a temporal mismatch that cancels the facilitation in the CROSS condition. The results also show that forward presentation overcomes the temporal mismatch, hence recovering the facilitation. Thus, spatial configurations of simultaneous stimuli might produce a decoralation of the internal response and alter our perception.

Neuroprotective potential of DJ-1 related peptides in models of Parkinson's disease

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Background: Parkinson's disease (PD) is one of the most common neurodegenerative diseases caused by both environmental and inherited factors. DJ-1 mutations were identified as a cause of familial PD. The function of DJ-1 is still unknown; however, it is associated with response to oxidative stress. Using in vitro cellular platform expressing various DJ-1 levels and transgenic DJ-1 mice we found that DJ-1 has a key role in the resistance to oxidative and neurotoxic insults.

Aim: We have developed DJ-1 related peptides in order to asses whether they could exert neuroprotection.

Methods and Results: Based on our knowledge on DJ-1 structure and function and a thorough bioinformatics survey we have designed DJ-1 related peptides and tested their ability to rescue from oxidative and neurotoxic insults. We found that short peptides based on DJ-1 significantly augmented cellular resistance of various cell lines and primary CNS cultures to various toxins. Furthermore, by using in vivo models of Parkinson's disease, MTPT and 6-hydroxydopamine hemiparkinsonian mice models, we found that the peptides had significant neuroprotective properties. Peptide treated mice demonstrated significant abrogation of the disease in both behavioral and biochemical tests.

Conclusions: These studies indicate that DJ-1 has a neuroprotective potential, and may be used as a platform for developing therapies. DJ-1 related peptides demonstrated protective effects in in vitro and in vivo models. These promising peptides might serve as the basis for development of a novel neuroprotective therapy for PD.

Localization of molecular correlates of memory consolidation to buccal ganglia mechanosensory neurons after learning that food is inedible in Aplysia

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Molecular processes underlying learning and memory occur in specific cells forming neural circuits. A fundamental challenge is to localize molecular processes to specific neurons, to understand how changed properties of neurons give rise to changes in behavior. *Aplysia* feeding is an excellent system to examine cellular processes underlying learning and memory. Our laboratory has characterized many neurons that organizes *Aplysia* feeding behavior, and has also developed a learning paradigm affecting feeding - **Learning That Food Is Inedible** (LFI).

Feeding is controlled by circuitry within the cerebral and buccal ganglia. The cerebral ganglia contain neurons responding to food and command-like neurons initiating feeding. The buccal ganglia contain a central pattern generator (CPG) organizing feeding, motor neurons effecting feeding, and neurons that bias the system to choose a specific feeding behavior. They also contain sensory neurons similar to those of mechano-afferents that are a

locus of learning and memory affecting *Aplysia* withdrawal reflexes. These respond to food within the mouth.

To localize memory formation to specific cells, we monitored key molecular changes necessary for long term memory formation in *Aplysia* and in other organisms. Via quantitative real time PCR, we measured the mRNA expression of C/EBP and Sensorin-A in after LFI training. C/EBP expression was increased only in the buccal ganglia. The increase was correlated with level of expression of long term memory. Both C/EBP and Sensorin-A mRNAs were expressed in two populations of buccal ganglia mechano-sensory cells innervating the interior of the mouth and the lips, with no increased expression in the rest of the ganglia. These sensory cells were found to be monosynaptically and polysynaptically connected with a CPG neuron having a key role in initiating feeding responses.

Our findings highlight the buccal ganglia sensory cells as a locus of long term memory formation that food is inedible.

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The nasopalatine ducts: A forgotten pathway to the vomeronasal organ

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Sexual and social behaviors in most animal species are mediated and regulated by pheromone cues detected by the vomeronasal organ (VNO), which sends projections to the accessory olfactory bulb and on to the medial amygdala. Pheromones usually reach the VNO through the nasal cavity by active sniffing. However, non-volatile pheromones can also reach the VNO through a much less studied pathway: the nasopalatine ducts which connect the VNO with the upper palate of the mouth. We explored the function of the ducts as an integral part of the vomeronasal system in mice by permanently blocking their oral entrance using a surgical cautery device. We subsequently exposed male and female mice to urine collected from mice of the opposite sex, and examined c-Fos expression in the medial amygdala as a marker for neuronal activity and pheromone detection. Our results revealed that both female and male mice with blocked ducts presented significantly reduced neuronal activity in the anterior and posterior medial amygdala when compared to mice with intact ducts. Furthermore, the neuronal activity of the blocked mice was similar in magnitude to the one observed in the medial amygdala of control mice that were exposed only to distal water stimuli.Taken together, our results suggest that pheromoneal transfer to the VNO is significantly diminished by blocking the ducts, which might imply a great importance of this pathway in regulating innate sexual and social behaviors.

Taste of the wild: different distribution patterns of taste buds in the nasopalatine ducts of wild caught and laboratory mice

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The vomeronasal system is considered a part of the olfactory sense responsible for communicating social signals between conspecific and regulating innate social behaviors such as reproduction, aggression and parental care. Pheromone signals, which carry the social cues, can reach the vomeronasal organ (VNO) either by the nasal cavity or by the oral cavity, via the nasopalatine ducts. Surprisingly, several structures of taste buds were found just at the entrance to the nasopalatine ducts in many animal species, but their functional roles were never examined. Using histological and immunochemistry methods we identified a significantly different morphological pattern of these taste buds in the ducts of wild-caught mice when compared to regular lab mice. Although the taste buds in both wild-caught and lab mice are located at the same anatomical position at the entrance of the ducts, wild-caught mice have twice as much taste buds as lab mice, and an increased density of them along the ducts. In addition, the pore of each taste bud was identified and marked, and its distance from the entrance of the nasopalatine duct was calculated. The results revealed a significantly different distribution pattern of the taste buds in wild caught and lab mice. Considering the distinct location of the taste buds at the entrance of the ducts and the behavioral differences between wild-caught and lab mice, we wish to suggest that these taste buds might function in cooperation the VNO as a dual sensory system for detecting and encoding pheromones, much like the reported sensory integration of the sense of taste and the primary olfactory system.

Kinematic analysis of crawling in the Octopus

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In nature, octopuses can be found in shallow waters and outside of the water for a few moments searching for prey. In these conditions the octopus employs a crawling movement. In our research, we kinematically analyze this movement in two stages: Analysis of a single arm attending the move and analysis of the coordination between the attending arms. This research poses a biological question, but it is also a part of an ongoing project of the UI intended for designing and building bio-inspired robots with embodied intelligent. Our project is aimed to assist in building an octopus robot, which will be able to crawl independently or with human control. Adult animals are put in shallow water and video-recorded from underneath while crawling. The video-clip is then cut into singe frames. Using a designated

software we developed for this purpose, the location and state (attached to the surface or not) of the arm suckers that are attending the movement are marked on all frames. The data is then analyzed to reveal the kinematic properties of the arm and of the coordination between the arms during the crawling movement. While crawling, the octopus uses only the arms opposite to the crawling direction for pushing its body. It does not utilize pulling or paddle-like pushing. One to four arms can attend the move simultaneously and the direction and speed of crawling is the combined vector of those arms. While crawling, the orientation of the octopus does not change. The single arm pushing is performed in five stages:(1) shortening the proximal part to some percent of its basic length,(2) attaching to the surface with some proximal suckers,(3) elongating its proximal part to be longer then its basic length,(4) releasing the attached suckers and (5) shortening again to its basic length. As seen in other movements of the octopus, it greatly reduces the number of Degrees Of Freedom while crawling, which greatly reduces the complexity of the calculations needed to perform the move.

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Scavenger receptor A is essential for disease progression in multiple sclerosis mouse model

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Background: Multiple Sclerosis (MS) is an autoimmune disease of the central nervous system characterized by damage to the neuronal myelin sheath, which results in different levels of muscle paralysis that can lead to neuronal death. Epidemiological studies have shown that the majority of patients with MS initially experience a relapsing-remitting (RR) form of disease which mostly develops into secondary-progressive MS. Experimental autoimmune encephalomyelitis (EAE) mouse model is commonly used to study pathogenesis of the disease and to test new therapeutic approaches. Understanding the mechanisms leading to cumulative neurological disability in MS, and further developing effective therapeutic strategies aiming at reduced disease progression is a major goal in MS research. The class A macrophage scavenger receptors (SR-A) have been implicated in inflammation-associated physiological and pathological processes such as in atherosclerosis. In this work we demonstrate the essential role of SRA in EAE progression, by showing a reduction of EAE progression in SRA-/- mice.

Methods: We investigated EAE progression in SRA-/- vs. WT mice using clinical score measurements and immunohistology staining. Furthermore we assessed pro-inflammatory cytokine response in cell culture using ELISA.

Results and conclusions: We discovered that SRA-/- mice have a significant reduction in clinical score of EAE mouse model of MS. Furthermore, we found a significant reduction of astrogliosis and macrophage infiltration into the spinal cord of SRA-/- mice as compared to WT. These results were correlated with demyelination process in the same area. Immunological assessment showed reduction in pro-inflammatory cytokines such as IFN-gamma and IL-17 that play a major role in EAE progression. We suggest targeting SRA as therapeutic application in MS.

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MRI reveals early life brain changes in ApoE4 human carriers

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The APOE gene and its protein product plays a crucial role in lipid metabolism. The APOE gene APOE-e4 allele presence is increased in Alzheimer's disease (AD) and several neurodegenerative diseases. Compared to non APOE-ε4 carriers, the carriers of one APOE-e4 allele have a 2-3 fold risk of developing AD. The effect and time line in which APOE-e4 influence the neurodegenerative diseases is not known, but previous studies showed significant brain differences in non affected individuals. Brain structural differences were shown as early as 50 years old, and glucose metabolitic differences in the brain were shown even in young 20 years old normal subjects. In our study 52 young healthy Ashkenazi Jews (ages 20-35), underwent a battery of cognitive tests (data not shown here), an MRI protocol which included DTI, structural T1 and T2 map. In addition the subjects gave either saliva or blood sample for further genotyping. Among the 52 total subjects, 29 were APOE-33, 11 were APOE-34, 8 were APOE-23, 2 were APOE-24 and 2 were APOE44. The structural T1 was used for VBM analysis and the T2 and DTI were used in VBA analysis. The DTI showed mainly significant differences in the parahippocampal gyrus, the hippocampus and the globus pallidus. VBM showed mainly significant differences in the parahippocampal gyrus, the hippocampus, the orbitofrontal cortex, and the dorsolateral prefrontal cortex. The brain differences that were found in this study are known to exist in old ages (50 years and above). By minimizing the genetic variance in our sample (only Ashkenazi Jews), and as a result of new and improved methodologies and the microstructural sensitivity of DTI we managed to show that this differences exist from early life stages. One implications of our study is that the influence of APOE4 presence is very strong in developmental stages.

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Unique role of the magnocellular visual system in word recognition

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Background: One major weakness of the magnocellular hypothesis of dyslexia is a lack of a causal mechanism explaining why the magnocellular system is crucial for accurate reading.

Methods: Aiming to examine the unique contribution of the magnocellular system to word reading, we tested skilled readers (n=31, study1) and individuals with developmental dyslexia (n=23, study2) for coherent motion detection and for word recognition, using a lexical decision task with three string types (words, non-words and adjacent anagrams). In order to verify that results were free from phonological influences, subjects' phonological skills were evaluated as well.

Results: Study1: motion detection thresholds were used to divide subjects into groups of poor and good motion detectors. Although all subjects were skilled readers, good motion detectors were significantly faster than poor motion detectors when responding to words presented to the right visual field. Phonological abilities did not differ between the groups. Study2: results from the dyslexia group revealed that motion detection, but not phonological abilities, significantly predicted word recognition. Phonological awareness was found to predict identification of non words. Finally, recognition of anagrams was predicted by both motion detection and phonological awareness but in opposite manners.

Discussion: Interpreted in light of the integrated model for visual processing [Bullier, J. (2001). Integrated model of visual processing. Brain Research Reviews, 36(2-3), 96-107], we propose that a low frequency representation of the letter string, delivered through the magnocellular system, primes a small set of words with resembling shapes or outlines. This priming facilitates the recognition of real words but hinders the correct identification of anagrams. The relevance of such low frequency representation is tested in a new priming experiment. Preliminary results from this study will also be presented.

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CRF drives purkinje cells to an upstate by reducing the membrane conductance

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Corticotropin-releasing factor (CRF) is a neuropeptide that plays a major role in stress response. CRF is also released from climbing fibers that originate in the inferior olive nucleus and innervate the cerebellar cortex. Previous studies have shown that CRF modulates Purkinje cell (PC) firing rate. In the present study, we focused on the effect of CRF on PC bi-stability investigating the underlying biophysical mechanisms.

In vitro whole-cell patch and cell-attached recording were performed from PC somata in parasagittal slices of cerebellar vermis (prepared from Sprague Dawley rats p13-27). CRF (0.1 μM dissolved in physiological solution) was pressure injected locally via a patch pipette.

Local application of CRF to the PC soma generated a prolonged episode of spikes firing superimposed on membrane depolarization. This response resembled a spontaneous shift to the PC's up-state. The onset latency of the up-state as well as its duration increased with the intensity, duration and proximity to the soma of the CRF application. Local application of CRF in the presence of TTX, DNQX and picrotoxin, resulted in a small hyperpolarization of the membrane potential, which increases with membrane depolarization. Plotting the time dependent I-V curve revealed that CRF decreases the membrane conductance.

The results show that the mechanism is most likely a reduction in membrane conductance. These results demonstrate that CRF modulates PC bi-stability, driving the cell toward its up-state. We suggest that this effect might underlie the inconsistent and contradictory observations regarding the firing behavior of Purkinje cells in awake animals.

ApoE4, the major genetic risk factor for Alzheimer's disease, induces synaptic deficits in young mice

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Background: ApoE4 is the most prevalent genetic risk factor for Alzheimer's disease (AD). Brain synaptic aberrations are a pivotal pathology in AD.

Aim: To examine whether the synaptic dysfunction induced by ApoE4 in target replacement (TR) mice starts at a young age and to investigate the specific pre-synaptic constituents which are damaged by ApoE4

Methods: Hippocampi of young (4 months old) ApoE3 and ApoE4 TR mice were subjected to western blot (WB) analysis and immunohistochemistry (IHC). The levels and localization of specific synaptic markers were measured.

Results: The hippocampal levels of Synaptophysin, a general marker of synaptic vesicles were similar in ApoE3 and ApoE4 mice as determined by WB (100±6.7 vs. 98±5.4 respectively ; P=0.81). In contrast, the levels of Vglut, a pre-synaptic vesicle transporter of excitatory glutamatergic synapses were reduced in ApoE4 mice (100±6.2 vs. 64±3.5 ; P<0.001). Immunohistochemical investigation of Vglut localization demonstrated that the effect is specific

to the CA sub-fields of the hippocampus, with no effect in the DG. The levels of the inhibitory GABAergic marker GAD67, as measured by WB, were also reduced in ApoE4 mice but to a lesser extent (100±6.3 vs. 82±4.9 ; P<0.05). In addition, the levels of the cholinergic pre-synaptic vesicular transporter, Vacht were also reduced in ApoE4 mice (100±8.9 vs. 77±4.9 ; P=0.05).

Conclusions: Young ApoE4 TR mice exhibit synaptic deficits. The observed ApoE4 induced decrease in vesicular transporters and not on the general vesicular marker, Synaptophysin, suggests a specific intra-synaptic mechanism. This will be addressed in the near future.

D-cycloserine improves cognitive deficits in a mouse model of neuroinflammation

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Background: Neuroinflammation can lead to significant and long lasting cognitive deficits in human subjects through an unknown mechanism. At present, there is no pharmacological intervention known to prevent or ameliorate cognitive deficits following a neuroinflammatory insult. In the present study, we examined the efficacy of D-cycloserine (DCS), a partial NMDA receptor agonist, on cognitive deficits induced in mice by intracisternal (ic) injection of endotoxin (LPS).

Methods: Male Sabra mice (N=10/treatment group) were given ic saline or LPS (10ug in 2ul) followed 24 h later by intraperitoneal saline or DCS (10ug/gr in 100ul/10gr). Memory function was assessed by the novel object recognition test (NORT) 2, 7, 16, and 30 days post LPS injections followed by electrophysiological recording of LTP (day 8). Animals killed after 8 days and their brains processed for in vitro quantitative autoradiography with [3 H]PK11195, an established marker of microgliosis, and [3 H]MK801, a specific NMDA receptor antagonist. Statistical analysis was performed by one-way ANOVA (NORT) or 2 way ANOVA by treatment and region (Autoradiography), followed by Fisher's PLSD posthoc test.

Results: Intracisternal LPS induced a significant and long-lasting deficit in novel object recognition; which was reversed by DCS. Similarly, LPS impaired LTP and its magnitude was restored by DCS. Moreover, DCS treatment of LPS mice led to a significant reduction of regional neuroinflammation, and to up-regulation of NMDA receptor density as assessed by autoradiography (p<0.0001 for region and treatment main effects).

Conclusion: These results suggest that neuroinflammation-induced cognitive deficits involve derangement of NMDAR function and can be prevented by DCS.

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Movement-related changes in local and long-distance synchronisation in Parkinson's disease revealed by simultaneous magnetoencephalography and intracranial recordings

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Insight into how brain structures interact is critical for understanding the principles of brain function and may lead to better diagnosis and therapy. To study interactions between the cortex and basal ganglia we recorded, simultaneously, local field potentials (LFPs) from deep brain stimulation (DBS) electrodes and magnetoencephalographic (MEG) signals from the cerebral cortex (CTF 275 channel system) from 17 Parkinson's disease (PD) patients with bilateral DBS electrodes in the subthalamic nucleus (STN). The patients performed self-initiated button presses, either with three fingers simultaneously (simple movements) or as a sequence (complex movements). The experiment was repeated with and without the dopamine prodrug levodopa. We examined the effect of movement complexity and drug on event-related power in the contralateral primary motor cortex (M1) and STN and on the coherence between activity in the two structures. Changes in mean power were similar in the two structures, but with the important exception that only M1 exhibited prolonged high gamma (50-90 Hz) activity in the complex task. Levodopa led to a wide-band increase in reactivity around movement onset in M1, but this effect was limited to the gamma band in the STN. There was also a significant increase in high-gamma coherence between M1 and STN around movement onset. This increase in coherence was potentiated by levodopa, but unaffected by complexity. The magnitude of the effect of treatment on the coherence between M1 and STN correlated with the degree of improvement in bradykinesia-rigidity. While high baseline coherence between M1 and STN was found in the beta band, this was only weakly modulated by movement and treatment. Our results demonstrate that movement-related spectral changes in M1 and STN reflect coupled but distinct physiological processes. We also demonstrate for the first time the clinical relevance of high-gamma coherence between the cortex and the basal ganglia.

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Neural correlates in the primate amygdala for acquisition, extinction, and retention of tone-odor associations

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Although acquisition and extinction of fear-conditioning is an influential model, we have little understating of how it is

processed in the primate brain. We developed a primate model in which monkeys acquire and extinguish tone-odor associations. We used odors as reinforcers because the olfactory system gains unique and direct access into the amygdala, and because odors are powerful primitive reinforces that elicit emotions. In addition, odorants provide a unique opportunity to compare positive and negative reinforcers of the same modality, by using pleasant and aversive odors. We developed an implicit behavioral measure to quantify valence and learning, by real-time monitoring of respiration cycles (breathing). Using it, we show that animals modify their breathing rate and reduce volume of breathing following a tone that predicts an aversive odor, and enhanced breathing towards a pleasant odor. We recorded single-cell activity (n=327) in the amygdala of two behaving monkeys (macaque fascicularis), during acquisition, extinction, and 24-hr retention of such associations. We have found periodic activity of neurons in the amygdala that locked to breath cycle, and show that the periodic activity is flexible and change during the different stages of the paradigm. In addition, we identified separate groups of neurons that code acquisition, extinction and 24 hours retention of the tone-odor association.

Experience-dependent plasticity of mature adult-born neurons

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The adult mammalian olfactory bulb is continuously supplied with new neurons throughout life. This unique population has been hypothesized to serve a role in the network's plasticity by the mere addition of young neurons to the network. In accordance with this hypothesis, immature neurons show enhanced structural and functional plasticity in response to manipulations of sensory experience. However, it remains unclear whether adult-born neurons retain their capacity for enhanced plasticity after they mature. To address this question, we labeled adult-born neurons with a GFP-tagged postsynaptic marker (PSD95-GFP), rendering their dendrites and putative synapses (PSD95-GFP puncta) visible. After adult-born neurons matured (~80 days post injection; DPI), we combined intrinsic signal imaging and in vivo time-lapse two-photon imaging of their dendrites and puncta. This enabled us to examine the effects of sensory enrichment on structural and synaptic dynamics in enriched and non-enriched loci in the same animal. Sensory enrichment did not affect the dendritic morphology of mature adult-born periglomerular neurons (PGNs; n=9 and n=7 neurons from enriched and non enriched foci, respectively; N=6 mice). In contrast, sensory experience doubled the level of PSD95-GFP puncta stability specifically in enriched loci (turnover ratio: 0.04±0.004 in enriched and 0.08±0.01 in non-enriched loci, n=454 and n=536 puncta, respectively; N=5 mice, p=0.006). Notably, this effect was specific to mature adult-born PGNs, as the spine dynamics of mature adult-born granule cells were not affected. Our work, therefore, provides evidence that synapses of mature adult-born PGNs, stabilize in face of sensory experience. This stability is different from that observed in young PGNs. Thus, in addition to young adult-born PGNs, mature adult-born PGNs might endow the olfactory bulb network with a long lasting substrate for plasticity.

Effect of traumatic brain injury on brain activation patterns in subjects performing a working memory task: an fMRI study

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Traumatic brain injury (TBI) is a major cause of death and disability. Cognitive deficits, especially memory deficits are extremely common in TBI survivors. The objective of this study was to compare the influence of memory load on patterns of brain activation during a working memory (WM) task in TBI patients and matched healthy controls.

Brain activation patterns in response to increasing WM load in an N-back task were assessed with functional magnetic resonance imaging (fMRI) using a 3 T MRI system (GE, HDx). Three TBI patients and 7 controls were scanned while performing an N-back task for letters. The task (0-, 1- and 2-back conditions) was presented using E-Prime software and results were analyzed using SPM8. In this preliminary study, all subjects reached >75% correct response.

Brain activations ($p<0.001$ uncorrected, in the 1-back vs 0-back condition) were found in both groups in Wernicke's area and anterior prefrontal cortex. The controls showed activation in one additional region (somatosensory association cortex). TBI patients displayed a more extensive and dispersed pattern of activations, with additional activations in the premotor, dorsolateral prefrontal and dorsal anterior cingulate cortex. Increasing memory load (2-back vs 0-back condition) did not affect the activation pattern in healthy controls, while TBI patients showed additional activations in the fusiform gyrus, middle temporal gyrus and orbito-frontal area. These results indicate that TBI is associated with a deranged pattern of brain activation and an exaggerated response to increased memory load compared

to healthy controls, while task performance was not affected.

Rapid neuronal coding with first spike latency in the whisker somatosensory system

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Untangling the neural code underlying sensory perception requires the mapping of physical stimulus parameters to neuronal responses. It is generally assumed the whisker primary afferents transmit information by their firing rates. However, the behavioral speed and neuronal reliability of this system suggest that a temporal coding scheme might be used to encode sensory stimuli. Here we show that the relative timing of the first impulses in an ensemble of neurons accurately and reliably conveys whisker velocity. We show that stimulus onset time can be estimated using stimulus-independent response latency of rapidly adapting neurons, while stimulus identity can be gauged by stimulus-dependent first spike latency of slowly adapting neurons. This estimation is robust, and is not affected by the addition of noise, or change of whiskers' resting position and direction of motion. This mechanism allows primary afferents to rapidly and reliably transmit tactile information with the very first spikes emitted by neuronal population.

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Neural activity associated with self-paced overt word generation - an fMRI study

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Word generation (WG) tasks are extensively used, in various forms, for neuropsychological assessment of pre-frontal brain function, particularly for testing the ability for self-generation of response. As such, this task has also been used in brain imaging studies to study the neural mechanisms of self-initiated behavior. However, due to motion artifacts, functional magnetic resonance imaging (fMRI) studies of WG commonly employ either covert versions of the task, lacking an online record of subjects' responses, or paced versions which hinder the self-initiation aspect. In the current study we have addressed this problem by creating a novel WG task, in which subjects are instructed to type self-generated words. The experiment consisted of two blocks: self-initiated and externally-driven, which were similar in visual and motor aspects, but differed in the type of generation. In self-initiated blocks, four letters were presented on a computer screen and subjects were required to self-generate as many meaningful words as possible, using the presented letters only, similarly to Scrabble. In externally-driven blocks, subjects were presented with four different letters and were signaled to type words that were chosen a priori. Seven subjects participated in the fMRI experiment. Contrasting brain activity during self-initiated blocks versus externally-driven blocks, self-initiative states were characterized in an overall increase in activity in right and left ACC, pre-SMA, SMA and dlPFC, as well as Broca's area in the left inferior frontal gyrus. This data is in accord with previous results based on covert and paced WG tasks. We are currently analyzing behavioral data and its relation to brain activity to assess the relative contribution of the different brain regions and their relation to word generation rate.

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Categorization - working strategy or cognitive style?

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The aim of the current research is to understand the basis of categorization process throughout the question of whether decision making is going under 'cognitive style' or a working strategy, which varies depending on the tasks, instructions or situations.

Two age groups participated: 197 young adults (27.4± 5.9 years) and 31 elder adults (72.4±9.6 years), completed computerized categorization task (CT), when 34 of the young adult participants performed the task under time limit condition. CT included stimuli of 4 words of items. Each stimulus has 2 extraordinary items. One verbal and the other one is on imagery basis. Participants were instructed to choose one extraordinary item out of four. Responses and reaction times were recorded.

According to selections (verbal/imagery), style index was created for all participants and each group was divided into two subgroups (Verbal or Imagery). Unlike Riding's CSA-classic task and others, we based our cognitive style index upon number of selections rather than RTs.

The results showed constancy in the percentage of visual/functional subjects in all three groups even under limitation of cognitive resources (age or time constrain). In addition, verbal styled subjects were persistently faster than imagery subjects even in visual selections (between t-tests and ANOVA, $p<0.05$). Furthermore, imagery subjects were faster in their verbal selections in comparison to their RT in visual selections (within t-tests, $p<0.05$). According to the results and Evan's dual-process theory, we discuss the toll/benefit of being imaginary vs. verbal styled subjects and relate our discussion to hemispheric dominance hypothesis.

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Deficit in learning under stress following viral vector-mediated CRF knock-down in the PVN

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Stress is known to both trigger psychopathologies (e.g. depression, PTSD) and to affect learning and memory. At the physiological level, Corticotropin-Releasing Factor (CRF) plays a crucial role in mediating the stress response, by initiating the activation of hypothalamo-pituitary-adrenal axis (HPA axis), but also by modulating activity in various brain areas. This modulation is adaptive following mild and acute stress, but the excessive activation of the CRF system and the HPA axis may initiate stress-related pathologies, in part by involving aberrant learning.

The objective of this work is to study the involvement of the CRF system in the interaction between learning and memory processes and stress-related disorders. We have used viral vector injection to down-regulate CRF expression in the paraventricular nucleus (PVN). The two-way shuttle avoidance task (TWSA) was chosen to assess learning and memory processes under stressful conditions. Animals learn to shuttle from one side to the other to avoid electrical foot shock by responding to a tone (conditioned stimulus [CS]).

Down-regulation of CRF expression in the PVN decreased the number of avoidance responses in a TWSA single session compared to control rats. This impairment was observed both when animals were trained under mild (0.8 mA) or strong (1.5 mA) CS. Furthermore, down regulating CRF expression also reduced the avoidance improvement resulting from prolonged training, suggesting a lasting impairment of the ability to learn under stress in CRF KD rats.

Both control and treated rats exhibited the same increase of corticosterone blood level after the TWS conditioning session, suggesting that the observed impairment was not a result of alteration in the activation of the HPA axis, but rather the result of reduced CRF impact on other brain functions. We continue to examine the impact of manipulating CRF expression on learning under stress and to search for the underlying neural mechanisms.

Dexamethasone modulation of antidepressant effects on MAPK signaling involves beta-arrestin: implications to the pharmacological treatment of Major Depression

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The plasticity hypothesis of major depression (MD) states that glucocorticoids stress hormones impair while antidepressants reconstitute cellular plasticity. Accordingly, we showed that the combined action of dexamethasone (DEX) and norepinephrine (NE), representing stress and antidepressant treatment, respectively, have an augmented effect on both the MAPK and the CREB pathways. The aim of this study was to substantiate a clinical relevance for this intracellular augmentation. Similarly to our previous findings with DEX+NE, we showed that prolonged stress, caused by pre-exposure of SH-SY5Y cells to DEX, followed by the addition of desipramine (DMI, a tricyclic antidepressant) caused an enhancement in MAPK pathway and CREB compared to DMI alone. DEX alone had no such effect. However, the enhancement caused by the co-treatment was blocked by both yohimbine and RU486, adrenergic (AR) and glucocorticoid (GR) receptors antagonists, respectively. We therefore suggested that co-treatment enhancement is caused by DEX effect on b-arrestin-induced internalization of AR. Our previous findings showed that b-arrestin is recruited to the membrane following treatment with NE, whereas following the co-treatment it is much more diffused throughout the cell. Imunofluorescence assessment showed a DEX-induced increase in b-arrestin density inside the cell, which was inhibited by RU486. Receptor internalization is rapidly modulated by Mdm2 (E3 ubiquitin ligase) binding to b-arrestin. Indeed, Mdm2 binding to b-arrestin, assessed by immunoprecipitation followed by Western blotting, was reduced in the presence of DEX in a time dependent manner. This effect was also abolished by the addition of RU486. The study suggests that DEX, through its interaction with GR, augments DMI intracellular effect by modulating Mdm2-dependent b-arrestin trafficking and thereby delays the internalization of the AR. This mechanism may contribute to the therapeutic effects of antidepressants in MD.

Reconstructing the real and the imaginary past: ventro-medial PFC and ventral striatum employ vividness to monitor episodic recollection

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How does the brain tell true memories from false ones? We investigated false memory to unveil monitoring mechanisms of episodic retrieval. The experimental protocol consisted of three sessions – Study, Manipulation, and Test. In the Study, participants watched a documentary movie, depicting a day in the life of a woman. In the Manipulation, three weeks later, false memories were induced using a memory questionnaire planted with details of scenes never depicted in the movie. In the final Test session, performed one week after the Manipulation,

participants completed a questionnaire while undergoing an fMRI scan, and indicated whether described events appeared in the movie or not. Participants endorsed more manipulated items than new ones, but less than movie items, which were also rated with higher confidence and vividness. Participants were classified as Naïve in regard to the manipulation or as Not-Naïve. Naïve participants were less accurate and showed different BOLD patterns. While in both groups activity in the retrieval network was higher for endorsed movie than for manipulation questions, the differences were larger in Not-Naïve. Two regions not in the retrieval network, the left ventral striatum (VS) and the left amygdala, also showed a higher BOLD for movie than for manipulation questions, and only in Not-Naïve the activity in these regions was parametrically correlated with vividness. Notably, BOLD differences between movie and manipulated items were not detected upon equating for confidence and vividness. Finally, we computed the co-activation among the ROI's. While for the Not-Naïve co-activation was similar for movie and manipulated items, in the Naïve the co-activation of the left Ventro-Medial prefrontal cortex (vmPFC) and of the VS with the retrieval network ROIs was markedly lower during manipulation trials. We propose that the VS functions in concert with the vmPFC to monitor and maybe control retrieval performance.

Involvement of the VEGF system in mediating the pathological effects of ApoE4 in targeted replacement mice

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Background: It has recently been shown that apolipoprotein E4 (apoE4) and Amyloid-beta (Abeta) interact synergistically following activation of the amyloid cascade. A growing body of evidence suggests that VEGF has neuroprotective and anti-Abeta activities. The main objective of this study is to examine the possible role of VEGF in mediating the synergistic pathological effects of Abeta and apoE4.

Methods: The expression levels of the VEGF system in apoE3 and apoE4 mice were tested utilizing RT-PCR, prior to and following the activation of the amyloid cascade by inhibition of the Abeta degrading enzyme, neprilysin. In addition, immunohistochemistry (IHC) was employed in order to determine the specific hippocampal localization of VEGF.

Results: RT-PCR measurements revealed that HIF-2a expression levels were elevated in hippocampal CA1 neurons, both in apoE3 and apoE4 mice following inhibition of neprilysin. In contrast, this treatment increased the levels of VEGF in CA1 neurons in apoE3 but not in apoE4 mice. These results were corroborated by complementary IHC experiments which also revealed that VEGF was increased in the CA1 of treated apoE3 mice, but not of the corresponding apoE4 mice.

Additional experiments with naïve non-treated mice showed that the VEGF and HIF systems were down-regulated under basal conditions in apoE4 compared to apoE3 hippocampi. This effect may play a role in predisposing the apoE4 mice to aging and brain insults.

Conclusions: The synergistic effect of Abeta and apoE4 is associated with impairments in the VEGF system. This suggests that at least part of the pathological effects of apoE4 is mediated by blocking the neuroprotective effects of VEGF.

Corticosteroid modulation of status epilepticus: the role of GRs and MRs

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Stress is among the most frequently self-reported precipitant of seizures in patients with epilepsy. It has not yet been clarified how stress and specifically the stress hormone, corticosterone, (cortisol in humans) modulates seizures. Two types of receptors, the glucocorticoid (GRs) and mineralocorticoid (MRs), are in charge of the corticosterone effects in the body. Both GRs and MRs can be expressed either at the cell nucleus or at the membrane and therefore play a different roles in cellular functions. We have studied the effects of stress and the targeted activation of GRs and MRs in the modulation of seizures in vivo by using an animal model of status epilepticus. Briefly, kainic acid (10 mg/kg) was. injected i.p. in 1 month old male Wistar rats either 30 s or 1 hr after their exposure to a 15 min. forced swim stress (FSS). Seizures latency was shorter in the animals that received kainic acid 30 s following FSS compared to control and to those treated with kainic acid 1 hr after the FSS. In addition, seizures reached a higher Racine's score in shorter time in the former group compared with controls. Interestingly, injection of diazepam halted seizures faster in the animals that received kainic acid 1 hr after FSS than in those that were treated 30 s following FSS. Surprisingly, blocking MRs or GRs receptors prior to the stressful exposure showed that MRs activation by stress enhanced the effects of kainic acid injection following FSS, while GRs activation suppressed these effects. In an effort to understand the mechanism of the differential MRs and GRs activation on seizures modulation, we performed whole cell patch-clamp recordings in acute slices of the hippocampus. We found that GRs and MRs differently regulate GABA-A currents. Respectively through membrane bound receptors, MRs reduce the frequency of IPSCs while GRs increase IPSCs amplitude. We conclude that stress and activation of MRs and GRs modulate seizures by differential regulation of GABAergic synapses

Talpiot Medical Leadership Program - The Chaim Sheba Medical Center

Towards early detection and personalized treatment of neurodegenerative diseases: an outlook

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Predictive, preventive and personalized medicine (PPPM) offers great promise for the future practice of medicine. People across all walks of life and socioeconomic status are increasingly demanding to be better informed of anticipated changes in their health status as they progress through life. Of paramount importance is communication among professionals– medical doctors, biotechnologists, computer-scientists, healthcare providers, policy-makers, educators– who are obligatorily involved in the paradigm change from delayed interventional to predictive medicine. This concept is considered as medicine of future.

This is particularly relevant to neurodegenerative disease such as Parkinson's and Alzheimer's diseases where the clinical diagnosis can be made generally when motor symptoms or behavioral/cognitive disabilities occur, though the disease has originated several years earlier. Thus, future efforts should be focused on this time window to begin a neuroprotective treatment. Among the diverse, significant challenges facing the clinicians, is the improvement of diagnostic measures in order to 1) detect early/subtle symptoms, a phase in which prevention efforts might be expected to have their greatest impact; 2) provide a measure of disease progression that can be evaluated objectively, while clinical measure are much less accurate; 3) provide evidence for relevant biological activity of an experimental drug; 4) delineate pathophysiological processes responsible for the disease.

Use of stem cell therapy in neurodegenerative disorders; translational animal models

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Stem cell therapy is a rapidly evolving field in regenerative medicine, with current advancement in stem cell technology aiming for personalized cell therapy, including that of the nervous system. Similar to drug discovery, stem cell therapy entails a process commencing from an idea to a product. This translational process proves challenging in the development of such technologies for the central nervous system (CNS), given its complexity, etiology, pathophysiology, disease-model limitations and target-organ exposure (the BBB), among other developmental challenges. The evaluation of stem cell technology using translational animal models is critical to early internal decision-making processes. Today, the paucity of existing disease-modifying agents, coupled with the lack of existing animal models that mimic a given human CNS disorder adequately, only serves as a testament to the complexity of developing CNS therapy. Stem cell therapy serves as a novel approach for effectively treating CNS disorders. While only established translational animal models will enable the study of stem cell therapy accurately, still, the research carried out in translational research institutions provides an insight into the capabilities of this promising novel therapy.

Presynaptic output regulates survival and synaptogenesis of adult-born neurons

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The adult mammalian olfactory bulb (OB) is continuously supplied with new neurons throughout life. Only ~50% of these neurons survive to fully-integrate into the pre-existing network and reach maturity. Manipulations of sensory activity and cell-intrinsic excitability have shown that activity is a major regulator of the survival of adult-born neurons. However, the factors that regulate synaptogenesis are still controversial. Here, we addressed this issue by genetically manipulating the presynaptic output activity of adult-born neurons by lentiviral-based expression of tetanus toxin light chain (TeTxLC); a protease which specifically cleaves VAMP2 (a protein essential for presynaptic release), thus inhibiting synaptic release. Using co-injection of TeTxLC-GFP and TdTomato (a red fluorescent protein), we analyzed the effects of TeTxLC expression on granule cell (GC) survival before (14 days post injection - d.p.i.), immediately after (30 d.p.i), and long after (45 d.p.i) presynapse formation. We find that TeTxLC expression decreases the survival of GCs only after presynapse formation (at 30 and 45 d.p.i.). Furthermore, we show that this effect is accompanied by impaired synaptogenesis, in the form of a reduction in the density of GC dendritic spines, as compared to control neurons (only after presynapse formation, at 30 and 45 d.p.i, but not at 14 d.p.i.). We are currently exploring spine dynamics in TeTxLC-expressing GCs using time-lapse in-vivo imaging. Our results suggest that presynaptic release is important for the survival and proper synaptic integration of adult-born neurons in the OB.

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The reward system in obesiy: sex differences throughout development

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Introduction: Deficits in the reward system have been shown to influence the development of obesity. Nevertheless sex differences in this system have hardly been investigated. We used the OLETF rat model of obesity, which was shown to have dopamine (DA) - related deficits in males, to evaluate sex-differences in developmental, food-reward-related measures.
Methods: DA-like-receptor type 1 (D1R) and D2R levels were examined in a reward-related brain area (NAcc) and sucrose preference was assessed at selected time points from weaning to adulthood (postnatal day [PND]90). We analyzed microstructural patterns of licking, taking into account estrous cycle changes in females
Results: Male OLETF rats expressed significantly lower D2R levels than LETO controls only on PND90. OLETF females, on the other hand, presented levels similar to those of LETO controls. In addition, OLETF males presented exaggerated preference for the high sucrose concentration that appeared already at PND 38. Females from both strains differed from males in their developmental patterns of sucrose preference. Moreover, while OLETF females did not present exaggerated preference for the high sucrose as the OLETF males, they failed to decrease the total amount of licking in the Estrous phase (compared to Diestrous phase) of the estrous cycle. Nevertheless, in the cluster size parameter (considered a measure of hedonic response) there was no significant difference between the strains.
Conclusion: OLETF males show deterioration in the functioning of their food-reward system that may result from the gradual worsening on their obese phenotype (characterized by abnormally high levels of leptin and insulin). Females did not show this pattern, and presented a profile similar to LETO controls. A possible delay in the appearance of this deterioration in obese females is being currently examined.

Spatial navigation and the hippocampus: encoding, retrieval, and remapping
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In humans the hippocampus plays a role in both episodic memory and spatial navigation. The relationship between the processing of episodic and spatial related inputs within the hippocampus is not obvious. I will discuss how a spatial representation can be linked to memory processing via remapping. Hippocampal pyramidal cells and granular cells in the dentate gyrus can alter their spatial representation of the environment, or remap, in response to changes in the environment. Such cue manipulation data indicate that the hippocampus can maintain multiple representations of altered environments. Remapping can occur even in a stable environment when the goal location and pathway the animal takes is altered. However, when trajectories are held constant very few cells show remapping. The paucity of remapping despite substantial changes in task demands is puzzling given the presumed role of the hippocampus in processing episodic memory. I will present data on the degree to which ensembles of cells throughout the hippocampus respond to changes in "cognitive" demands despite no apparent change in the physical environment or trajectory taken by the animal.

Transient artistic creativity following left fronto-temporal damage
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The neurocognitive mechanisms underlying creativity are poorly understood. While deficits in creativity and divergent thinking are common consequences of lesions to prefrontal cortex (PFC), recent evidence suggest that left fronto-temporal degeneration involving deterioration of language abilities may actually promote artistic creativity (Seeley et al., 2008). Here, we report two lesion studies which demonstrate the inhibiting role of the left fronto-temporal region in creativity. In Experiment 1 patients with localized lesions in the medial prefrontal cortex (mPFC), inferior frontal gyrus (IFG), and posterior parietal and temporal cortex (PC) were assessed by two tasks involving divergent thinking and originality. Results of the experiment indicate that lesions in the mPFC involved the most profound impairment in originality and that lesions in the left IFG and left PC were associated with elevated levels of originality. Moreover, a positive correlation between creativity scores and left PC lesions indicated that the larger the lesion in this area the greater the originality. Experiment 2 was a case study of a patient, E.P, who following a left fronto-temporal hemorrhage involving Broca's aphasia exhibited transient artistic creativity. Following a stroke, E.P began to experience a strong drive to paint and gradually, his paintings became more and more complex. Interestingly, as language abilities recuperated and the hemorrhage receded, his urges to create art diminished to the point where he no longer felt the urge to paint at all. We propose a neural and cognitive model of a right fronto-parietal network for creativity. We demonstrate that acquired lesions in the left frontal and parietal lobe are associated with improved originality, while lesions in the right fronto-parietal area are associated with reduced originality, indicating that inter-hemispheric connections may play an inhibiting role on the right hemisphere's role in creativity.

Does face recognition depend on the viewing pattern?
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Although most studies assume that healthy humans are experts in face recognition, there is much diversity in this skill between different people. For example, when walking down the street some will recognize a former school buddy after decades of not seeing one another, while others will mistakenly ignore a current work colleague. In this study we investigated whether different scanning patterns correspond to different face recognition scores, both within and between subjects. To establish face recognition scores we used a short questionnaire and three face recognition experiments that were performed while the subjects' eye position was monitored:

1. Old/New experiment, in which subjects were asked to study a few faces/objects/patterns and then were asked to recognize them among new images. The objects and the patterns served as controls.
2. A Celeb experiment, in which subjects observed pictures of celebrities and were asked to recognize them.
3. Att Old/New experiment, where subjects performed the Old/New face experiment once again while their attention was directed to the eyes or to the mouth and nose of the observed faces.

Not surprisingly, results indicate that in the first two experiments subjects fixated mostly on the eyes, nose and mouth of the observed face. The location of fixations did not correlate with subjects' scores. However, directing attention to the nose and mouth resulted in reduced performance, while directing it to the eyes did not. In the Old/New face experiment, higher number of fixations during the study phase led to greater success in the test phase. Specifically, if a subject made more saccades on a specific face presentation in the study phase, he was more likely to recognize this face during the recognition phase. This was not true for the control (object /pattern) stimuli. To conclude, we found that when recognizing a face, attention to the eyes is essential, while attention to the nose and mouth is not. Furthermore, more saccades (during a fixed observation time) can lead to better face recognition.

Brain plasticity across a lifetime

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Studies in animal and human models have demonstrated that the mammalian brain is fundamentally plastic across the lifespan, and that all or nearly all plasticity mechanisms are, by their nature, reversible. We have documented the general reversibility of plasticity processes in two simple rat models. In the first, we broadly defined differences in the functional and physical brains of young vs old adults. By virtually every index, old brains were functionally and physically degraded (slower, less accurate, less reliable, noisier, demyelinated, connectionally simplified, disinhibited, etc.) re the young adult brain. We then trained old animals in simple ways that restored (reversed) ALL of the degraded functional and physical indices that characterized the old brain. In a second series of studies, we showed that strategies that substantially increased neural noise in the brain of an animal in the prime of life drove accelerated "aging" – or from another perspective (given the reversible nature of plasticity processes) drove the cortex backward in its functional and physical status, in an infant-ward direction. Two basic conclusions of these studies: 1) From the perspective of fundamental information processing in the brain, very old = very young. 2) Plasticity processes can drive rapid changes in a degrading or a refining direction, at any age in life.

Some of the important practical extensions of these studies shall be discussed.

A multifaceted action of dopamine on the GABAergic synapse on ventral tegmental area dopamine neurons

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Dopamine (DA) neurons in the ventral tegmental area (VTA) constitute the origin of major dopaminergic neural pathways associated with essential functions including reward, motivation and cognition. Hence, regulation of VTA DA neurons excitability is of important significance. Like other neurons, the activity level of VTA DA neurons is considerably determined by excitatory and inhibitory synaptic inputs.

Using rat midbrain slices we have previously found that DA causes an immediate inhibition of GABA receptor type A ($GABA_AR$) mediated evoked-IPSCs (eIPSCs), recorded from VTA DA neurons. The DA-induced inhibition probably results from the activation of presynaptic G-protein coupled inwardly-rectifying potassium (GIRK) channels associated with DA receptors type 2 (D2-like receptors).

Recently, a DA-induced enhancement, rather than inhibition, of $GABA_AR$ eIPSCs was detected. This effect was obtained in the presence of GIRK blockers, appears following DA washout and lasts for at least 20 minutes. Here again, D2-like receptors were found to mediate the eIPSCs enhancement. Moreover, under conditions of GIRK blockade, cocaine and GBR12909 affect the $GABA_AR$ eIPSCs as DA itself, and this DA-induced delayed enhancement probably results from activation of nitric-oxide (NO) signaling.

Taken together, a multifaceted action of DA on GABAergic synapse on VTA DA neurons is proposed. Hence, occurrence of an immediate short-duration inhibition or a delayed prolonged enhancement of $GABA_AR$ eIPSCs depends on the recording conditions. We hypothesize that

the DA-induced eIPSCs inhibition and enhancement may reflect different pathological conditions associated with elevation of DA level in the mesolimbic system. Surprisingly, both effects are localized to the presynaptic locus and involve activation of D2-like receptors. While the mechanism of the inhibitory effect involves the GIRK channels, the mechanism for the enhancement effect involves production of NO.

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TRP channels: what are they and why are they important as a new target for neuroprotection

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TRP channels constitute a large and diverse family of proteins that are expressed in many tissues and cell types. The TRP super-family is conserved throughout evolution from nematodes to humans. The name TRP is derived from a spontaneously occurring *Drosophila* mutant lacking TRP that responded to a continuous light with a Transient Receptor Potential (therefore, it was designated TRP by Minke). The *Drosophila* TRP and TRP-like (TRPL) channels, which are activated by the inositol lipid signaling cascade, were used later on to isolate the first mammalian TRP homologues. TRP channels mediate responses to light, nerve growth factors, pheromones, taste, mechanical, temperature, pH, osmolarity, vasorelaxation of blood vessels, metabolic stress and pain. Furthermore, mutations in members of the TRP family are responsible for several diseases. Although a great deal is known today about members of the mammalian TRP channels, the exact physiological function and gating mechanisms of most channels are still elusive. We discovered that the *Drosophila* TRP and TRPL are readily activated by metabolic stress. Accordingly, hypoxia rapidly and reversibly open these Ca2+ permeable channels and induces massive Ca2+ influx into the photoreceptor cells in the dark leading to toxic increase in cellular Ca2+. Furthermore, mitochondrial uncouplers or depletion of ATP in photoreceptor cells also induce this effect. Recent studies showed that two members of the mammalian TRP family, TRPM2 and TRPM7 are Ca2+ permeable channels, which are sensitive to oxidative stress and are modulated by PIP2. TRPM2 was shown to be activated by Aß and TRPM7 is crucial in neuronal cell death caused by oxidative stress. Together, TRP channels that are both Ca2+ permeable and vulnerable to ischemia constitute a new target for neuroprotecting drugs.

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Immunomodulation of experimental autoimmune Myasthenia Gravis by recombinant human alpha–fetoprotein

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Alpha-fetoprotein (AFP) is a 65KDa oncofetal glycoprotein found in fetal and maternal fluids during pregnancy. Clinical remissions during pregnancy have been observed in several autoimmune diseases, such as multiple sclerosis (MS), myasthenia gravis (MG), rheumatoid arthritis and thyroiditis, and are attributed to the immunosuppressive effect of AFP. Previous results in our lab showed that recombinant human AFP (rhAFP) markedly improved the clinical manifestations of experimental autoimmune encephalomyelitis (EAE), a T cell mediated disease that serves as a model for MS. RhAFP treatment reduced disease severity and CNS inflammation. In the present study, we tested the effect of rhAFP on experimental autoimmune MG (EAMG). MG is a B cell-mediated, T cell-dependent autoimmune disorder due to antibodies directed to the nicotinic acetylcholine receptor (AChR) at the post synaptic membrane. We examined the effect of treatment with rhAFP on EAMG in Lewis rats and c57bl mice. Daily treatment with 60ug/rat/day rhAFP starting from the appearance of the chronic phase reduced both disease severity and its incidence by 42% and 59% respectively. In addition, EAMG rats treated with AFP showed normal response (4.2+1.7%) to repetitive nerve stimulation, at 3 Hz, whereas control EAMG rats showed a mean decremental response of 18.8+3.2%. Furthermore, immunological examination indicated that rhAFP treatment reduced T-cell reactivity and inflammatory cytokine production both in the rat and mouse models. The ability of the natural protein AFP to affect the immune system makes it a potential candidate for treatment of MG and other autoimmune diseases.

(# equal contribution)

Pressure selective modulation of NMDA receptor subtypes' currents may reveal 3D structural differences

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Background: Divers exposed to hyperbaric pressure (HP) may suffer from cognitive and motor impairments, termed high pressure neurological syndrome (HPNS). This syndrome is associated with augmented responses of the

excitatory glutamatergic N-methyl-D-aspartate receptor (NMDAR). NMDAR is an ionotropic receptor constituted of different combinations of 'NR1' (1a, -1b, etc.) and 'NR2' (A-D) subunits. Presented are our analyses of HP effects on eight NMDAR subtypes. 3D model analysis of selected subtypes is discussed.

Methods: Xenopus laevis oocytes were injected with RNAs for expression of eight functioning NMDAR subtypes. After 3-5 day incubation, individual oocytes were placed in a recording chamber and perfused with frog Ringer's solution without Mg^{2+}. Oocytes were voltage-clamped at -70 mV. NMDAR currents were acquired under control (0.1-0.3 MPa) and HP (10.1 MPa, helium compressed) conditions at 25°C. 3D structure models of the external N-terminus domains (NTD) of NR1-1a+NR2A and NR1-1b+NR2A subtypes were created and compared

Results: At HP, only the NR1-1a+NR2A subtype ionic current was augmented and, surprisingly, NR1-1b+NR2A current was depressed. Both NR1-1a+NR2B and NR1-1b+NR2B subtypes were resistant to HP. Both NR1-1a+NR2C and NR1-1b+NR2C currents were significantly depressed by HP. NR1-1b+NR2D current was significantly reduced whereas NR1-1a+NR2D seems to be HP resistant. NR1-1a is 21 amino acids shorter than the NR1-1b, which is clearly observed in the superimposition 3D modeling.

Conclusions: These results support the notion that NMDAR subtypes' diversity and spatial distribution in the mammalian CNS may lead to selective effects of HP on different brain regions. Some brain areas/structures may be susceptible to the deleterious HP effects whereas other may be 'HP resistant'. 3D models analyses may provide initial clues for understanding the biophysical selective HP effects.

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Graphic processing unit (GPU)-based Wavelet analysis of rhythmic s-EMG data in spinal cord injury patients.

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The wavelet transformation (WT) and wavelet coherence (WTC) algorithms have been successfully used for nonstationary analyses of the output of spinal central pattern generators under different experimental conditions. The massive computing power required for these analyses imposes serious limitations on our ability to characterize the components of lengthy time-series in the time/frequency domain and examine linear and non-linear correlations between different frequency bands of these series. Here we show that these constraints are alleviated by a combined use of CPU computing and graphical processing units (GPU)-based parallel processing. GPU based analyses of long data stretches of surface EMG (s-EMG) signals recorded from flexors and extensors of the ankle joint in healthy subjects and spinal cord injury patients during various motor tasks, revealed locomotor and spastic-related components that exhibited slow systematic variations with time. Higher-order interactions were observed between 6-8 Hz spastic bursts (myoclonus) and body-weight-supported stepping-rhythm in spinally injured persons. Analyses of the s-EMG intensities calculated using wavelet techniques followed by principal component analysis (PCA), revealed similar spectral patterns in the gait cycle of healthy subjects and variable patterns in different spinal cord injury patients. Further studies are required to clarify whether the combined WT/PCA analyses of s-EMG signals are sufficient to detect and classify the type of damage inflicted on the spinal cord in different spinal cord injury patients.

Olfactory-learning induced enhancement of intrinsic neuronal excitability in basolateral amygdale neurons

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Rats trained in a particularly difficult olfactory-discrimination (OD) task demonstrate a dramatic increase in their performance capabilities once they have learned the task ('rule learning'). Pyramidal neurons in the piriform cortex (PC) and the hippocampus show enhanced intrinsic neuronal excitability during different stages of OD rule-learning, which last for several days in each area. While enhanced excitability occurs in hippocampal neurons during rule-learning only, it persists in the PC for as long as subsequent training in the task is continued. Enhanced intrinsic excitability is mediated by reduction in the post-burst after-hyperpolarization (AHP), which is generated by repetitive generation of action potentials.

The basolateral amygdala (BLA) is suggested to encode the motivational significance of olfactory cues and encode information used to guide goal directed behavior during olfactory-discrimination learning. Here we examine whether intrinsic neuronal excitability in BLA pyramidal neurons is also modified by OD rule learning and explore the time course by which such intrinsic neuronal modifications occur and then disappear.

We show that enhanced neuronal excitability and reduced post burst AHP occur in BLA neurons at a well distinguished stage; when rule learning is established, at the same time when similar modifications appear in the PC. However, intrinsic enhancement in BLA neurons lasts for 1 day only, outlasted by intrinsic modifications in PC neurons. We suggest that such intrinsic plasticity in BLA neurons enhances the BLA ability to signal the PC

regarding the value of correct performance in the olfactory maze, and is thus essential for achieving OD rule learning.

An exact statistical analysis of visual inference by a neural population amid eye movements

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Sensory information is generally corrupted by neural noise, but also by confounding signals. For example, research on high-acuity visual perception has focused on the limits imposed by variability of retinal spike responses. However, a second limit results from random eye movements during fixation. We study the effects of both sources of variability on Vernier hyperacuity in estimating a gap between two parallel bars presented simultaneously. Introducing a model of neural variability and eye movement statistics, we exactly derive the optimal estimator of the gap and compare its accuracy with psychophysical data. A main assumption of our model is that the brain estimates the eye position and the gap using exclusively the retinal ganglion cell spike trains. We calculate the exact joint probability distribution for the eye position and the gap in our model and derive the optimal Bayesian estimator. The estimator depends on one dimensionless parameter: the root mean squared displacement of the eyes between subsequent spikes in any two ganglion cells, divided by the receptive field width. For slow eye movements, the decoder uses all the spikes to estimate each bar's position. For fast eye movements, only near-synchronous spike pairs arising from the two bars are used. These spikes provide snapshots of the visual stimulus during brief temporal windows, minimizing blurring due to eye movements. The optimal estimator bounds the performance of biological neural systems on this task. We also construct simpler estimators that could be implemented by neural circuits and analyze their performance. By incorporating temporal filtering in spike generation, our model explains the psychophysical phenomena of Bloch's law, relating the Vernier threshold to stimulus duration and contrast. Our work provides insight into fundamental limitations imposed on the visual system by fixational eye movements and suggests how neural circuits of the visual system may cope with this challenge.

Swartz Program in Theoretical Neuroscience

Overlapping representation of perception and action in the human brain

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Mirror neurons are brain cells which respond not only when the animal performs a goal-directed action (e.g. grasping a peanut), but also when it perceives the same (or a similar) action performed by others. In experimental animals, such cells have been demonstrated in brain regions predominantly associated with motor output. Since the activity of these cells maps the perceptual attributes of actions performed by others onto the motor repertoire of the perceiver, they have been implicated in various behaviors such as learning by observation, and action understanding. In humans, however, despite indirect evidence suggesting the existence of neuronal networks with similar mirroring properties, direct evidence for mirror neurons was still lacking. In the current study, we recorded extracellular activity of cells in the medial frontal and temporal cortices of patients undergoing clinical evaluation for potential surgical treatment of epilepsy while they passively observed or actively executed goal-directed actions. Our results indicate that not only pre-motor brain regions, but also regions involved in perception and memory contain cells with mirroring properties. These findings in humans, suggest a widely distributed multimodal system for both integration and differentiation of perceptual and motor aspects of actions performed by self and others.

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Advances towards patterned ultrasonic neuro-stimulation

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Ultrasound, a non-invasive and widely used diagnostic modality, has also been shown to stimulate neuronal activity. We present our early work towards generating acoustic stimulation patterns, as required for the formation of a meaningful precept.

We adapted optical computer generated holography (CGH) algorithms from the field of optical field sculpting to pattern the ultrasonic (US) fields and assessed their performance via simulations and MR-thermometry. The new CGH-inspired algorithm resulted in more efficient and uniform generation of sparse patterns when compared to a predominant algorithm in the field of ultrasonic hyperthermia. A second version of the same algorithm succeeded in overcoming the difficulties in generating contiguous patterns as well. The achievable resolution of multiple spot-patterns is very similar to that of a single focal spot, on the order of 0.5 mm. These results also constitute a first step towards the design of ultrasonic neuro-prostheses.

Incensole acetate – a potential novel mood stabilizing agent

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Background: Mood disorders, specifically mania and depression, are extremely disabling psychiatric conditions with very high lifetime prevalence. Patients suffering from mood disorders often spend years switching from one medication to another, simply trading one set of side effects for another, without finding a solution which would enable them to enter the workforce and find their way in life. Furthermore, approximately 30% of the afflicted population does not respond whatsoever to the currently available therapies. Thus, there is a real need for alternatives to the drugs currently on the market.

Methods: In our laboratory we examine the therapeutic properties of Incensole Acetate (IA), which is a major component of Boswellia resin. Burning of Boswellia resin as incense has been part of religious ceremonies for millennia, and is believed to contribute to the spiritual exaltation associated with such events. It was shown recently that an acute IA administration causes anxiolytic- and antidepressive-like behavioral effects in wild-type Sabra mice. We evaluated the effect of IA upon behavior of selectively bred submissive animals using the dominant-submissive relationship (DSR) test to measure the chronic effects of mood stabilizers and antidepressants. We treated animals chronically with two doses of IA (1 and 5 mg/kg) for the three consecutive weeks. During the treatment period, animals' behavior was evaluated daily using the DSR test. RESULTS. We found that IA dose- and time-dependently reduced submissive behavior in comparison to the vehicle-treated controls. After the treatment period, the animals' blood corticosterone levels were evaluated. Both doses of IA significantly reduced corticosterone levels in comparison to control animals.

Conclusions: Our study demonstrates that Incensole acetate may represent a potential novel antidepressant with better efficacy and fewer side effects.

AdE-1, a novel Cardiotonic peptide from the sea anemone Aiptasia diaphana: chemistry and mode of action

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Heart failure (HF) is a syndrome that reduces quality of life and has a high mortality rate. The need for new pharmacology is urgent. Sea anemones (Anthozoa:Actinaria) are ancient predators which have developed chemical mechanisms that mediate their complex interactions in the marine environment. Aitasia diaphana is a sea anemone which can paralyze crustaceans, insects and fish but its sting evokes no sensation in humans. In this study we aimed to isolated cardiotonic peptides from Aiptasia diaphana, characterize its chemical properties and its physiological effects on isolated rat's cardiomyocytes. Column chromatography was used to fractionate proteins from the whole body crude water extract of the Aiptasia. The fractions were examined for their effects on cardiomyocytes contractility. Novel cardioactive peptide, AdE-1, with a molecular weight of 4907D was isolated. Full length cDNA encoding AdE-1 was identified by degenerate RT-PCR, 3' and 5'RACE. Amino acid (AA) sequence of the precursors was deduced from the cDNA sequence, revealed a 46AA leader and mature peptide of 44 AA which shares low sequence identity with other toxins identified to date. AdE-1 increases the amplitude and slows the relaxation velocity of cardimyocyte contractions. It prolonged the action potential (AP) and decreased its amplitude. AdE-1 inhibits Na+current inactivation and increases its amplitude and In contrast to other recognized toxins, it significantly increased the transient K+current's amplitude and shifted the current threshold to a more negative membrane potential. Collectively- AdE-1 prolongs AP duration, augments contraction and decreases AP amplitude of the cardiomyocytes, apparently by modulating the Na+and K+currents. AdE-1 is probably the first peptide to be characterized which increases the Na+and transient K+currents simultaneously. The chemical and physiological uniqueness of AdE-1 make it an invaluable research tool and potential target for drug development.

Neural adaptation in the auditory system: can it be a neural-correlate of habituation?

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Habituation, the decline in the behavioral response to a repetitive stimulus, is the most basic form of learning. Yet very little is known about its underlying mechanism. In many cases habituation is specific to the stimulus. At the neuronal level, stimulus-specific adaptation (SSA) is a phenomenon in which the response is decreased when the same stimulus is repetitively presented and recovers when a different stimulus is presented. Neural SSA resembles in many aspects the typical habituation pattern and thus may act as a basic neuro-correlate of behavioral habituation. However, a major caveat of this hypothesis is that SSA in the auditory system has been mostly demonstrated with stimuli presented at inter stimulus intervals (ISIs) of 1-2 sec. Behavioral habituation, on the other hand, is achieved to stimuli presented at intervals of tens of seconds to minutes. This dramatic time gap obscures the attempts to

link SSA with habituation. In the current research we aimed to overcome this gap by studying neural adaptation to stimuli with long ISIs. For this purpose, we presented sequences of sounds with ISIs of 10, 15 and 60 sec. We first report that the auditory responses of neurons in the optic tectum (a midbrain gaze control center) significantly adapt at all ISIs tested (up to 60 s). By presenting an alternating train consisting of two different stimuli we show that this adaptation is specific to the stimulus and therefore can serve as a neural-correlate of behavioral habituation. Second, we recorded from different areas along the auditory pathways and found no adaptation at long ISIs in the thalamo-fugal pathway but clear adaptation in the tectofugal pathway. The results suggest that the tecto-fugal but not the thalamo-fugal pathway is related to behavioral habituation in the owl.
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A triple urocortin knockout mouse model reveals an essential role for urocortins in stress recovery
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Responding to stressful events requires numerous adaptive actions involving integrated changes in the central nervous and neuroendocrine systems. Numerous studies have implicated dysregulation of stress-response mechanisms in the etiology of stress-induced psychopathophysiologies. The urocortin neuropeptides are members of the corticotropin-releasing factor family and are associated with the central stress response. In the current study, a triple-knockout (tKO) mouse model lacking all three urocortin genes was generated. Intriguingly, these urocortin tKO mice exhibit increased anxiety-like behaviors 24 h following stress exposure but not under unstressed conditions or immediately following exposure to acute stress. The inability of these mutants to recover properly from the exposure to an acute stress was associated with robust alterations in the expression profile of amygdalar genes and with dysregulated serotonergic function in stress-related neurocircuits. These findings position the urocortins as essential factors in the stress-recovery process and suggest the tKO mouse line as a useful stress-sensitive mouse model. The authors Neufeld-Cohen A. and Tsoory M. M. contributed equally to this study.

The toll of toll-like receptor 3 on cns plasticity and cognitive behavior in rodents and humans
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Toll-like receptors (TLRs) are a family of innate immune system receptors that respond to a variety of pathogen and tissue damage-related ligands. TLR signaling may play roles in the pathogenesis of stroke, Alzheimer's disease and multiple sclerosis and may also influence multiple dynamic processes in the developing and adult central nervous system including neurogenesis, axonal growth and synaptic plasticity. Using mice deficient for TLR3 (TLR3-/-), mice treated with intracerebroventricular infusion of TLR3-specific agonists, as well as lentiviral mediated over-expression and knockdown of TLR3, we have characterized the roles of TLR3 in mediating hippocampus-dependant cognitive learning and memory processes. TLR3 deficiency in mice resulted in enhanced hippocampus-dependent working memory in the Morris water maze, novel object recognition and contextual fear conditioning tasks. In contrast, intracerebroventricular infusion of a TLR3 agonist to the lateral ventricles resulted in impaired working memory. Additionally, TLR3 deficiency impaired amygdala-related behavior and anxiety in the cued-fear conditioning, open field and elevated plus maze tasks. We further investigated neuroanatomical and molecular changes in the hippocampus of TLR3-/- mice, and found that TLR3-/- mice exhibited increased hippocampal CA1 and dentate gyrus volumes, increased hippocampal neurogenesis and elevated levels of GluR1 in the CA1 region of the hippocampus. In addition, levels of active ERK and CREB were elevated in the hippocampus of TLR3-/- mice, suggesting that constitutive TLR3 signaling negatively regulates pathways known to play important roles in hippocampal plasticity. Similarly to rodents, in which genetic deletion of TLR3 enhanced working memory, humans with SNPs in different introns of their TLR3 gene showed altered performance in working memory tasks. Our findings reveal novel roles for TLR3 as a suppressor of hippocampal cellular-plasticity and working memory retention.

Neuro-imaging genetics studies in basal ganglia calcification as a model to understand brain resilience
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Imaging genetics is a promising strategy to integrate genotypic with phenotypic data and several studies already explored this approach in neuropsychiatric disorders. However, this methodology was limited used to explore the phenotypic variability of neuroimaging findings in familial idiopathic basal ganglia calcification (Fahr´s Disease). Idiopathic brain calcinosis presents a heterogeneous clinical profile, including a variable combination of motor and cognitive symptoms. Some individuals may be

symptom free despite having extensive deposits; however, symptomatic subjects have a significantly larger number of deposits in comparison to asymptomatic subjects. In this study we performed 3D models analysis from the 2D cross-section computerized tomography (CT) and Nuclear Magnetics resonance (NMR) images available from 6 families. Some of them were also genotyped for a candidate polymorphism.We have observed a constant autossomal dominant pattern of inheritance, additional evidence for heritability for lesions placement, and curiously, milder or absent symptoms in patients with cerebellum calcifications. Despite extensive calcifications in some asymptomatic cases, the apparent functionality of affected brain structures is remarkably efficient, suggesting an intrinsic compensation mechanism and also a threshold for triggering. Further case studies and genetics approaches are needed to elicit this and other important questions towards the explanation of the heritability for basal ganglia calcifications and its patterns of anatomical distribution. The study of new families with this condition will be crucial to confirm our findings.

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POm involvement in whisking control: an inactivation study

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Although functionally and anatomically segregated afferent pathways are known within the closed-loop of the vibrissal system, the overall circuitry of the system and its operational principles have yet to be determined. Each of the known afferent pathways of the whisking system synapses on a different nucleus in the thalamus (Yu et al., 2006). The paralemniscal system, carrying whisking signals, ascends through the posterior complex (POm) of the thalamus. In this study, the whisking behavior of freely-moving rats in a natural-like environment was recorded using high-speed, high-resolution videography at times prior to and following inactivation of the POm using a $GABA_A$-agonist, muscimol. Subsequent analysis of these videos showed that total whisking power between 5 and 25 Hz (the range of whisking frequencies for rats) declines significantly after inactivation of the POm in comparison to power levels before inactivation. Analysis of whisking trajectories revealed that the mean amplitude and duration of both protraction and retraction decreases significantly after POm inactivation. These effects depended on the concentration of muscimol; in spatial and concentration controls no significant effects were observed. These results suggest that the POm is part of the loop(s) that control whisking behavior.

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Mobilization of synaptic vesicles depends on synaptic vesicle endocytosis

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The synapsins are a multi-member family of phosphoproteins that interact with synaptic vesicles as well as with components of the cytoskeleton. They control the number and distribution of synaptic vesicles within the presynaptic terminal and influence synaptic vesicle dynamics. Consequently, they play an important role in the regulation of basic neurotransmission properties and of certain forms of short term synaptic plasticity. However, how they modulate synaptic vesicle clustering, and conversely, mobilization of reserve vesicles, remains unclear.

At rest the synapsins are clearly localized to synaptic vesicle clusters. However, it was shown that strong stimulation disperses the synapsins from the synapses into the axon, in parallel to the mobilization of reserve vesicles from the vesicle clusters. Because phosphorylation changes the affinity of the synapsins to the cytoskeleton, it has been assumed that this serves as a switch for vesicle mobilization. However, we now show that when neurons are rendered incapable of exocytosis by either Tetanus Toxin or by deletion of Munc13, the synapsins did not disperse from the presynaptic puncta during strong stimulation, even though they were phosphorylated. This indicates that phosphorylation of the synapsins is insufficient to induce vesicle mobilization, even though it does modulate the affinity of the synapsins to the cytoskeleton and to the vesicles. Furthermore, we find that blockage of endocytosis, without affecting exocytosis, also blocks synapsin redistribution, but not its phosphorylation. This suggests a vital role for endocytosis in synaptic vesicle mobilization process. We propose that endocytosis activates a signaling feedback route to the mobilization of the reserve pool.

Long-term effects of diisopropylfluorophosphate administration during pre-weanling period on fear behaviors in adult BALB/C and C57 mice

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The association between developmental neurotoxicity and organophosphate (OP) pesticide exposure in human is an important health concern. Irritability, depression, and anxiety were found after exposure to OP substances in

adults. In rodents perinatal exposure led to impulsive behaviour and sex-dependent changes in spatial and discrimination learning. Experimental studies in human and rodents have confirmed that a relatively short exposure to low doses of OP during perinatal periods can cause cognitive deficits. OPs act as acetylcholinesterase-inhibitors (AChE-I). The developing brain may be particularly vulnerable to OPs, because of the role of acetylcholinesterase (AChE) on neuronal development and the effects of cholinergic pathways on the behavioral and hormonal response to stress. In addition, a growing body of evidence has shown that exposure to AChE-Is or stress induce the expression of the rare 'readthrough' splice variant of AChE, AChE-R and may play a role in modulating the fear response.

Two strains of mice, BALB/C and C57, which differ markedly in emotionality, were pretreated with 1 mg/kg of diisopropylfluorphosphate (DFP), a cholinesterase- inhibitor or saline on postnatal days 4-10. Pavlovian fear conditioning was tested in adult mice of both sexes at 3-5 months.

BALB/C and C57 showed differences in context and cue related fear acquisition and retention. DFP pretreatment enhanced freezing in BALB/C males compared to saline-treated mice. Induction of AChE-R splice variants was examined in the cortex and hippocampus using real time PCR. BALB/C pre-treated with DFP showed relatively low levels of both AChE-R (and AChE-S) splice variants in the cortex compared to BALB/C pretreated with saline. However, in the hippocampus these pretreated mice showed a high level of AChE-R mRNA expression compared to BALB/C pretreated with saline or C57 pretreated with DFP. The strain difference in fear conditioning may be associated with AChE-R splice variant expression.

A body-part map in the occipito-temporal cortex

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Large-scale topographic representations of the body have long been established in the somatosensory and motor cortices. Using converging fMRI methods, we identified a topographically organized body-part map within the occipito-temporal cortex (OTC), with distinct clusters of voxels showing clear preference for different visually presented body-parts. In a phase-encoding experiment participants viewed a "double-wedge", rotating around the central fixation , which contained pictures of five different body parts (faces, necks, upper limbs, trunks, lower limbs) presented sequentially in a fixed order. Cross-correlation was applied in order to identify voxels showing preference for a specific body-part. To corroborate the body-part map we used a standard block-design paradigm, while pictures of different body-parts and their scrambled versions were presented centrally.

To further verify that the body-part specificity is robust and did not merely reflect shape differences between categories we divided each of our original body categories into two finer body-parts, which are distinct in shape from one another (e.g. hands and elbows as sub-parts of the upper limb, knees and feet for the lower limb , lips and chin for the lower face, etc.). We found that a voxel's response to one sub-category (e.g. hand) highly predicted the response to its paired member (i.e., elbows), suggesting that the body-part preference of a given voxel was not determined by its selectivity to a particular shape.

Finally, execution of (unseen) movements with different body-parts resulted in a limited topographic representation of the limbs and trunk, which partially overlapped with the visual body-part map. This motor-driven activation in the OTC could not be explained solely by visual or motor imagery of the body-parts. This suggests that visual and motor-related information converge within the OTC in a body-part specific manner.

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Sculpting the hippocampal cognitive map: experimental control over the coded parameter space

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Although much work in the field of reinforcement learning has been devoted to understanding how animals and humans learn to perform the best action in each state, strikingly scant work targets the question of what constitutes such a state. In initial phases of learning, an animal or a person cannot know which facets of its rich experience should be attended to in order to identify their 'state'. Here we focus on parameter coding by hippocampal primary neurons. The hippocampus serves an important role in learning and memory. In humans, it is associated with declarative episodic memory. Single unit recordings of hippocampal neurons in freely behaving rats have shown that many of them act as place-cells, confining their firing to well-defined locations in space. We recorded the activity of hippocampal primary neurons in a specially devised olfactory space, in which rats foraged for reward based solely on olfactory cues and studied the dependence of the activity of these neurons on their availability. We show that classical place-cells perform superb encoding of olfactory space, when this is the only reference frame that is relevant for reward collection. Furthermore, the same cells shifted

their firing fields from room coordinates to olfactory coordinates as animals learned to rely on them in order to obtain reward.

What can non-invasive neuroimaging teach us about learning in the brain?

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Background Learning durably reorganizes ongoing brain activity to improve fitness and efficiency. Behaviourally, this reorganization is often associated with dynamical features such as spacing effects, history-dependence, and intermittency. Lately, non-invasive neuroimaging studies in humans have started investigating the neural correlates of learning from a system level perspective. These studies showed some forms of brain activity reorganization, but learning was not described as a process at the time scales at which it occurs. Results could not directly account for observed dynamical features and had no predictive value.
Methods We propose to characterize learning-related brain dynamics with observable functions of brain activity having explicit physical meaning. The brain is thought of as an out-of-equilibrium system subject to energy, entropy, and information fluxes, showing complexity at multiple spatial and temporal scales. At the time scales typical of some forms of learning, brain activity displays *glassy* properties viz. relaxation times much larger than typical experiments' durations, non-Gaussian scale-free statistics, long-term memory, aging, and metastable dynamics. Learning fulfils its main functions by acting on these glassy properties. Dynamical, statistical, topological, and thermodynamical aspects of learning-related reorganization can be described using non-invasive neuroimaging data by defining: i) functionally motivated order parameters through which learning-induced brain activity becomes observable; ii) phenomenological dynamical models capable of generating known learning properties; iii) numerical methods to quantify order parameter's dynamics.
Conclusions Non-invasive neuroimaging techniques can be used to describe the learning process, even at time scales much larger than the typical experiments' duration, but also to assess prior learning, and predict individuals' potential for future learning.

Mechanisms of magnetic stimulation of single neurons

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Transcranial magnetic stimulation (TMS) is a noninvasive method in which a magnetic coil generates a magnetic field in an area of interest in the brain. This magnetic field induces an electric field that modulates neuronal activity. The spatial distribution of the induced electrical field is determined by the coils geometry and location. While TMS has been used for several decades, the biophysical basis underlying the stimulation of single cells in the central nervous system (CNS) remains unknown. To address this problem we developed a numerical scheme enabling us to combine magnetic stimulation (MS) with compartmental modeling of neurons with arbitrary morphology. The induced electric field for each location in space around the simulated neurons was numerically calculated. This spatial electric field was combined with standard compartmental modeling software to calculate the membrane current generated by the magnetic field for each segment of the neuron. In agreement with previous studies, the simulations suggested that peripheral axons were excited by the spatial gradients of the induced electric field. However, our simulations show that the effect on peripheral nerve differs from the effect on CNS neurons. Stimulation of CNS neurons was induced by depolarization of the soma followed by initiation of an action potential (AP) in the initial segment of the axon. This mode of activation is very similar to neuronal stimulation by intracellular current injection at the soma, due to soma size. The simulations predict that neurons with low current threshold will be more susceptible to magnetic stimulation. Moreover, our simulations suggest that dendritic regenerative mechanisms will not be triggered directly by MS. Thus, our results may be relevant for the design of multi- intensity TMS protocols, may facilitate the construction of modern magnetic stimulators, and may aid the interpretation of results obtained following TMS of the CNS.

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Preattentive processing of statistical properties of the visual scene in patients with unilateral spatial neglect

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Chong and Treisman (2003, 2005, 2008) found that people judge the mean size of a set of circles as quickly and accurately as that of a single item, suggesting that statistical properties may be processed without focused attention. The lack of awareness of left-side input in cases of Unilateral Spatial Neglect (USN) has been attributed to an inability of focusing attention to the left side, suggesting that the processing of statistical properties may be spared. Five USN patients and five controls compared size of a reference circle to a single circle or to the average size of a briefly

presented cloud of circles in either the right or left visual fields or spanning both sides. When spanning both sides, their separate averages were either identical or different (difference from reference in ratio 1:4), with the 'different' condition used to assess relative impact of each side in judging the mean. USN patients were able to make comparisons and average size in either hemifield, though their left-side performance was somewhat degraded. In the spanning condition, while the controls indeed averaged across sides, lowering their threshold, patients showed a higher threshold when needing to depend on the left side of the cloud (when the right-side cloud was closer to the reference). However, they did use both sides of the cloud so that their spanning-condition thresholds were intermediate between those of controls and those expected if they attended only to the right side. We conclude that USN patients perform a weighted average across sides, giving double weight to the right side, perhaps due to "extinction". The ability of USN patients to extract the statistical properties of the visual scene on the neglected side points to a relatively spared spread-attention mechanism serving this operation.
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"All Chinese do not look alike": A short perceptual training improves recognition of other-race faces

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It is well established that recognition of faces of other races is much poorer than recognition of own-race faces (e.g., worse recognition of Asian faces by Caucasian individuals). The current experiment examined whether short individuation training may improve recognition of other race faces. During training subjects were asked to learn the names of 18 Chinese faces. Training included five stages that were given on 3 consecutive days, 20-30 minutes on each day. In the first stage subjects were asked to memorize the name of each face. In a second stage they were asked to press the first letter of the name that was presented on the screen. In the third stage subjects were asked to perform a sequential matching of a face to a name and got feedback for incorrect responses. In the fourth stage they were asked to perform the same discrimination task without feedback. In the fifth stage subjects were presented with a name followed by one of the faces and had to decide whether they are matched or not. During the first two days subjects learned the names of 9 faces and during days 2 and 3 of 9 additional faces. Before and after training, subjects performed an old-new recognition task with Caucasian and Chinese faces. Performance for Caucasian faces was significantly better than Chinese faces before training. Following training recognition of the trained Chinese faces was much better than recognition of Caucasian faces. Importantly, recognition levels were also better for novel Chinese faces that were not presented during the training session than of Chinese faces before training. Our findings show that short individuation training with relatively small number of faces can improve recognition of other race faces. The effect of training on eye movements during recognition of own and other race faces is currently investigated to explore possible strategies that may be beneficial for improved face recognition abilities.
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Association between DRD4 polymorphism and self-report dispositional-envy

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Envy is a competitive emotion speculated to involve an interaction between two different neural networks: The mentalizing network, which processes the other's mental and emotional state, and the reward system, which mediates motivation and the experience of pleasure and displeasure. In line with this, we have recently demonstrated that envy involves activation in regions related to the reward system (Dvash et al., in press). Given the well-established role of Dopamine in reward processing and in social cognition, it may be speculated that envy is modulated by the dopaminergic system.

The dopamine D4 receptor (DRD4) is highly distributed in prefrontal and limbic regions. The 48 bp VNTR in the DRD4 exon III varies between 2 and 11 copies, with the 4-repeat being the most common in Caucasians (Vallone, Picetti, & Borrelli, 2000). The 7-repeat has been associated with novelty seeking, extraversion and ADHD, in some but not all studies. In the present study 115 participants were genotyped for DRD4 exon III polymorphisms, using PCR amplification and gel electrophoresis to analyze the genotype. Participants completed a self-report single-factor Dispositional Envy Scale (DES), measuring individual differences in the tendency to envy (Smith et al., 1999), and a nonverbal task of social cognition. The results indicated that DRD4-7 participants rated themselves as less envious than the DRD4-not-7 participants. Additionally, DRD4-7 participants were less accurate in the understanding non-verbal social cues. These findings suggest that the DRD4-7 allele, which has been related to a less functional dopamine receptor (Asghari et al., 1995) and the efficiency of receptor maturation (Van Craenenbroeck et al., 2005), may be associated with imbalanced reward system and impaired mentalizing abilities which may explain the lower levels of envy ratings reported here.

Motor system contributions to our understanding of others: evidence from EEG activity in the mu frequency range

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Motor actions suppress EEG activity over the sensory-motor cortex, in a frequency range between 8-12 Hz. This modulation has been labeled mu-suppression, to distinguish it from the modulation of alpha oscillations in the same frequency range, which reflects reactivation of the cortex by any type of visual input that captures attention. Mu-suppression is induced not only by actual movements but also while the participant observes actions executed by someone else. This characteristic putatively associates the mu rhythms with the Mirror-Neurons System, which, in humans, has been suggested to contribute to social skills abilities. In this talk, I will present data from different experiments, relating mu suppression to social interaction skills such as understanding others' intentions, interacting in a social game, and empathizing with others in pain. These data were collected in EEG experiments with university students (24-30 participants in each experiment), and mu suppression was measured compared to a base line of viewing a rolling ball. In addition, I will present data showing the effect of Oxytocin, a neuropeptide hormone which has been linked with a wide range of human social cognitive functions, on EEG suppression in the mu/alpha and beta bands. In concert, these data suggest that the motor system, reflected by mu suppression, is involved not only in action perception and execution but also in higher social cognitive processes such as mediating our understanding of others.

The emotional valence of a conflict: implication from synesthesia

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According to synesthetes' reports, synesthesia involves an emotional experience in which a conflict between the photism and presented color of a stimulus may evoke a feeling of discomfort. In order to investigate the impact of this experience on performance, two experiments were carried out. Participants were presented with stimuli (numerals or words) in colors and were asked to name the color of the stimulus and to ignore its meaning. Not surprisingly, an incongruent color (e.g., 5 presented in yellow to a synesthete that sees 5 in red) slowed down color naming. Conflict situations (e.g., a numeral in an incongruent color) created a negative emotional experience. Most importantly, coherence between a conflict or non-conflict emotional experience and the emotion elicited by the color of the stimulus for a given synesthete, modulated performance. In particular, synesthetes were faster in coherent than in incoherent situations. This research contributes to the understanding of emotional experience in synesthesia, and also suggests that synesthesia can be used as an instrument to investigate emotional processes in the wider population.

Influence of abstinence and intervals between extinction trials on the expression of cocaine conditioned place preference

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Drug seeking can be triggered by exposure to cues previously paired with the drug. Disruption of such association can be an effective means to decrease relapse. Conditional place preference (CPP) is a widely used behavioral model based on associative learning, and it is subject to extinction. In this study we aimed to determine the effects of different drug-free periods on cocaine-CPP in rats with or without non-reinforced exposure to drug-associated stimuli. Male-Sabra rats were trained for cocaine-CPP (5, 10 or 15 mg/kg,i.p.) in CPP apparatus. Prior to conditioning the rats were allowed to freely explore the apparatus, and the compartment which was inpreferable was chosen to be paired with cocaine. During 8-days conditioning rats have received 4 injections of cocaine and 4 of saline alternatively. Different groups (n=6-16) have been tested in a drug-free state 1 to 3 times following conditioning. The CPP score was calculated and CPP consider to be extinguished if mean CPP-score did not differ significantly from 0. All groups of rats treated with 10 mg/kg or 15 mg/kg cocaine displayed high and equal magnitude of CPP in the first test made 1, 4, 7 or 14 days following conditioning. The group treated with 5 mg/kg expressed the same rate of CPP at an interval of 1 day, but clear decline on 14 day. Rats treated with any dose being tested three times, at the intervals of 1-4-7 days or 1-7-14 days did not display CPP on the third test. We also found that CPP after treatment with 10 mg/kg or 15 mg/kg cocaine has already been extinguished in the second test, but only for an interval of 1-14 days. Reinstatement of drug seeking in response to conditional cues was evident at least two weeks after conditioning for the higher doses of cocaine. Extinguished CPP can be obtained after a single extinction trial made closely to the original training and followed by prolongs abstinence. However, with low dose of cocaine, abstinence alone may be sufficient to disrupt drug-cue association.

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Viewed actions are mapped in retinotopic coordinates in the human visual pathways

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Viewed object-oriented actions (such as grasping a mug) elicit widespread fMRI activation in the dorsal and ventral visual pathways. Previous studies showed that this activation was noticeably stronger in the hemisphere contralateral to the visual-field in which action was seen. However, since participants kept fixation at the same screen position throughout the scan, it was impossible to infer if the representation of viewed actions is in a retina-based coordinate system, or a more elaborated one. Here, we address this issue by instructing participants to change their gaze between experimental conditions, such that some conditions shared the same retinotopic coordinates (but differed in their screen position), while other pairs of conditions had the opposite trait. The degree of similarity between the patterns of activation elicited by the various conditions was assessed using multi-voxel pattern analysis methods. Regions of interest, showing robust overall activation, included the intraparietal sulcus (IPS) and the Lateral Occipital Complex (LOC). In these extensive areas, the correlation between patterns of activation for conditions sharing the same retinotopic coordinates was significantly higher than those having different retinotopic coordinates. In contrast, the correlations between activation patterns for conditions with the same spatiotopic coordinates were not significantly greater than for non-spatiotopic conditions. These results suggest that viewed object-oriented actions are likely to be in retinotopic coordinate frame of reference.

Antagonistic relationship between gamma power and evoked potential revealed in human visual cortex

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Recently scalp magnetoencephalography (MEG) studies using the "double pulse" paradigm revealed a rapid evoked response adaptation where one visual stimulus suppresses the evoked response (ERP) to the second stimulus. We investigated this effect using subdural intracranial recordings in humans (ECoG). Our results show that the suppression of the ERP does not involve a reduction in neuronal activity - since gamma band responses remained unaffected. Rather, the ERP suppression was tightly related to the level of gamma activity preceding the event, and this effect was independent of the interstimulus interval. We propose that the ERP suppression is due to a desynchronization of neuronal firing resulting from recurrent neural activity in the vicinity of the freshly stimulated neurons and not an attenuation of the overall neural activity. This evoked potential suppression (EPS) effect can threfore serve as a robust marker for gamma-band activity even in non-invasive scalp EEG recordings. Due to its neuronal selectivity the EPS could provide a unique tool to study the tuning properties of human cortical sub networks.

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Dark exposure in adulthood lowers the threshold for visual perceptual learning in a rodent model of severe amblyopia

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A significant reduction in synaptic plasticity over cortical development, and a considerable degradation of feed-forward excitation resulting from chronic disuse are the primary obstacles to recovery from severe amblyopia. We have recently used a rodent model to demonstrate that chronic monocular deprivation, from eye opening to adulthood, induces severe amblyopia and decrease in excitatory synaptic density in the visual cortex. Nonetheless, stimulation of the chronically deprived eye continues to evoke physiological responses in the primary visual cortex. although single unit activity has lost orientation tuning and evoked synaptic potentials are unreliable and rapidly fatigue. Dark exposure initiated in adulthood can be used to reactivate robust ocular dominance plasticity in the visual cortex, which promotes the recovery from severe amblyopia. Chronic monocular deprivation followed by dark exposure and reverse deprivation stimulates the slow recovery of spatial acuity, which can be accelerated by repeated daily exposure to a two-choice spatial discrimination task. The speed of the recovery is controlled by the number of repetitions of the task, while the magnitude of the recovery is determined by the age at initiation of the chronic monocular deprivation. Remarkably, the recovery in spatial acuity is not restricted to the orientation of the visual stimulus used in the discrimination task. No emergence of spatial acuity is observed in subjects that receive chronic monocular deprivation, but do not receive dark exposure before reverse deprivation. This suggests that dark exposure lowers the threshold for perceptual learning, and that dark exposure and reverse deprivation encourage the transfer of perceptual learning to other features of the visual stimulus.

The therapeutic impact of Exendin-4 on cognitive and behavioral impairments in mice following mTBI

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Traumatic Brain Injury (TBI) affects 1.4 million people annually in USA, causing substantial suffering, currently with no effective treatment. Mild traumatic brain injury (mTBI) is a common neurological event, which exists in 75% of the TBI patients. Previous experiments from our lab have shown that mTBI may lead to short and long-term cognitive, emotional, and behavioral deficits. In the present experiments we examined the neuroprotective properties of Exendin-4 (Ex-4) on cognitive performances following mTBI in mice when Ex-4 was given post trauma. Ex-4 is a 39 amino acids, Glucagon-like peptide-1 receptor (GLP-1R) agonist, that increases the anti-apoptotic pathways. Previous studies have shown that GLP-1 protects hippocampal neurons from apoptosis, and enhances associative and spatial learning. The non-invasive closed-head weight drop model was used to induce mTBI utilizing a 30 gr. weight. ALZET osmotic mini pumps were implanted subcutaneously in mice immediately after the trauma. Behavioral tests were conducted at two time points, 7 and 30 days post trauma using the "Novel object recognition", the "Y maze" and the "Passive avoidance". The mice subjected to mTBI showed impaired cognitive behaviors that were improved following administration of Ex-4. MTBI mice exhibited impairments in visual and spatial memory, which were corrected when Ex-4 was administrated post-trauma. No statistical differences were found between groups at the "Passive avoidance". These findings may offer a new potential therapeutic way to treat damages caused by mTBI. Presumably, the neuroprotective effect that was obtained is due to the binding of Ex-4 is to the GLP-1 receptor, hence generating a cascade that eventually leads to cell survival and neurite outgrowth. Further studies will investigate this disorder for a better understanding of the mTBI and Ex-4 mechanism.

Signalling by the GnRH receptor: role of protein kinase C

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GnRH is the first key hormone of reproduction. GnRH analogs are extensively used in in vitro fertilization, and treatment of sex hormone-dependent cancers, due to their ability to bring about 'chemical castration'. The interaction of GnRH with its cognate type I receptor (GnRHR) in pituitary gonadotropes results in the activation of Gq/G11, phospholipase Cβ (PLCβI), PLA2 and PLD. Sequential activation of the phospholipases generates the second messengers inositol 1, 4, 5-trisphosphate (IP3), diacylglycerol (DAG) and arachidonic acid (AA), which are required for Ca2+ mobilization, the activation of various protein kinase C isoforms (PKCs) and the production of prostaglandin (PG) and other metabolites of AA, respectively. PKC isoforms are the major mediators of the downstream activation of a number of mitogen-activated protein kinase (MAPK) cascades by GnRH, namely: extracellular signal-regulated kinase (ERK), jun-N-terminal kinase (JNK) and p38MAPK. The use of selective inhibitors and dominant negative plasmids for the various PKCs has revealed that PKCβII, PKCδ and PKCε mediate ERK2 activation by GnRH, while, PKCα, PKCβII, PKCδ and PKCε mediate ERK2 activation by PMA. Also, PKCα, PKCβII, PKCδ and PKCε are involved in GnRH- and PMA-stimulation of JNK-1 in a cell-context dependent manner. We present preliminary evidence that persistent vs. transient redistribution of selected PKCs, or re-distribution of a given PKC to the perinuclear zone vs. the plasma membrane may dictate its selective role in ERK, or JNK activation. The activated MAPKs initiate the transcriptional activation of the gonadotropin subunit genes and the GnRHR.

Cannabinoid receptors activation and glucocorticoid receptors deactivation in the amygdala block the effects of stress on a negative learning experience

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The enhancement of emotional memory is clearly important as emotional stimuli are generally more significant than neutral stimuli for surviving and reproduction purposes. Yet, the enhancement of emotional memory following exposure to stress may result in dysfunctional or intrusive memory that underlies several psychiatric disorders.

Presenting a decrease in the magnitude of the expected quantity of reinforcements in an alley maze creates a psychological state of frustration and arousal that is manifested by increased secretion of peripheral hormones and decreased levels of motivation and behavioral responding. Here, we were interested to examine whether (i) exposure to a stressful event would enhance the consolidation of a negative learning experience of frustration and (ii) cannabinoid receptor agonist and glucocorticoids receptors (GRs) antagonist administered into the rat basolateral amygdala (BLA) could prevent this stress-induced enhancement.

We found that exposure to stress enhanced the consolidation of a frustrating learning experience, and that microinjecting the GR antagonist RU-486 (RU; 10 ng/side) or the CB1/CB2 receptor agonist WIN55,212-2 (WIN; 5 μg/side)

into the BLA prevented the stress-induced enhancement of memory consolidation for a frustrating learning experience. This suggests that exposure to stress enhances the consolidation of a frustrating learning experience and that cannabinoids and GRs in the BLA are important modulators of these stress-induced alterations.

Central pattern generator networks and their interaction in the locust stomatogastric nervous system

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The insect stomatogastric nervous system (STNS) is comprised of a set of inter-connected small ganglia, which controls foregut movements during feeding and ecdysis-related air swallowing behaviors. The complex motor patterns constituting these behaviors are the result of interactions among distinct but functionally related central pattern generator circuits (CPGs), each having the ability to produce a variety of different motor patterns depending on sensory and modulatory inputs. Our work provides insights into the neuroanatomy and neurophysiology of the STNS of the desert locust, Schistocerca gregaria. We identified rhythmic patterns endogenous to both, the frontal ganglion (FG), a major source of innervation to the foregut, and the hypocerebral ganglion (HG), which is connected to the FG and innervates the crop. Furthermore, we investigated functional interactions between the pattern of rhythmic movements of mouth appendages, governed by the sub-oesophageal ganglion (SOG), and foregut movements. Neuromodulatory-Induced SOG fictive feeding patterns had an indirect excitatory effect on spontaneous FG rhythmic activity in fully isolated and inter-connected Brain-SOG-FG preparations. Correlation between fictive motor patterns of the two ganglia was demonstrated by simultaneous changes in burst frequency. These interactions were found to be mediated by the brain. Hence our work demonstrated the presence of CPG networks in the STNS and indicated on intricate neuromodulation-mediated circuit interactions, in the absence of sensory inputs. These may be instrumental in generating the complex rhythmic motor patterns of the mouthparts and gut muscles during locust feeding or ecdysis-related air swallowing. Ongoing work further characterizes the locust STNS networks, their modulation and interactions in different behavioral contexts.

Long lasting glutamatergic modulation induced byneonatal GABA enhancement in mice hippocampus

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The role of GABA in neuronal circuit formation is related to its depolarizing action, supporting activity dependent synaptogenesis. We hypothesize that elevated levels of GABA in the immature brain may modify synaptogenesis in excitatory synapses and consequently behavior. In support of this theory, we have previously shown that neonatal exposure to a GABA-transaminase inhibitor Vigabatrin (GVG) during the switch in GABA function from a depolarizing to a hyperpolarizing substance modifies the expression of presynaptic proteins and suppresses excitatory synaptic potentials. Here, we examined the effect of GVG applied during postnatal days 4-14, on postsynaptic elements of the excitatory synapses. GVG 50 mg/Kg or saline (Ct) were applied daily to balb/c newborn mice. Key molecules in the glutamatergic synapse were analyzed by western blot and real-time PCR.

Similar level of the AMPAR subunits GluR2-3, GluR1 and pGluR1 were obtained in the crude cytoplasmic fraction (S2) of GVG and Ct groups. Lack of change was observed for the NMDAR NR2A subunit, while decrease in NR2B level was found for the GVG vs. Ct group (37%, $p<0.05$). To gain information on the subcellular distribution of these proteins the plasma membrane enriched fraction was analyzed; neonatal GVG treatment reduced the ratio of GluR1/GluR2 (67%, $p<0.01$), in appose to unchanged ratio of NR2A/NR2B in the GVG group compared to Ct. GVG effect on the subunits ratios was maintained in cytoplasmic mRNA expression.

Several regulatory proteins involved in glutamate receptors expression and localization analyzed in synaptoneurosomes revealed a global modulation due to GVG treatment, as shown by increased levels of PSD95 ($p<0.05$), PKA (135%, $p<0.05$), g,d and a CAMKII (176%, $p<0.01$; 148%, $p<0.01$; 135%, $p<0.01$, respectively), GluR1 (197%, $p<0.01$) and GluR2 (154%, $p<0.01$) compared to Ct.

The data support the involvement of GABA in the long-term regulation of the glutamatergic synapse.

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Are all judgments created equal? An fMRI study of semantic and episodic metamnemonic predictions

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Metamemory refers to the ability of individuals to monitor and control their own memory performance. Although little theoretical consideration of the possible differences between the monitoring of episodic and of semantic knowledge has been published, results from patient and drug studies that used the "feeling of knowing" (FOK) paradigm show a selective impairment in episodic monitoring but not in its semantic counterpart. Similarly, neuroimaging studies provide indirect evidence for separate patterns of activation during episodic or semantic FOKs. However, the semantic-episodic distinction hypothesis has not been directly addressed. In the current event-related fMRI study, we used a within-subject, within-experiment comparison of the monitoring of semantic and episodic content. Whereas the

common neural correlates of episodic and semantic FOKs observed in this study generally replicate the previous neuroimaging findings, several regions were found to be differentially associated with each task. Activity of the right inferior frontal gyrus was modulated by the semantic-episodic factor only during the negative predictions of retrieval, suggesting that negative predictions are based on partially distinct mechanisms during each task. A posterior midline network, known to be activated during episodic retrieval, was activated during episodic and not semantic monitoring, suggesting that episodic FOKs rely, to some extent, on common episodic retrieval processes. These findings suggest that theoretical accounts of the etiology and function of FOKs may benefit from incorporating the prediction directionality (positive / negative) and the memory domain (semantic / episodic) distinctions.

A method to study synchronized synaptic input to a single neuron for long time scales

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While synaptic dynamics between stimulated neuron and responding postsynaptic potentials has been studied extensively, long-term functional interactions between polysynaptic input to a neuron and its response action potential are yet to be analyzed. Therefore we wanted to design a method to investigate the dynamics of neuronal response to synchronous input from a large synaptic population that can be monitored over extended timescales. By electrical stimulation of cultured neuronal networks and recording of their response spikes with micoelectrode arrays (MEA), two types of early (<15 ms) neuronal responses can be evoked: (i) Extremely reliable spikes with high temporal precision (jitter <0.1 ms) that were described previously to be generated by direct stimulation of a neuron, and (ii) spikes with high reliability and lower temporal precision (jitter ˜1 ms). In this work we show that these are synaptically mediated responses. Unlike direct responses, early synaptically activated spikes are modified by application of synaptic blockers; as blocker concentration is increased, response latency becomes higher and jitter increases. At even higher concentrations, response probability gradually decreases until spike generation is completely abolished. Thus, changes in the synaptic population input are expressed in the response latency and probability of these neurons. The response characteristics to different stimulation amplitudes and frequencies provide further insight into synaptic population dynamics. Synaptic response latency decreases with increasing stimulation amplitude, probably due to stronger activation of the synaptic population. Continuous stimulation of these neurons results in increased response latency, already at low frequencies (1-0.25 Hz), where direct response latency is barely affected. In conclusion, the early synaptic responses in neuronal cultures offer an accessible experimental system for the study of synaptic population input in a controlled manner.

Effects of odor enrichment on microglial number and morphology in the olfactory bulb

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Over the last decade, it became evident that microglia play a dual role in adult hippocampal neurogenesis: During neuroinflammatory conditions activated microglia were implicated in neurogenesis suppression, whereas during normal quiescent conditions microglia were shown to promote neurogenesis following exposure to enriched environment. To explore the generality of the latter finding, we examined the number and morphology of microglia in the olfactory bulb (OB), following 40-days odor enrichment, during which adult male mice were exposed daily to one of 20 odorants. To facilitate this examination, we used mice with microglial-specific transgenic expression of green fluorescent protein (CX3CR1-GFP mice). The results show that at the completion of the enrichment period, enriched mice displayed significantly improved odor recognition memory. Specifically, they could recognize a test odorant for up to 240 min after its first presentation, as compared with only 30 min in controls. The number of new neurons within the OB, assessed by BrdU administration on day 21 of the enrichment, was greater in the enriched, as compared to non-enriched mice. The number of microglia, assessed by enumerating GFP-labeled cells, as well as cells labeled with the microglial activation marker Iba-1, was similar in the enriched and control groups. Moreover, microglial morphology (length of the processes) and proliferation (GFP/BrdU double-labeling) was also comparable in the two groups. The results suggest that in contrast with the effects of environmental enrichment on hippocampal microglia, there are no effects of specific sensory (odor) enrichment on microglia in the OB

Auditory aversive learning increases discrimination thresholds

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Animal studies of discriminative fear-conditioning traditionally employ stimuli that are remote in physical features and hence easily distinguished perceptually. Independently, human studies have shown that training mostly improves discrimination thresholds. We combine these paradigms and show that aversive learning actually induces an increase in discrimination thresholds, and that subjective aversion during conditioning predicts the individual threshold change. This counterintuitive performance deterioration occurs when using odors or sounds as aversive reinforcers,

and is not due to attentional distraction or decision bias. In contrast, positive reinforcement or mere exposure induce the typically reported decrease in thresholds. Our findings show that aversive outcomes induce wider stimulus generalization by modulating perceptual thresholds, and hence indicating the engagement of low-level mechanisms. We suggest that for risk- or loss-related stimuli, less specificity could be a benefit, because it invokes the same mechanisms that respond fast and efficiently in the face of danger.
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Holographic optogenetic control of neural activity in the retina

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Background: Direct optogenetic stimulation has recently been introduced as an alternative method for temporally precise, minimally-intrusive control of neurons. Up to now, targeted activation was enabled by targeted gene expression of light sensitive channels in specific cell types excited using full field stimuli. In our work we developed and applied a new optical method based on digital holographic projection that in conjunction with genetic techniques enables a precise control of light sensitive neurons in an intact tissue.
Methods: This method enables high temporal precision (msec) and efficient use of light power because the use of phase-modulating spatial light modulators (SLMs) and light diffraction allows an efficient use of input light. Our system directs light from a blue laser onto a Ferroelectric liquid crystal SLM that displays binary holograms. Light patterns are coupled into the camera port of an inverted microscope and projected onto retinas, whose responses are measured using a Multi-Electrode Array (MEA).
Results: We demonstrate for the first time responses of a population of retinal ganglion cells to patterns of light holographically projected on Channerhodopsin-II expressing retinas where visual neurotransmission was pharmacologically blocked. The neurons exhibit spatially-selective responses and have effective receptive fields.
Conclusions: The presented system is shown to be a suitable photo-stimulation modality towards the development of a non-contact retina neuroprosthetic device, capable of eliciting thousands of spikes per second, with millisecond timing precision. It can also be applied in experimental studies of the visual system requiring ultra-high-rate stimulus control.

Dorsal vs. Ventral hippocampus and amygdala ERK2 activation following an exposure to a contextual reminder of an underwater trauma

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Persistent re-experiencing is a core symptom in posttraumatic stress disorder (PTSD) which includes elements of recurrent and intrusive recollections. Such intrusive recollections are believed to often be triggered by reminder cues associated with the traumatic event (DSM-IV-TR. APA, 2000).
Mediation of the formation and recollection of memories, particularly emotional ones, can partially be attributed to the activation of the Amygdala and the Hippocampus (Akirav & Richter-Levin, 2006). Privies studies in our lab have demonstrated that exposure to a contextual reminder of a traumatic event can lead to changes in behavior, Amygdala (BLA) ERK2 and CREB activation and long term potentiation (LTP) in the dorsal dentate gyrus (DG) (Richter-Levin, 1998; Ilin & Richter-Levin, 2009; Ardi & Richter-Levin, in press).
In the present study, we set out to examine the possible impact of re-exposure to the context of a stressful experience (i.e. underwater trauma) on the activation of basolateral amygdala (BLA) and hippocampal formations (CA layers, DG) in the adult' rat brain.
Rats were first exposed to underwater trauma and 24 hours later were re-exposed to the context of the trauma. 30 min following the context re-exposure rats were decapitated and the hippocampus (CA layers, DG) and BLA brain regions were harvested. Phosphorylation of the extracellular signal-regulated kinase (ERK2) was used as a biochemical marker for the activation of the relevant brain regions, following the context re-exposure.
Significant increase in activation of ERK2 in the BLA and ventral hippocampus was found following an exposure to the underwater trauma and 24 hours later to its context. Additionally, results point to a distinct pattern of hippocampus ventral regions and BLA activation, differing both within the inter regions correlation and between re-exposed and un-exposed rats.

Abl protein level in thalamus is decreased following unpaired but not paired CS-US presentation

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We are interested to study the molecular mechanisms of fear and safety memory formation in brain. Toward that end, we screened the level of 507 proteins in brain areas involved in fear and safety learning. These proteins are involved in synaptic function, signal transduction or regulation of gene expression. Rats were trained using protocols shown previously to lead to fear conditioning memory (tone (conditioned stimulus; CS)–footshock (unconditioned stimulus; US) pairing) or safety learning (unpaired CS and US presentation). The auditory thalamus, auditory cortex and lateral amygdala were dissected 6 hrs after training (paired (n=22) and unpaired (n=22)).

Proteins were extracted, labeled and subjected to antibody microarray. The level of Tau-5, Abl, IL-1β and Bog proteins was found to be decreased in unpaired group compared with the paired group in thalamus. We further monitored the level of Abl protein in thalamus of paired, unpaired and naïve (exposed to conditioning chamber only) groups using the Western blot technique. The level of Abl was significantly reduced ($p<0.05$) in unpaired group ($n=19$) when compared to naïve group ($n=20$). The level of Abl in paired group ($n=16$) was not significantly different from naïve group. These results show that safety learning protocol, but not fear conditioning, leads to decrease in the level of Abl protein in auditory thalamus. Reduction in Abl level may affect neuronal processes, such as morphogenesis, shown to be intimately regulated by this kinase.

A unified network model of coexisting dynamical regimes in hippocampus

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Hippocampus exhibits different regimes of activity in different behavioral states of the animal. During locomotion, hippocampal activity oscillates at theta frequency and cells fire at specific locations in the environment (place fields). As the animal runs through a place field, spikes are emitted at progressively earlier phases of the theta cycles. During immobility, hippocampus exhibits irregular bursts of activity, with occasional rapid orderly activation of place cells expressing a possible trajectory of the animal. It is not known how these different regimes emerge and what causes the switch between them. We propose an attractor network model which encodes a map of the environment in its recurrent connections endowed with short-term synaptic depression that accounts for such a diverse range of behaviors. Network behavior can be rapidly controlled via modulation of the external inputs. Thus attractor networks with short-term plasticity are flexible enough to subserve different behavioral states of the animal.

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mTor in the nucleus accumbens contributes to neuroadaptations underlying alcohol abuse disorders

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Alcohol exposure leads to neuroadaptations that result in the development of compulsive drug seeking and taking, and increased propensity to relapse. We found that repeated cycles of voluntary excessive alcohol consumption and withdrawal in rodents cause the activation of mTOR (mammalian target of rapamycin)-mediated signaling pathway in the nucleus accumbens (NAc), a key component of the mesolimbic reward pathway that underlies the reinforcing actions of all drugs of abuse and alcohol. The kinase mTOR has been implicated in synaptic plasticity, learning and memory by controling protein translation, and we found that excessive alcohol intake in rodents results in the increase in the synaptic proteins HOMER and GluR1 via a mechanism that requires mTOR. Importantly, we have shown that the selective inhibition of this pathway with the FDA-approved drug rapamycin reduces excessive alcohol consumption, alcohol seeking, reward and sensitization. Our study therefore suggests that the mTOR pathway in the NAc contributes to maladaptive forms of learning and memory that underlie alcohol-drinking behaviors, and provides a potential valuable target for the treatment of alcohol use and abuse disorders.

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PKMzeta overexpression induces spine modification in cortical neurons

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Studies in rodents revealed that maintenance of long-term memory (LTM) in the hippocampus, amygdala and cortical areas requires the persistent activity of an atypical protein kinase C isoform, protein kinase M Zeta (PKMzeta). Furthermore, in-vitro studies suggest that the role of PKMzeta in memory storage is mediated by up-regulation of AMPA receptor trafficking to postsynaptic sites, thus increasing synaptic efficacy and maintaining long term potentiation (LTP). Despite these findings, the cellular changes due to PKMzeta expression and activity are as of yet poorly understood. We approach this issue by examining the morphological changes correlated with the overexpression of PKMzeta in primary cortical neurons in culture. Towards this end, cortical neurons were transfected with vectors containing either the PKMzeta gene (PKMzeta OE) or its dominant negative (DN) form under the CMV promoter and were characterized morphometrically.

Neurons overexpressing PKMzeta displayed a specific repertoire of dendritic spines compared to both DN and control. The percentage of stubby spines was significantly higher in the PKMzeta OE group whereas the percentage of long spine (≥2micron) and filopodia was smaller than controls. Overall, PKMzeta overexpression led to an increase in mature spine density. Furthermore, total spine length was significantly reduced in neurons overexpressing PKMzeta. No differences in total spine density and dendritic branching were found.

Our data indicate that PKMzeta plays an important role in dendritic spine structure and maturation in rat cortical neurons and hints that these morphological changes may play a role in memory storage. Further investigations,

including localization dynamics of PKMzeta may address the roles of PKMzeta in neuronal plasticity.

Perturbation in mitochondrial network dynamics and in complex I dependent cellular respiration in schizophrenia

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Mitochondria have been suggested to be involved in the pathology of psychiatric disorders including bipolar disorder (BD) and schizophrenia. However, the mechanism underlying mitochondrial dysfunction is unclear. Mitochondrial network dynamics, which reflects cellular metabolic state, is important for embryonic development, synapse formation and neurodegeneration. This study aimed to investigate mitochondrial network dynamics and its plausible association with abnormal cellular oxygen consumption in schizophrenia. Viable EBV-transformed lymphocytes (lymphoblastoids) from DSM-IV diagnosed patients with schizophrenia (n=17), BD (n=15) and healthy controls (n=15) were assessed for mitochondrial respiration, mitochondrial dynamics and relevant protein levels by oxygraph, confocal microscopy and immunoblotting, respectively. Respiration of schizophrenia-derived lymphoblastoids was significantly lower as compared to controls, and was twice as much sensitive to dopamine (DA)-induced inhibition. Unlike DA, haloperidol inhibited complex I driven respiration to a similar extent in both schizophrenia and the control cells. Both drugs interact with complex I yet at different sites. At the site of DA interaction we found alterations in protein levels of three subunits of complex I in schizophrenia. In addition, we observed structural and connectivity perturbations in the mitochondrial network, which was associated with alterations in the pro-fusion protein OPA1. None of these alterations were observed in the BD cells, which were similar to control cells. In schizophrenia we show impaired mitochondrial network dynamics associated with reduced cellular respiration and complex I abnormalities. If these findings represent disease-specific alterations, they may become an endophenotype biomarker for schizophrenia.

Developmental changes in extinction of contextual vs. auditory fear conditioning following single vs. double exposure to stress

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Current research data show that there are developmental differences in extinction of fear conditioning, suggesting that the neural networks mediating extinction of fear change throughout development. Contextual vs. auditory fear conditioning (FC) are modulated by different areas of the brain; therefore, extinction of these two forms of conditioned fear may be differentially susceptible to behavioral manipulations. We and others have reported that in adult rats, extinction of fear memories is impaired following exposure to behavioral stress. In the present work, we studied the effects of a single vs. double exposure to elevated platform stress on the ability of pre-juvenile (pre-JUV; pre-weaning), juvenile (JUV; post-weaning pre-puberty) and adult rats to extinguish contextual vs. auditory FC.

The pre-JUV group failed to extinguish the contextual FC, but showed sufficient extinction of auditory FC. Both forms of FC were successfully extinguished in JUV and adult rats. Single stress exposure impaired contextual FC in pre-JUV and adult rats, but did not affect auditory FC. In contrast, double exposure to stress rescued the extinction of contextual FC in pre-JUV and adults. Our results show differential pattern of effects of stress on extinction of contextual and auditory FC at different stages of development, suggesting age-related differences in mechanisms underlying the disorders characterized by impairments of fear extinction. The dependency of these differential effects on NMDA receptors is under current investigation.

Theory of spike timing based neural classifiers

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Neural network models of supervised learning are usually concerned with processing static spatial patterns of input intensities or of neurons firing rates. A famous example is the perceptron, a model for learning in a single-layer binary neuron. However, in most neuronal systems, neural activities are in the form of time series of spikes. Furthermore, stimulus representation in some sensory systems, like the salamander's retina, the rodent olfactory system and the human tactile system, are characterized by a small number of precisely timed spikes, suggesting that the brain possesses machinery of extracting information embedded in the timing of spikes, not only in their overall rate. Thus, understanding the computational power and limitations of spike-timing based computation and learning is of fundamental importance in computational neuroscience. Gütig and Sompolinsky have recently suggested a simple model, the tempotron, for decoding information embedded in spatio-temporal spike patterns. The model consists of a simple error-correcting on-line learning algorithm applied to an Integrate and Fire neuron.

In this work we present a theoretical study of the computational power of the tempotron. Our theory enables

us to calculate the tempotron's capacity and the statistical properties of the tempotron's membrane potential and output spikes as a function of the various time scales of the system's dynamics.

The strong non-linear nature of the tempotron's classification entails that the common and intuitive assumption that a neurons function is characterized by its synaptic efficacies no longer holds. Similar classifications can be performed by neurons with very different synaptic efficacies and vice versa, neurons with similar synaptic efficacies can perform completely different classifications. This is a general property of any Integrate and Fire neuron and also holds for more realistic models of a neuron.

Using Drosophila primary neuronal cultures to model Alzheimer's disease

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Alzheimer's disease (AD) is a devastating and currently incurable neurodegenerative disease, with constantly rising prevalence rates. Animal models of AD, among them the genetically powerful Drosophila model, aided in gaining insights into the pathological processes involved in AD, especially in implicating the amyloid-beta (Aβ) peptide as a key player involved in neuronal dysfunction and degeneration. Nevertheless, the mechanism by which Aβ induces neurodegeneration or contributes to other pathological effects remains to be discovered. Cultured neuronal networks provide an excellent opportunity to advance in this direction. Neuronal networks are a bridging link between single cells and the structurally and functionally complex brain. As such, they provide exceptionally high-resolution access into both cellular and intercellular processes. In this study, cells derived from the nervous system of Drosophila were cultured under carefully controlled conditions. Cultured neurons were found to undergo a specific and consistent organizational process: the cells begin as single dissociated units and then regenerate and grow neurites, allowing them to establish elaborate connections with one another. This is followed by cell migration that leads to cluster formation and re-arrangement of the neurites into thick nerve-like bundles. The network's development, along with its vitality and functionality, can be continuously monitored, allowing for the effect of different perturbations to be studied. It is suggested that primary neuronal cultures from transgenic Drosophila expressing human Aβ will show clear deficiencies and alterations in comparison to cultures obtained from wild type controls. A close comparative investigation of the development of these two types of cultures could both, help us understand the mechanism of Aβ pathological action and serve as a platform for testing novel therapeutic agents.

Mesenchymal stem cells induced to secrete neurotrophic factors attenuate excitotoxicity: autotrasplantation stem-cells based therapeutic potential for Huntington's disease

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Background: Huntington's disease (HD) is a hereditary, progressive and ultimately fatal neurodegenerative disorder. Excitotoxicity in the striatum and reduced availability of neurotrophic factors may play important roles in pathogenesis of HD. An induction protocol was developed to induce adult human bone marrow derived mesenchymal stem cells (MSC) into neurotrophic factors secreting cells (NTF^+ cells). Currently, an efficacy measurement of treatment with such NTF^+ cells in the quinolinic acid (QA) rat model for excitotoxicity was performed.

Methods: Human MSC were passed through a medium-based induction protocol. Rats were treated with QA injected into the left striatum followed by cellular treatment (either MSCs of NTF^+ cells). Apomorphine induced ipsiversive rotations were measured repeatedly, followed by a histological study.

Results: NTF^+ cells reduced rotational behavior in the QA-lesioned rats by a mean of 80% ($p<0.05$) in comparison to PBS-treated rats. 19.2±4.5% of the transplanted NTF induced cells survived for over six weeks after surgery. Lesioned striatal volume (as percent of the contralateral side) had increased from 62% in the QA group and 62% in the MSC group to 75% in the NTF^+ cells group ($p<0.05$). MSC from HD patients were found to differentiate into NTF^+ cells in a similar manner as controls, and that transplantation of these cells protects against QA-induced excitotoxicity as well. Repetitive T_2-mapping MRI scans were additionally performed, and demonstrated an increase of T_2 value in the untreated QA-lesioned group, while a decrease in T_2 values was noted in the cellular treated groups, suggesting beneficial effects in the QA-injected regions. Only a minority (0.3%) of the surviving NTF^+ cells co-expressed huntingtin, indicating low probability of aggregated mutated protein.

Conclusions: The novel NTF^+ cellular treatment may be beneficial in the future as auto-transplantation therapy for HD patients.

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Stimulating category-selective lateral-occipital areas enhances selectivity of event-related potentials: a simultaneous TMS-EEG study

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Faces and bodies are known to elicit a highly selective neural response in occipital–temporal cortex: functional MRI studies reveal body- and face-selective brain areas in the lateral occipital cortex and the fusiform gyrus; event-related potential studies reveal high N170 and VPP (vertex positive potential) amplitudes to face and body stimuli. However, it is still unknown whether early category selectivity in occipito-temporal areas plays a role in the generation of the category-sensitive ERP responses to their respective stimulus categories. In the current study we applied Transcranial Magnetic Stimulation (TMS) simultaneously with EEG recording. Two consecutive TMS pulses were administered 60 and 100 ms after the onset of face or body stimuli, either over the right Occipital Face Area (rOFA) or the right Extrastriate Body Area (rEBA). TMS-related artifacts were removed offline from the recorded scalp potentials via the subtraction of a noise template from the ERP to each stimulus category. Results show a significant signal enhancement to faces following rOFA stimulation, and a significant signal enhancement to bodies following rEBA stimulation, both for the N170 and the VPP. This interaction provides direct evidence that activations of face- and body-selective areas in the lateral occipital cortex as early as 60-100 ms after stimulus onset play a role in the generation of sensitive ERP responses to faces and bodies 150-200 ms after stimulus onset, respectively.

Mordekhay Medvedovsky

Antidepressive-like effect of AS101 in rat models of depression

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Depression is the second leading cause of disability worldwide, with only 50% of all patients showing full remission. Successful antidepressant treatment is accompanied with increase levels of both brain-derived neurotrophic factor (BDNF) and α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate receptor (AMPAR); mainly in the hippocampus. Furthermore, recent finding points to dramatic involvement of both proteins in the pathophysiology of depression. For example, postmortem analyses reported decreased hippocampal BDNF levels in depressed suicide victims; and AMPA potentiators were found to serve as antidepressant agents.

Ammonium-trichloro-(dioxoethylene-O,O''-)-tellurate (named AS101) is a non-toxic immunomodulator compound with a pleiotropic activities that was found to increase BDNF levels in neuronal primary cell culture in vitro. In the present study, following successful Porsolt forced swim test, we examined AS101 potential as an anti-depressant agent using 2 different models of depression.

Initially, we found that AS101, when administrated systemically, reduced the duration of immobility time in the Porsolt swim test, indicating anti-depressant potential. Next, AS101 was administer to rats following chronic mild stress (CMS) procedure, and to a depressive rat line (DRL). In both models, AS101 normalized depressive-like behavior in several behavioral tests, including sucrose preference and the modify forced swim test. In addition, AS101 increased spatial memory in the Morris water maze. At the molecular level, AS101 up-regulated BDNF in reward-related brain areas, and increased the expression of AMPA receptor subunit GluR1 in the dorsal hippocampus.

In the present study, AS101 treatment was found to have antidepressant-like effect in both the CMS and DRL models. Therefore, AS101, which have a wealth of potential therapeutic applications and a proven safety profile in humans, might serve as a novel anti-depressive therapy

Motor-sensory convergence in human tactile perception

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Most of our perceptual tasks involve active sensing, in the sense that our sensory organs move in order to acquire sensory data. Here we studied the dynamic process leading to tactile perception in a novel task. Human subjects were asked to compare the horizontal location of two poles using artificial whiskers that were attached to their fingers. Finger location and contact forces were continuously measured. We found that improvements in the perception of object location were mediated by increased hand coordination and reduced hand velocity and not at all by increased sensory acuity. The dynamics underlying the emergence of perceptual decisions depended on task difficulty and involved gradual changes of motor variables. Our results indicate that at least in some tasks, motor and not sensory variables underlie rapid improvements of tactile perception, and that tactile perception emerges from iterative interactions with the object via motor-sensory convergence processes.

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Developmental changes in effects of stress on neuronal excitability and synaptic plasticity in the PFC-BLA circuit

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Stress differentially affects the brain and behavior at different stages of life. Amongst the effects that a stressful experience may exert on the brain are changes in plasticity-related processes in the circuits related to emotion and memory. We investigated in the rat the effects of an acute exposure to elevated platform (EP) stress on neuronal excitability and synaptic plasticity in the medial prefrontal-cortex (mPFC- basolateral-amygdala (BLA) circuit, implicated in acquisition and extinction of fear memories. The effects of stress exposure were compared in the juvenile (post-natal day (PND) 27) to those of the adult (PND 60) rats. Rats were exposed to EP for 30 min, and their baseline responses in the BLA to stimulation of the mPFC (neuronal excitability), as well as long-term potentiation (LTP; synaptic plasticity) were measured. Baseline responses were significantly weaker in the juveniles than those of the adult rats. In the naïve juvenile rats high-frequency stimulation (HFS) of the mPFC resulted in long-term depression (LTD) in the BLA, but no change in the synaptic plasticity was observed in the adults. The exposure to EP stress had no effect on neuronal excitability in the juveniles, but significantly reduced it in the adult rats. Moreover, stress released the plasticity of the BLA from LTD in juvenile rats, and resulted in LTP in the adults. These results suggest developmental differences between the juvenile and adult rats in both neuronal excitability and synaptic plasticity in the mPFC-BLA circuit, as well as effects of stress on these processes.

Touch gives new life: mechanosensation modulates spinal cord adult neurogenesis

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The ability to respond to a wide range of novel touch sensations and to habituate upon repeated exposures is fundamental for effective sensation. In the present study we identified spinal cord adult neurogenesis as a potential novel player in the mechanism of tactile sensation. By exposing mice to novel mechanosensory stimuli for varying periods of time and of different diversity, we found that novel sensory stimuli induce progenitor cell proliferation in the sensory dorsal pathway of the adult spinal cord, and that the duration of the stimulation and its diversity affect their subsequent neuronal differentiation and survival. Single exposure to a novel mechanosensory stimulus induced immediate proliferation from an apparent reservoir of progenitor cells (DCX+/NG2+; Sox2+). In contrast, repeated exposures to the same stimulus induced neuronal differentiation and survival of the new cells, mostly into immature (DCX+, NG2-, NeuN-, Calbindin-) GABAergic (GABA+, GAD 65/67+) neurons (NSE+, HuC/D+, Calretinin+), and inhibited their additional proliferation. We propose that these newly generated GABAergic immature neurons serve a transient neuromodulatory role, which is part of a mechanism in which niche plasticity is finely tuned and regulated both temporally and spatially. Introducing adult neurogenesis as a potential mechanism of response to a novel stimulus and for habituation to repeated sensory exposures opens up potential new directions in treating hypersensitivity, pain and other mechanosensory disorders.

Spatial localization of stimuli in early auditory processing is based on both allocentric and egocentric coordinate systems

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The localization of auditory stimuli is based on an estimation of an objects position relative to head orientation, as well as information regarding the head's position and orientation in space. We can therefore distinguish between a basic egocentric (or head centered) coordinate system and a more complex allocentric system, which determines an objects position in space. While early auditory localization mechanisms utilize binaural information and form a head-centered representation, it is the body- or world-centered (allocentric) view that eventually guides our actions. However, little is known about the neural coding of these distinct representations. In an ERP experiment, we attempted to dissociate the two coordinate systems and reveal in which manner spatial representation is organized in the human auditory cortex. We used MMN (Mismatch Negativity), a well studied EEG effect evoked by acoustic changes from an established regularity. Subjects (N=11) were instructed to reorient their heads after hearing a series of repetitive auditory stimuli ("standards"). This was followed by a similar auditory stimulus ("deviant") located in one of two distinct locations: either deviating from the standards in an egocentric manner (i.e located in a different position relative to head orientation); or in an allocentric manner (i.e located in a different absolute position). Our findings reveal that both egocentric and allocentric systems take part in early processing: we observed significant MMNs for both allocentric and egocentric deviant stimuli, with similar scalp distributions. These findings may imply that there are multiple representations of stimuli location in the auditory cortex. Whether they are served by different (yet proximate) populations of neurons, or by the same neurons, remains for future research.

Blood-brain barrier dysfunction: a target to prevent secondary stroke complications?

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Stroke is one of the leading causes of morbidity and death worldwide, leaving a third of the survivors left disabled or suffering from a wide range of sequelae. Following brain ischemia Blood-brain barrier (BBB) dysfunction is typically observed in the peri-infarct region. Based on imaging experiments in the photothrombosis model, comparison of published gene array data from rat brains exposed to medial cerebral artery occlusion or BBB breakdown, and electrophysiological recordings, we propose that: (1) the ischemic insult is followed by rapid changes in gene expression leading to delayed dysfunction of the BBB within the penumbra; (2) BBB opening is associated with transformation of astrocytes and a local inflammatory response; (3) BBB dysfunction can lead to delayed structural and functional changes in the neuronal network within the penumbra. We propose that BBB dysfunction may be critically involved in functional recovery (and deterioration) after stroke and underlies common clinical complications including hemorrhage, epilepsy and delayed cognitive and neurological dysfunctions. We thus point to BBB damage and repair as potential targets for the treatment of stroke.

Postnatal maternal environment programs adult leptin sensitivity and exerts long term behavioral and neuroendocrinological effects in obese OLETF and lean LETO female rats

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The OLETF rat model of obesity spontaneously lacks CCK1 receptors. Young OLETF rats present abnormal eating and adiposity profiles already during lactation, with a sharp leptin surge around postnatal day (PND) 7. This pre-obese profile results from the interaction of the "hungry" pups with their obese mother that nurses them longer and provides them with high fat milk. To further examine the effects of the early environment on long term obesity and leptin sensitivity, we performed a partial-fostering study, where half of the females were switched with females from the opposite strain on Postnatal (PN) day 1. On PN Week 8, females underwent a behavioral leptin sensitivity test followed by 4-day palatable food challenge. LETO (control) females reared by OLETF dams (OdLp) became overweight during lactation, but recovered early post weaning. However, despite being lean, they lost their sensitivity to peripheral leptin, which was reflected by malfunctioning of Arcuate nucleus (ARC) leptin receptors, leading to decreased c-fos response to peripheral leptin administration. In the food challenge, a high preference for fat was revealed in those females, exposing an acquired sensitivity to diet induced obesity. While OLETF females were leptin resistant and obese as adults, OLETF females reared by LETO dams (LdOp) showed an improved response to leptin in the ARC and reduced preference for fat despite being obese. This study provides an important insight into the influence of the early postnatal environment on later life leptin sensitivity and food preference, which can predispose to or protect from diet induced obesity.

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Inflammatory responses in the brain – studies on interleukin-1 receptor-mediated activity and microglial responses to β-amyloid

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Inflammation is now recognized to be closely related to the neurodegenerative process in brain disorders such as Alzheimer's disease (AD). Furthermore, inflammatory cytokines are implicated in normal brain physiology. Interleukin-1 (IL-1) is one of the most important proinflammatory cytokines in the response to infection, and also associated with neuroinflammation in brain disorders. Effects of blocking IL-1 receptor (R)-mediated activity in the brain have been analysed using a mouse strain overexpressing human soluble IL-1R antagonist (TghsIL-1ra) under control of the GFAP-promoter. Studies in young and ageing mice, and upon kainic acid-induced excitotoxicity, show a blunted neurogenesis response in the TghsIL-1ra mice. Similarly, the reaction of astrocytes and microglia to either acute or chronic inflammation was dramatically reduced. Neuronal IL-1 expression is enhanced following LTP, but exogenously added IL-1, or blocking IL-1 receptors inhibits the consolidation of memory. Studies on learning ability in the TghsIL-1ra mice support the role of IL-1R-mediated signalling in long-term memory. Analysing the activity-regulated cytoskeleton-associated protein (Arc) provides evidence for impaired synaptic strengthening underlying the learning defects.

Microglial cells represent the main source of inflammatory cytokines in the brain. Another feature is their capacity for phagocytosis. A human microglial cell line was used to characterise the phenotype of phagocytosing cells and to stimulate the uptake of b-amyloid (Ab)-peptide. Microglia that phagocytosed Ab1-42 exhibited a higher expression of IL-1R type I and iNOS. IFN-g, but not IL-1b, stimulated the uptake. Considering the presence of inflammation in AD, it may be suggested that the combined effect of Ab,

IL-1b and IFNg on the secretion of BDNF from microglia may contribute to neuronal pathology in AD, indicating a failure to reach resolution of the inflammation.
Swedish Res Council, Swed Brain Power, Wallenb Found, Swed Alz Found, Stohne stift, Sthlm County

The roll of sexually dimorphic AVPV neurons in regulation of social & reproductive responses
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Mammalian reproduction depends on the coordinated expression of behavior with precisely timed physiological events that are fundamentally different in males and females. The anteroventral periventricular nucleus of the preoptic region of the hypothalamus (AVPV) contains a sexually dimorphic population of neurons that are known to be involved in regulation of reproductive functions such as preovulatory gonadotropin surge in female rodents and possible sex differences in puberty onset. One of the sexual dimorphic populations is tyrosine hydroxylase (TH) positive neurons which their number is grater in females compare to males. The function of these TH positive neurons is still un-known nor is the reason for their sexual dimorphism. Our hypothesis is that these dimorphic neurons play a role in pheromone mediated reproductive behavior. In this project we use viral vectors to genetically manipulate the AVPV TH positive neurons. Lentiviruses which contain knock-down and over-expression of TH were previously constructed in our lab and tested in-vitro and in-vivo. These viruses are going to be bilaterally microinjected to the AVPV area of both male and female mice. These transgenic mice will be then analyzed for hormone level and tested in a variety of behavioral tests which include aggression, sexual and maternal behaviors. By comparing the transgenic animals with the control group we hope to characterize the function of the AVPV TH positive neurons and the reason for their sexual dimorphism.

Targeting the role of astrocytes in mediating neuroprotection in stroke model.
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Background: Stroke is one of the leading causes of death in the world, resulting in the death of approximately five million people per year. Astrocyte cells are the main glial cells that play a fundamental role in maintaining the homeostasis of the CNS. Furthermore, astrocytes are important for protection, and aid the brain in the functional recovery from injuries. Stress conditions following ischemia may lead to impaired glutamate uptake by astrocytes or glutamate release that can facilitate further neuronal death under hypoxic conditions. It is well established that the brain can be prepared to withstand an ischemic insult by a process known as preconditioning. Preconditioning can be achieved by subjecting the brain to transient ischemia in vivo or oxygen and glucose deprivation (OGD) in vitro.
Methods: We investigated whether preconditioning of primary astrocytes with specific levels of oxygen and glucose deprivation can lead to better astrocyte survival and to neuroprotrective features, by measuring cytokine, protein and gene expression levels.
Results and conclusions: We discovered that preconditioning with 100 μM of H2O2 and glucose deprivation may induce astrocytes better resistance to different OGD conditions as shown by MTT and methylen blue assays. Furthermore, we discovered that this preconditioning leads to increased expression of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and insulin-like growth factor 1 (IGF-1), together with increased secretion of the anti-apoptotic cytokine IL-10. Moreover, we found that conditional media from astrocyte exposed to OGD preconditioning protected neurons from OGD. We further found higher expression level of the mitochondrial heat shock protein - mortalin in the preconditioned astorcytes that may lead to neuroprotection. We suggest that targeting mortalin in astrocytes may be a useful strategy for treatment in ischemic brain injury.
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What the retina just can't catch: motion perception during smooth pursuit
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In many instances in everyday life we perceive sensory information and react upon it at the same time, thus causing a difficult problem for the cognitive system: How can the sensory information remain accurate in the face of motor interference? An example of such a challenge is accurately perceiving the speed and direction of a moving object, while tracking it with the eyes. Under precise smooth pursuit conditions, the object is moving in the world (in head-based or spatiotopic coordinate frame), but in retinal coordinates it is practically still. How can we perceive motion of a visual stimulus that doesn't move on the retina? We addressed this question in a series of psychophysical experiments by employing an adaptation method. We used the motion after effect phenomenon to induce adaptation to motion that was either present only in retinal coordinates (Retina condition) or only present in head-based/spatiotopic coordinates (Screen condition), while keeping pursuit eye movements and other factors constant. We measured the subjects' detection thresholds for rightward and leftward motion, as well as their eye movements, with and without

adaptation. Adaptation biased perception toward the non-adapted direction, in both Retina and Screen conditions, but its effect was significantly larger for the latter. In addition, adaptation caused reduced motion detection sensitivity, apparent by a decrease in the psychometric curves' slopes. In a second set of experiments, only pursuit speed and retinal motion were manipulated thus keeping Screen motion constant. The results showed that apart from Screen motion, the degree of adaptation was more influenced by the pursuit speed factor.

Taken together, these data demonstrate that the visual system can compute motion using head-based/spatiotopic coordinates when retinal motion is absent, and that motor signals are important in the process of extraction of motion features under smooth pursuit conditions.

Inhibition of PKMzeta in the nucleus accumbens shell abolished the expression and reinstatement of cocaine-induced conditioned place preference

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Drug addiction is caused, in part, by powerful and long-lasting memories of the drug experience. Recent evidence suggest that drugs of abuse can hijack synaptic plasticity mechanisms in key brain circuits related to reward processing in the brain. PKCzeta is a member of the protein kinase C isozyme family, and it plays a role in both induction and maintenance of long term potentiation (LTP). It has recently been shown that inhibition of PKCzeta by a Zeta Inhibitor Peptide (ZIP) causes loss of previously acquired long-term memory without activation of the memory trace. Based on these studies we hypothesized that cocaine induced conditioned place preference (CPP) can be disrupted by inhibition of PKCzeta. Therefore, we used cocaine-induced CPP protocol in rats followed by microinjection of the ZIP peptide into the nucleus accumbens (NAc), a key brain area known as target of drugs of abuse that mediate drug reward.

We found that inhibition of PKCzeta in the nucleus accumbens shell (NAc Shell) completely abolished cocaine-induced CPP and prevented the reinstatement of CPP following prolonged extinction period. In an attempt to reveal the molecular mechanism of ZIP behavioral effects, we evaluated proteins levels at the post synaptic density that are related to synaptic function, learning and memory. We performed Western Blot analysis three days after conditioning to cocaine and ZIP injection, or two weeks later. We found that NR1, a member of glutamate receptor family is elevated three days but not two weeks after conditioning. A sustained elevation in CamKII was observed in both time points. Finally, PKCzeta protein levels were elevated after three days, but not two weeks after CPP.

Taken together these results suggest that PKCzeta in the NAc shell is likely to play a major role in mediating cocaine-induced CPP and reducing its activity can potentially erase memories associated with cocaine use and ultimately can prevent relapse.

The role of contextual associations in the encoding of briefly glimpsed scenes: memory for the gist or for the details?

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Objects typically appear within cluttered scenes, where they compete for limited processing resources. Visual contextual regularities may streamline object recognition, by reducing input complexity and by increasing scene coherence. What is the nature of *memory-encoding* of object-to-object contextual associations during a *brief* visual glance? Ample research has suggested that under very rapid viewing conditions only the 'gist' of a scene is grasped, while little visual detail is accessed and retained in long-term memory. In the present research we investigated whether contextual associations may enhance memory of visual details, even when objects are merely glimpsed. Participants viewed pairs of contextually-related and unrelated objects (e.g., a kettle and a mug; a shovel and a vase, respectively), presented for an extremely short exposure duration (24 ms, masked). Subsequently, participants performed a memory-recognition test, in which one of two objects within a pair was replaced by a novel object from the same basic category. Participants differentiated old objects from novel object exemplars, while these were presented with their original counterpart pair object. Results demonstrated higher levels of correct recognition for contextually-related than for unrelated object pairs (recognition rates in the latter did not differ from chance level). Furthermore, when object stimuli in the recognition test appeared *alone*, i.e., without a corresponding pair object serving as a memory-retrieval cue, results remained virtually identical. Namely, memory for specific visual details remained higher for objects initially appearing within contextually-related, than unrelated, object pairs. These results strongly suggest that while contextual information may provide a coarse 'schema' that enables memory of meaningful visual input (i.e., the 'gist' of a scene), it also enhances the representation of *specific visual details* in the scene, even within a mere glimpse.

Preferential sharing of recycling vesicles rather than reserve pool vesicles between adjacent synapses

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Neuronal transmission relies on the synaptic vesicle cycle, which incorporates all mechanisms supplying vesicles for fusion at the plasma membrane. The various segments of this cycle are controlled by a large group of pre-synaptic proteins, of which synapsin is one of the most abundant. The synapsins are a multigene family of phospho-proteins which reversibly bind to synaptic vesicles, to each other, and to the cytoskeleton, thus managing the reserve pool of vesicles. Recent studies have shown that vesicles are not confined to individual presynaptic terminals as is widely believed. Rather, it was observed that functional vesicles move between adjacent synaptic boutons, effectively forming a large super-pool of shared vesicles.

We focused on the phenomenon of vesicle mobility along axons using Fluorescence Recovery After Photobleaching (FRAP) to investigate how synaptic vesicle clustering by the synapsins affects vesicle sharing between synapses. Synaptophysin I-EGFP (Syp-EGPF) expression was utilized to label the complete vesicle population, while FM 1-43 served to specifically label the recycling pool. We show that FRAP of Syp-EGPF is faster in synapsin-devoid neurons as compared to wild type ones, suggesting that a decrease in vesicle clustering due to the absence of synapsin increases the rate of vesicle mobility between synapses. Moreover, in WT neurons FRAP of FM 1-43 is faster as compared to FRAP of Syp-EGFP, while in synapsin-devoid neurons no such difference was observed. These results indicate that the recycling pool is more motile than the reserve pool, and that synapsin affects mostly the mobility of the latter. Our results further imply that the super pool of vesicles draws vesicles more easily from the recycling pool than from the more tightly bound reserve pool.

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Is there a hemispatial bias in detecting errors and in error awareness?

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Important everyday tasks, such as driving or machine operation, often have a significant lateralized aspect. Patterns of attentional dysfunction in patients reveal that attention is distributed asymmetrically across space, and indeed studies find a subtle but reliable asymmetry in attention distribution also in healthy subjects. Does it follow that we are more aware of errors on one side of space? While error detection and error awareness have been studied in the past two decades using Event Related Potentials (ERPs), the lateralization of errors and their awareness has not been directly examined. The purpose of the current study was to investigate this lateralization in healthy individuals under laboratory conditions. 16 subjects performed a 2-choice RT Lateralized Error Awareness Task (LEAT) whilst their EEG was recorded. The LEAT enabled sorting errors into two categories – errors made due to stimuli on the left (Left Errors), and errors made due to stimuli on the right (Right Errors). After each trial, the subjects had an explicit option to change their response if they noticed that they had made an error, allowing us to determine error awareness on a single trial basis. The results did not show any significant difference between Left and Right Errors in their number, in the RTs or in their awareness rates. The ERP results show that while the components associated with error processing (Ne) and error awareness (Pe) showed the consistent 'error awareness effect' (no difference between the Ne for aware and unaware errors, an enhanced Pe for aware errors only), there was no significant difference in the effect between Left and Right Errors. Thus, no hemispatial bias was found for errors and error awareness in the behavioral or the electrophysiological results. The implication is that this task can now be used to study error detection and awareness in patient populations who have a lateralized attentional bias like hemispatial neglect.

Correction of Parkinson's disease phenotype by the modulation of alpha-synuclein oligomerization using engineered fragments of an endogenic inhibitor

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The intracellular oligomerization of α-synuclein is associated with Parkinson's disease and appears to be an important target for disease-modifying treatment. Yet, to date there is no specific inhibitor for this aggregation process. Using unbiased systematic peptide array analysis, we indentified molecular interaction domains within the β-synuclein polypeptide that specifically binds α-synuclein. Adding such peptide fragments to α-synuclein, significantly reduced both amyloid fibrils and soluble oligomer formation in vitro. A retro-inverso analogue of the best peptide inhibitor was designed to develop the identified molecular recognition module into a drug-candidate. While this peptide shows indistinguishable activity as compared to the native peptide, it is stable in mouse serum and penetrates α-synuclein over-expressing cells. The interaction interface between the D-amino acid peptide and α-synuclein was mapped by Nuclear Magnetic Resonance spectroscopy. Finally, administering the retro-inverso peptide to a Drosophila model expressing mutant A53T α-synuclein in their nervous system, resulted in a significant recovery of the behavioral abnormalities of the treated flies

and in a significant reduction in α-synuclein accumulation in the brains of the flies. The engineered retro-inverso peptide can serve as a lead for developing a novel class of therapeutic agents to treat Parkinson's disease.
DIP, ISF

Revealing drug effects utilizing brain network activation (BNA): A working memory study

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Finding tools to evaluate drug effects on brain processes is a true necessity in drug development targeting neurodegenerative and psychiatric disorders. Drug testing may be done on healthy volunteers treated with substances associated with reversible cognitive effects such as scopolamine, an acetylcholine antagonist, and ketamine, a NMDA antagonist. Both drugs have previously been used as models of Alzheimer and schizophrenia respectively, and showed electrophysiological abnormalities associated with these disorders. We have recently developed a novel algorithm to extract brain network activation (BNA) patterns that reveal in an unsupervised manner spatio-temporal networks from EEG data. In this study BNA analysis was used in order to assess changes in brain networks in 15 healthy volunteers following administration of scopolamine (0.4 mg) and ketamine (100 mg) in a double-blinded, placebo-controlled, crossover study. Subjects (18-45 y) performed a working memory task in which they determined whether two consecutive face stimuli were identical, while EEG was recorded from 64 channels. The networks showing the activation differences between placebo and scopolamine revealed a delay in posterior face processing activity and a fronto-central, widely distributed activity around 250 ms following scopolamine administration. The later activity was restricted to pre-frontal areas under placebo. The placebo-ketamine differentiating networks showed that the frontal negativity at 250 ms peaked earlier, and was lateralized to the right under placebo, while ketamine administration disrupted this hemispheric asymmetry - a known phenomenon in schizophrenia. To conclude, this study shows that BNA analysis can automatically detect significant changes in brain states between different conditions, validating its use for investigating effects of pharmacological treatments on CNS diseases.

Cannabinoid receptor activation prevents the effects of chronic stress on emotional learning

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A link between stressful life events and psychiatric illness has been found over the years. Chronic mild stress (CMS), an animal model of depression and anxiety disorders, is ought to mimic that effect by administrating several moderate stressors such as food or water deprivation, over night lighting, paired caging, wet bedding etc. The current study aimed to test whether the CB1/2 receptor agonist WIN55,212-2 (WIN) would prevent CMS-induced alterations in emotional learning. To that end, adult rats were exposed to 21 days of CMS or handling. On days 20-22, an intraperitoneal injection of WIN (0.5 ml/kg) or vehicle was administered. Drinking of 1% palatable sucrose solution as a measure of anhedonia and body weight changes were monitored throughout. After CMS or handling rats were tested in an inhibitory avoidance procedure. CMS animals showed less sucrose intake than controls and gained less weight compared to controls. Furthermore, CMS rats demonstrated enhanced conditioned fear and impaired extinction as measured in the avoidance task. Importantly, WIN reversed the CMS-induced alterations in avoidance conditioning and extinction, but not in sucrose consumption or body weight. These findings suggest a protective effect of cannabinoids against some of the symptoms induced by an intensifying stress experience and provides evidence to support the use of cannabinoids for the treatment of stress-related disorders such as depression.

The role of TSPO in mediating cell death induced by nitric oxide

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Both the mitochondrial 18 kDa Translocator Protein (TSPO) and nitric oxide (NO) are known to affect oxidative stress, the mitochondrial membrane potential ($\Delta\Psi m$), cell death, and inflammation. Both the TSPO and NO are considered to have anti-cancer properties. A potential physical link connecting the TSPO and NOS has also been described. To study actual interactions between NO and TSPO, we induced cell death by applying the nitric oxide donors S-Nitroso-L-glutathione (GSNO) and Sodium nitroprusside (SNP) to the human glioblastoma U118MG and rat pheochromocytoma PC12 cell lines. To assay cell viability, we measured Trypan blue inclusion, Propidium Iodide (PI) labeling, lactate dehydrogenase (LDH) release, and DNA fragmentation. Assays using 2,3-bis[2-methoxy-4-nitro-5-sulphophenyl]-2 H-tetrazolium-5-carboxyanilide (XTT) and 5,5',6,6'-tetrachloro-1,1',3,3'-tetraethyl-benzimidazolylcarbocyanine chloride (JC-1) detected changes in mitochondrial activity and $\Delta\Psi m$. To detect mitochondrial reactive oxygen species (ROS) generation, 10-N-Nonyl-Acridine Orange (NAO) fluorescence intensity was measured. Expression and binding characteristics of TSPO were assayed with Western blotting and binding analysis. The

involvement of the TSPO in NO donor effects was assayed by applying TSPO knockdown by siRNA, and the TSPO ligand PK 11195. TSPO knockdown and PK 11195 significantly counteracted cell death induction and mitochondrial activity otherwise caused by SNP. PK 11195 did not exert its effects after TSPO knockdown. Interestingly, SNP did not interfere with [3 H]PK 11195 binding to the TSPO, nor did it affect TSPO protein expression. However, TSPO is S-nitrosylated following SNP application. Thus, our studies show that activation of TSPO by the NO donor SNP, leading to ROS generation, including cardiolipin oxidation at mitochondrial levels, collapse of the $\Delta\Psi m$, and cell death, appears to involve S-nitrosylation of the TSPO.

Mild stress vs. moderate stress: effects on plasma corticosterone (CORT) and hippocampal activity

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Stress, which is correlated with an increased release of CORT, is well known to modulate hippocampal-dependent learning and memory (de Kloet et al., 2005). However, recently, studies have found dissociation between the effects of stress on hippocampal sub-regions and suggest that the effects might depend on the type and severity of the stress as well as the timing of stress induction (Vouimba et al., 2006). This study aims to continue studying the significance of different stressors, on synaptic and local circuit plasticity in the hippocampus sub-regions. In the present experiment we examined plasma CORT levels after a stressor at different intensities.

Initially, SD rats were divided into 4 groups of 8 animals that were injected with different doses of CORT (5, 10, 20 mg/kg and vehicle). In the second part, animals were divided into 3 groups of 8 animals that were given electrical foot shock at two different intensities (0.2, 0.9 mA and control). After 45 min. blood was collected and analyzed with CORT ELISA.

The 0.2 mA group and the 0.9 mA group showed in the first ITI, significantly higher freezing level compared to control group and to 0.2 mA group respectively. Both 0.2 mA group and 0.9 mA group reached a ceiling effect at the second ITI, and were significantly higher than the control group. Surprisingly, ELISA analysis showed similar plasma CORT levels for 0.2 mA group and control group, but 0.9 mA group had significantly higher plasma CORT levels. Although previous results showed significant differences between CORT 10 and CORT 20 measures of long and short-term plasticity, CORT ELISA analysis revealed no significant differences. CORT 5 resulted in marginally significantly lower level compare to the higher doses. Thus, a correlation was found between the freezing response and plasma CORT levels. However, we continue to examine the impact of different levels of CORT and of stress severity on synaptic and local circuit plasticity in the hippocampus

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Protease-activated receptor-1 at the synapse

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Proteases and their receptors (PARs) are involved in the central and peripheral nervous systems function and pathology. We have previously localized PAR-1 to the node of Ranvier in the sciatic nerve. We have found that PAR-1 activation cause conduction block in the sciatic nerve and LTP and spontaneous activity in brain slices. High resolution methods have not, however, been used to study the expression and localization of PAR-1 in the synapse. Synaptosomes are known to contain mainly pre but also post and peri- synaptic elements and may thus serve a tool to study protein localization at the synapse. We currently studied the localization of PAR-1 in the synapse using brain slices and synaptosomes.

The presence of PAR-1 in the synaptosomes was measured by means of standardized western blot. The localization of PAR-1 in rat brain slices and synaptosomes was studied by means of high-resolution immune-fluorescence staining and analyzed using confocal laser microscopy (CLSM). Brain slices were further studied using immune-electron microscopy (iEM) staining.

We detected PAR-1 protein in the synaptosomes preparation. In brain slices PAR-1 was localized mainly to the hippocampal CA-3 region. The highest co-localization level was seen between PAR-1 and the glial marker GFAP. Immuno-EM staining demonstrated that PAR-1 is scattered between 2 compartments of the synapse. The highest level of PAR-1 was observed in the peri-synaptic glial compartment, and to a lesser extent in the post synaptic compartment. PAR-1 reactivity wasn't found in the pre-synaptic area.

This is the first high resolution description of PAR-1 localization in the CNS synapse. Together with the physiological evidence this data implicates glial PAR-1 in regulation of synaptic activity. This may be relevant to the effects of proteases which increase during inflammatory and neuro-degenerative diseases

Is sniffing contagious?

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Contagious behavior is the unconscious transmission of actions or emotions from one individual to another, such as contagious yawning, laughter or crying. Contagious behav-

ior onset is triggered by seeing, hearing, reading, or thinking about another person performing the behavior. The mechanisms that drive contagious behavior are yet unknown; yet a candidate mechanism for this behavior is the mirror neuron system. These neurons fire during the observation of an action carried out by another, and not only when carrying out the action itself. The mirror neuron activity could be related to action understanding, imitation and even theory of mind and empathy.
Sniffing patterns are modulated without conscious awareness, e.g., during asleep. Here we set out to ask whether sniffing is a contagious behavior. We recorded nasal respiration, galvanic skin response (GSR), electromyogram (EMG) and blood saturation from 10 participants while watching the movie " Perfume". Subject respiration was analyzed in relation to sniffing events in the movie. Inhalations peak and time to peak did not reveal any significant difference between sniffing events and non-sniffing events in the movie (all F (9) 0.38). Based on our preliminary results, we do not see an indication for contagious sniffing. Further investigation in a more natural environment is required.

Practice makes retinotopically perfect: the coordinate frame of motion learning

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Training-induced performance improvement, also known as perceptual learning, has been well established in motion perception. The training effect is quite specific to the trained stimulus, both in its position and direction of motion. However, since position specificity was demonstrated by showing the learning did not transfer to other positions on the screen with constant fixation (at the screen center), a given position on the screen always corresponded to a specific location on the retina. This study was designed to differentiate between a specificity in retinotopic coordinates vs. one in spatiotopic coordinates. This was done by testing the degree of transfer of learning to new stimulus locations that share the same retinotopic location as the learned position (but differ in their screen position), and vice versa. Participants trained on a motion discrimination task in which they were asked to report whether the direction of a motion is tilted to the right or to the left of the vertical axis. During the learning phase, lasting 5 sessions, the fixation point and the dot array were always presented in the same location. Thus, the stimulus position was constant both in its retinal and spatiotopic coordinates. Next, the level of transfer of learning was examined. Gaze direction and the dots` array location were systematically changed, creating four different configurations: one matching the retinotopic learned location, one matching the spatiotopic learned location, another that is horizontally symmetrical to the learned location and a control location that is neither retinotopic, nor spatiotopic or symmetrical. A decrease in the discrimination threshold to a level similar to the learned configuration (e.g. full transfer) was most apparent in the retinotopic learned position and the mirror-symmetric . We conclude that under the current task's conditions, motion discrimination, is likely to rely on retinotopic coordinate reference frame.

Medial amygdala stress components specifically regulate social interactions

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Although deficits in social behavior are maladaptive and characterize most psychiatric disorders, (Cacioppo 2007) the neuronal and molecular substrates that translate social signals to social behavior are still poorly understood (Insel 2010). In an aim to get new insights into this complex behavior, we designed an automated test (the 'social maze') that monitors social behavior and characterize the social dynamic between freely moving mice. We found that male mice deficient for corticotropin-releasing factor receptor type 2 (CRFR2) or urocortin 3 (Ucn3), a neuropeptide that specifically activates CRFR2, are severely impaired in social behavior compared to their wild-type littermates. In rodents, the medial amygdala (MeA) is the first brain station that process and classifies pheromone information. We applied gene targeting and pharmacological techniques to test whether CRFR2 and Ucn3 in the MeA participate in the processing of male/male social signals. Using a lentiviral-based system of RNA interference, we found that knockdown of CRFR2 levels, specifically in the MeA, but not in the Lateral Septum (LS), results in maladaptive social interaction with male conspecifics. Interestingly, no differences were detected in exploration or anxiety like behaviors between treated and control mice. We further found that administration of Ucn3 to the MeA improves the ability to confront a social challenge whereas administration of CRFR2 antagonist prior to Ucn3, severely impairs social behavior. These results demonstrate a specific role for MeA Ucn3/CRFR2 system in translating social signals into social behavior.

The role of Dlgap2 in post synaptic density (PSD) zone organization; Implication to PTSD

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Disks Large-Associated Protein (Dlgap) family is one of the less studied components of the PSD zone. It was proposed

to mediate the translocation of the scaffolding protein PSD95 from the cytosol to the membrane and its communication with sub-synaptic molecules. Impaired expression of Dlgap1 was reported both in schizophrenia patients and rat model. Accordingly, we have shown that abnormal Dlgap2 expression is associated with maladaptation to trauma in PTSD-like rats. The aim of this study was to delineate the mode of action of Dlgap2 using hippocampal primary culture from P1 sprague-dawley rat. Glia proliferation was restrained by adding ARA-C for 2 days in-vitro (DIV), resulting in about 30% immunoreactive glia. Time dependent changes in the mRNA levels of Dlgap2, PSD95, Neuroligin 2 (NLG2), NMDA receptor subunit (NR2B), neuronal Tubulin beta3, glial GFAP and the reference genes RSB3K, CypB and beta-actin during 4-29DIV were assessed by qRT-PCR. Intracellular location of Dlgap2 and related proteins were analyzed by immunohistochemistry. In addition, Dlgap2 was silenced by lentivirus-delivered shRNA in the hippocampal cultures. Higher Dlgap2 mRNA levels were associated with reduced glia content, suggesting that Dlgap2 is expressed mostly in neuronal cells. Time dependent Dlgap2 expression showed a bell shape curve and was positively correlated with that of PSD95 levels. However, the increase in PSD95 expression was delayed by 2 days as compared to Dlgap2, while corroborated with the enhancement in the expression of PSD-related genes, NLG2 and NR2B. This, together with morphological changes suggests a role for Dlgap2 and the PSD-related genes in neuronal sprouting. The effects of Dlgap2-silencing on PSD-related genes and neuronal morphology will be discussed. We believe that this study will unravel a role for Dlgap2 in PSD zone, which may be of relevance to postsynaptic function, which is believed to be impaired in PTSD.

Protective effect of PACAP through regulation of anti-oxidative potential

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Pituitary adenylate cyclase-activating polypeptide (PACAP) is a neuropeptide isolated from the ovine hypothalamus and PACAP and its receptors are distributed in the hypothalamus as well as other regions in brain. Although numerous in vitro and in vivo studies have revealed the neurotrophic and neuroprotective functions of PACAP in brain but only a few reports were focused on the effect of PACAP in protecting the oxidative stress. The present study is to clarify the role of PACAP on protecting the oxidative damage using PACAP-deficient mice. While PACAP does not show the anti-oxidative potential in vitro, intravenous injection of PACAP38 in mice significantly reduced the oxidative stress level and increased anti-oxidative potential in the plasma with a dose-dependent manner. These protective effects are not demonstrated by VIP and the anti-oxidative potential was cancelled by co-treatment with PACAP receptor antagonist, PACAP6-38. Aged PACAP-deficient mice evidently showed an oxidative stress in their plasma and in the hippocampal regions. Antioxidants expression in the hippocampal region of the aged PACAP-deficient mice significantly decreased compared with the age-matched wild-type mice. The aged PACAP-deficient mice were found to be impaired with the learning and memory task in some behavior tests. These results strongly suggest that PACAP has a function of protecting anti-oxidative stress as well as learning and memory with aging.

The effect of the inflammatory cytokine Interleukin-1 beta on glucose uptake

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Interleukin-1 beta (IL1) has a marked effect on memory that follows an inverted-U curve: physiological levels facilitate memory, while higher or lower levels yield memory deficits. Previous work in our laboratory indicates that astrocytes mediate these effects. We thus explored possible mnemonic-related mechanisms initiated by IL1 in astrocytes. A major role of astrocytes and a crucial condition for memory processes is glucose uptake (GU). IL1 was previously shown in-vitro to augment GU by astrocytes, but a concentration-response curve was yet to be constructed. To this aim, we utilized novel glucose fluorescent probes which, unlike traditional probes, do not necessitate glucose deprivation. In preliminary experiments, astrocyte-enriched cultures (90%) were extracted from neonatal mice cerebra and incubated for 4 days. Cells were then loaded with either 50 μM GB1 or 50 μM GB2, both cy3-labled glucose probes, in order to establish relative efficiency. Both probes reached saturation at 40 minutes. GB2 signal was 250% stronger than GB1. Both probes gave much stronger signals than traditional probes, e.g., 2-NBDG. GB2 was thus used in subsequent experiments. For concentration-response curve measurements, cells were incubated for 24 hours with either 0, 0.1, 1, 15, 100 or 500 pM human IL1, and then loaded with 6 μM GB2 for different times, to estimate effect on uptake kinetics. Immunostaining for GFAP, an astrocytic marker, was performed to verify the astrocytic localization of the probe. Our results indicate that the IL-1-GU concentration-response curve follows an inverted-U, with a peak at 15 pM. Furthermore, in three independent experiments, cells given IL1 showed less absorption of GB2 after 10 minutes,

relative to control. Thus, IL1 is suggested to slow down GU but increase saturation point. We propose that the inverted-U shaped effect of IL1 on memory could be the result of its effect on GU in astrocytes. This should be further explored in memory tests in-vivo.

In search of motor skill learning representation in the brain: training-dependent changes in speed-accuarcy trade-off functions

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Motor skills are highly prized in sports and rehabilitation. Surprisingly, the study of motor learning has largely neglected skill as improvement in movement execution. We designed a novel speed-accuracy trade-off task, the 'arc-pointing' task, defining motor skill learning as a training-induced change in the speed-accuracy function (SAF), and examined the effect of training speed on SAF changes. Interestingly, learning was not uniform across all test speeds, instead the shape of generalization changed as a function of training speed. Unexpectedly, improvement could be greater outside the training range: training at medium speeds resulted in more improvement at an untrained fast speed than training at the fast speed itself. This distinct pattern of generalization suggests that motor skill learning is computationally, and perhaps neurally, distinct from other forms of motor learning, such as adaptation and trajectory optimization. To investigate the neuronal representation of skill, we designed an fMRI version of our speed-accuracy task. Subjects were scanned, before (day 1) and after training (day 5), while they performed the task at three different speeds. We adopted this 2-factor design (day, speed) in order to separate learning from changes in performance (speed) due to learning, and potentially identify the interaction between performance and learning. The main analysis addressed changes pre-defined ROIs (superior parietal lobule (SPL), primary motor cortex (M1), premotor dorsal (PMd), putamen and cerebellum). We found a main effect of learning (day) in M1 and SPL and an interaction between movement speed and day on the proportion of task-related voxels in PMd. This interaction might be the neural correlate of the speed-dependency of skill generalization. These imaging data suggest that motor skill learning is neuroanatomically distinct from adaptation and action selection.

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What can functional imaging tell us about motor skill learning?

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In motor skill learning a superior level of performance is attained through practice. We designed an fMRI-compatible task to capture skill learning, defined as a shift in the speed-accuracy trade-off function (SAF). In the arc-pointing task, subjects were instructed to make horizontal pointing movements with their wrist while staying within a specified hemi-annulus. After training, the SAF changed significantly, signifying acquisition of a skill. Subjects were scanned before (day 1) and after training (day 5), while they performed the task at three different speeds. This 2-factor design (day, speed) was chosen in order to separate changes due to learning from changes in performance (speed) due to learning, and to potentially identify an interaction between performance and learning. Three different analysis approaches were used: (1) Multivariate, looking for qualitatively different patterns of activation as a function of day and speed across the whole brain. (2) ROI analysis, searching for quantitative local changes in pre-defined ROIs (superior parietal lobule (SPL), primary motor cortex (M1), premotor dorsal (PMd), putamen and cerebellum). (3) Within-ROI analysis, looking for changes in the proportion or the intensity of task related voxels within ROIs. We posit that the former is an imaging analog of cortical map expansion and the latter reflects increased signal transmission in a map of fixed size.

Multivariate analysis revealed a qualitative change associated with day, and speed by day interaction. ROI analysis revealed a main effect of day in M1 and SPL and an effect of speed in PMd and the putamen. Within-ROI analysis showed an interaction between movement speed and day on the proportion of task-related voxels in PMd. This interaction might reflect the uneven improvement in skill seen across speeds.

Skill learning, in contrast to adaptation and action selection, leads to neural changes in a cortical circuit but not in the putamen or in the cerebellum.

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Yes Ican: mechanisms underlying long-lasting sensory responses of accessory olfactory bulb mitral cells

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The ability to detect and process social information is essential for all social species and usually mediated, at least partially, by olfactory cues. In mammals, two of the sensory systems that deal with this kind of information are the main olfactory system (MOS) and the vomeronasal system (VNS), which are associated with reproduction, aggression, and parental behavior. Sensory neurons at the main olfactory epithelium project to the main olfactory (MOB), while sensory neurons at the vomeronasal organ project to

the accessory olfactory bulb (AOB) where they synapse on AOB mitral cells. We previously showed that mitral cells of these two systems are characterized by different intrinsic properties and response patterns. Previous studies that used extracellular recordings from behaving mice showed that responses of AOB mitral cells to natural stimuli are long-lasting. Here we use whole-cell recordings from acute mouse olfactory bulb slices to show that a brief (0.1 ms) stimulation of the sensory afferents elicits a long-lasting firing response in AOB mitral cells, response that lasts between 10-60 s. Synaptic-like current injections into the cell's soma (SL) generated a similar long-lasting response, despite the presence of glutamate and GABA receptors antagonists. These results suggest a postsynaptic mechanism underlying these prolonged responses, rather than a network activity. We hypothesized that this property of AOB neurons is mediated by a calcium-activated non-selective cationic current (Ican). Indeed, the intracellular presence of BAPTA, a calcium chelator, reduces firing duration response of AOB mitral cells to SL stimulation by 45.7% and to synaptic stimulation by 89.5%. Application of the Ican blocker flufenamic acid to the recording chamber reduces the duration of AOB mitral cells firing response to SL stimulation by 43.9% and to synaptic stimulation by 79.8%. These results suggest that Ican activity is essential for AOB mitral cells prolonged responses.

Tuning to pitch and spatial location in the human auditory cortex

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Background: Little is understood about the representation of space in the auditory system. Although we are relatively successful at locating sources of sounds in space, organization of the auditory system is known to be primarily tonotopic, whereas no analogical mapping of external space is known to exist. A possible explanation that might account for early tonotopic mapping along with space representation would be that auditory neurons are tuned to both pitch and location. The present study aimed at testing the existence of such neurons, using the fMR-adaptation paradigm.

Methods: Fifteen subjects were tested in a sparse fMRI experiment, using individually tailored sounds to create a virtual sound space. We presented combinations of two sounds of different pitches presented from one or two locations in the right hemispace. This created the following types of blocks: Single Location blocks, in which both sounds were presented from one location, Fixed Mapping blocks in which each sound was constantly presented from a fixed location, and Mixed Mapping blocks in which sounds and locations were mixed so that each sound appeared equally from each location. Only neurons which are tuned to both location and pitch should be differentially adapted by the Mixed and Fixed mappings. We measured BOLD activation to test the relative extent of repetition suppression in the different conditions.

Results: Our findings revealed higher activation in the auditory cortex for Fixed Mapping blocks than for Single Location blocks, reflecting adaptation to spatial location. Importantly, activation was higher for Mixed Mapping blocks than for Fixed Mapping blocks, despite the fact that in both conditions the two sound pitches and the two locations were equally presented.

Conclusion: These results confirm that spatially tuned neurons in human auditory cortex are also tuned to tone pitch, reflecting the overlapping maps of different acoustic features in auditory cortex.

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Wnt signaling pathway overcomes the disruption of neurogenesis induced by oligomeric amyloid ß-peptide

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Background: The neuronal loss associated with Alzheimer's disease (AD) affects areas of the brain that are vital to cognition. Adult Neurogenesis in the subgranular zone (SGZ) is thought to play a role in learning and memory and impaired neurogenesis is associated to memory dysfunctions. Previous studies have shown that Wnt signaling has a major role in neural stem cells proliferation and differentiation. Moreover, Wnt signaling major components are found to be reduced in AD.

Methods: In this study, we investigated the efficacy of Wnt signaling to promote neurogenesis in in vitro model of AD. We cultured embryonic hippocampal progenitors (HP) and evaluated the effect of Wnt3a on Aβ42 treated cells differentiation. Changes in Wnt signaling components were analyzed by using immunocytochemistry, real-time PCR and In-cell western analysis.

Results: We demonstrated that oligomeric Aß42 reduced neuronal differentiation in vitro accompanied with reduction of active β-catenin levels and proneural gene expression. Wnt3a was able to increase neuronal differentiation at the expense of astrocyte differentiation from HP treated with Aß42 and its effect was also mimicked by treatment with the GSK-3 inhibitor L803-mts. We demonstrated that the effect of Wnt signaling was not due to increased

proliferation or the rescue of neurons, but by committing HP differentiation to the neuronal lineage.

Conclusions: Our data show that Wnt signaling interruption induced by oligomeric Aß42 may contribute to the impairment of neurogenesis in HP. We propose that activation of Wnt signaling or inhibition of GSK-3 may enhance neurogenesis and improve cognitive state in AD patients.

Reduced survival of homozygote inositol monophosphatase-1 knockout mice on inositol-deficiency diet

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Background: There are three major sources for intracellular myo-inositol:

1. recycling in the phosphatidylinositol (PI) cycle.
2. de-novo synthesis from glucose-6-phosphate by myo-inositol-1-phosphate synthase and inositol monophosphatase (IMPase)1 encoded by IMPA1.
3. inositol of dietary origin taken up from extracellular fluids by the sodium-myo-inositol transporter (SMIT)1.

Knockout (KO) of IMPA1 inhibits recycling and blocks de-novo synthesis leaving dietary inositol as the only source of intracellular inositol. Therefore, dietary inositol-deficiency should enhance the effects of IMPA1 KO.

Methods: Homozygote (HO) IMPA1 KO mice received either a diet calculated to be 99% inositol free or an identical diet replenished with the amount of inositol present in a normal diet.

HO IMPA1 KO mice that survived 45 days on inositol-deficiency diet were studied in the pilocarpine-induced seizures sensitivity test.

Results: Nine out of 13 HO IMPA1 KO mice on inositol-deficiency diet (69%) died within 45 days compared to none out of eight HO IMPA1 KO mice with normal inositol intake that were on this diet for 26 days (Yates corrected Chi-square=7.1, $p<0.01$).

Three out of four HO IMPA1 KO mice (75%) that survived the 45 days on inositol-deficiency diet seized following the administration of just 50 mg/kg pilocarine compared with 100 mg/kg pilocarpine required to induce seizures in 12 out of 19 IMPA1 KO mice (63%) with normal inositol intake.

Conclusions: IMPA1 is essential for life in a state of inositol-deficiency diet.

We plan to study postmortem pathology of IMPA1 KO mice on inositol-deficiency diet to see whether death is due to brain edema, since inositol is an important brain osmolite.

Our results suggest that more moderate inositol-deficiency diet could enhance the reported behavioral effects of IMPA1 KO. This would support the possible clinical utility of inositol-deficiency diet as a strategy for enhancing the therapeutic benefits of lithium, an IMPase inhibitor.

The effect of juvenile stress on the course of inflammation

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The interplay between the nervous, endocrine, and immune systems becomes readily apparent during stress. Life events and stress have detrimental effects on the immune function, including interrupting the balance between pro and anti inflammatory cytokines and reduced NK cell activity.

Our research objective was to study the long term effects of psychological juvenile stress on local peritoneal inflammatory response in rats.

S.D. male rats were divided into 2 groups: juvenile stress (JVS) and control. The JVS group was exposed to the juvenile stress protocol (27-29 PND). All animals were examined in adulthood in the Elevated plus maze, open field and novel setting exploration test (58-59 PND). The immune system functionality was challenged (60 PND) using I.P. Carrageenan. The rats were sacrificed 4, 16, 48 or 72 hr post induction of inflammation in order to evaluate the different stages of inflammation. Cytokines secretions from peritoneal macrophages and from microglia were detected using ELISA. The activity of NK cells was evaluated and CORT concentration in sera was determined using ELISA.

Our results indicate that peritoneal macrophages exhibit altered activity as a response to the early life events, although the potential to be activated was not affected. Additionally reduced NK cell activity was demonstrated in adult rats after juvenile stress.

Keywords: Juvenile stress, Inflammation, Cytokine.

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Synapsin is not involved in the potentiation of spontaneous synaptic release by forskolin

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Synaptic vesicles (SVs) mediate neural transmission by fusing with the membrane at the active zone and releasing neurotransmitter into the synaptic cleft. Synapsin is the most abundant group of phosphoproteins associated with the SV membrane. They tether SVs to each other and to the actin-based cytoskeleton, thus creating the reserve pool (RP) of vesicles. Synapsin-synapsin interactions control the association of SVs within the RP, and thereby regulate the supply of vesicles from the reserve pool to the active zone. The N-terminal A domain of all major synapsin isoforms

contains a phosphorylation site (site 1) recognized by cAMP-dependent protein kinase (PKA) and CaM Kinase I. Phosphorylation of synapsin at this site during neurotransmission causes declustering of the reserve pool, releasing SVs to migrate to the active zone.

By activating adenylyl cyclase, forskolin induces phosphorylation of synapsin at site 1. In addition, the frequency of spontaneous synaptic release is significantly elevated by forskolin.

We examined whether synapsin phosphorylation participates in elevating the frequency of spontaneous postsynaptic events after forskolin application. For this purpose, intracellular recording of spontaneous events were performed in dense cultures of hippocampal neurons. The effect of forskolin on cultures from wildtype and synapsin triple knockout (TKO) mice was compared. We observed that the initial rate of spontaneous events in both cultures was not different. Moreover, forskolin induced a significant but similar increase in the frequency of spontaneous release. These results suggest that synapsin does not play an important role in determining the effect of forskolin. Thus, other mechanisms, perhaps phosphorylation of Epac, are involved in increasing the probability of spontaneous release by forskolin, rather than the availability of mobilized vesicles.

No brain-response to a human chemosignal in congenital anosmia

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Non-human chemosignaling is mediated by a combination of several chemosensing subsystems. For example, rodent social chemosignaling is mediated in part by the vemoronasal system. The functionality of human chemosensing subsystems beyond the main olfactory system remains poorly understood. To test for such non-olfactory chemosensing, we set out to use brain imaging in order to measure the brain response to a chemosignal in otherwise congenitally anosmic individuals. We hypothesized that if human social chemosensing is mediated by subsystems beyond the main olfactory system, than such anosmic individuals should nevertheless display a brain-response to a chemosignal. We used the sweat-derived compound 4,16-androstadien-3-one (AND), which has been widely considered in the context of human chemosignaling. An olfactometer delivered 6 blocks of 30 seconds of AND followed by 30 seconds of clean air, with a constant sniffing rate of once every 6 seconds (5 sniffs per block). We used a 3-Tesla Siemens Tim-Trio scanner, with acquisition parameters of 30 slices, slice thickness= 4 mm, gap=0, TR=1500 msec, TE=23.

Group analysis revealed an AND-induced response in the normosmic, but not anosmic subject ($p<0.05$). Those results are consistent with those obtained by Savic et al in conductive anosmia, and together suggest that the human brain response to the chemosignal AND are mediated by the main olfactory system. However, single-subject analysis revealed AND-induced responses in some anosmics. This suggests one of two alternatives: either that AND is processed by another subsystem, or that some diagnosed anosmics are not truly anosmic.

Combining transcranial magnetic stimulation with brain mapping techniques to study human motor control

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In the last decade, the combination of transcranial magnetic stimulation (TMS) and neuroimaging has greatly expanded the potential of human brain mapping. The relative timing of TMS in relation to neuroimaging determines which neuroscientific questions can be addressed with the combined TMS-neuroimaging approach. When TMS is given online (i.e. during neuroimaging), neuroimaging can reveal how focal cortex stimulation acutely modifies the activity and connectivity in the stimulated neuronal circuits. TMS and neuroimaging can also be separated in time (offline approach). A conditioning session of repetitive TMS (rTMS) may be used to induce rapid reorganization in functional brain networks. Neuroimaging can subsequently map the temporospatial patterns of TMS-induced reorganization. Alternatively, neuroimaging may be performed first to localize brain areas subserving a given task. The temporospatial information obtained by neuroimaging can be used to define the optimal site and time point of stimulation in a subsequent "virtual lesion" experiment in which TMS disrupts neural processing in a cortical area during a specific task. This talk will first touch on some general methodological issues that need to be taken into account when combining TMS with neuroimaging in studies of human motor control. The main focus will be on highlighting current applications of the online and offline TMS-neuroimaging approach. Finally, it will be discussed how TMS can be combined with structural brain imaging to study regional structure-function relationships in the brain.

Simulation of the vibrissal brainstem loop reveals effects of sensory feedback on whisking and active touch

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The vibrissa sensory-motor system is organized as nested loops. In the lowest order loop in the brainstem, sensory

neurons in the trigeminal nucleus project to the motoneurons in the facial nucleus. Retrograde axonal tracing show both excitatory and inhibitory projections to the facial nucleus. We ask: what is the role of excitatory and inhibitory sensory feedback to the facial nucleus in controlling whisker movements? We explore this issue using a simplified model of the loop, which includes motoneuron pool driven by external CPG that control whisker movements (Simony et al., in press) via intrinsic and extrinsic muscles, and receive inhibitory and excitatory sensory feedback driven by various cell types of the trigeminal ganglion (TG). We show that synaptic adaptation in the loop (Nquyen et al., 2005) leads to stabilization of whisking amplitude, and that the magnitude of the effect of sensory feedback peaks around 35 ms from protraction onset. Our preliminary results suggest that experimentally observed whisking "stuttering" or "pumps" in free-air (Towal et al., 2008) or upon object contact (Deutsch et al., this meeting) can be explained by the brainstem loop. Our analysis suggests that the frequency of rhythmic whisking (e.g., Gao et al. 2001) is controlled by higher sensory feedback loop that includes the CPG whereas the brainstem loop directly controls muscle force.

Regulation of hippocampal plasticity: from dynamics of single synapses to Alzheimer's Disease

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It is widely believed that memories are encoded and stored in the pattern and strength of synaptic connections. Individual synapses, the elementary units of information transfer, encode and store new information in response to the environmental changes through structural and functional reorganization. The number and plasticity of synapses are largely maintained through adulthood, but slowly decline during ageing and rapidly deteriorate in a variety of neurodegenerative diseases including Alzheimer's disease. However, the key mechanisms that normally maintain plasticity of synapses during adulthood or initiate synapse loss in neurodegenerative diseases remain elusive.

A persistent challenge in unraveling mechanisms that regulate memory function is how to bridge the gap between inter-molecular dynamics of single proteins, activity of individual synapses and emerging properties of neuronal circuits. To target this question, we developed an integrative approach to correlate structure and function at the level of single synapses in hippocampal circuits. Utilizing FRET spectroscopy, optical imaging, electrophysiology and molecular biology we explore the casual relationship between the pattern of ongoing neuronal activity, structural rearrangements within the synaptic signaling complexes and plasticity of single synapses and whole networks. Our results suggest that ongoing background synaptic activity critically determines the number and plasticity of synapses in hippocampal circuits.

The role of AKT phosphiorylation in acquisition and extinction of conditioned taste aversion.

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Association between a novel taste and a visceral malaise produces conditioned taste aversion (CTA); repeated presentation of the taste without the malaise causes aversion extinction. In the brain, the acquisition and extinction of CTA are suggested to be mediated by the insular cortex (IC)-basolateral amygdala (BLA)-prefrontal cortex (PFC) circuit. AKT is a main kinase of the PI 3-kinase cascade, implicated in long-term memory and synaptic plasticity and we hypothesized that it may be differentially involved in the IC-BLA-PFC neural network in the acquisition and extinction of CTA. To that end, we inhibited AKT phosphorylation by injection of LY294002 (LY; the PI 3-kinase cascade inhibitor) into the IC at different stages of the acquisition or extinction of CTA in rats. Inhibition of AKT phosphorylation in the IC prior or after the first extinction training (T1) facilitated the acquisition and consolidation of extinction on T2. In contrast, microinjection of the LY into the IC before T2 impaired the retrieval of extinction memory. These effects were transient, and extinction behavior returned to baseline levels on T3. Interference with AKT phosphorylation after T2 had no effect on extinction, suggesting that after being well consolidated, extinction is resistant to disruption by the AKT inhibitor.

These results suggest that AKT in the IC is differentially involved in acquisition and extinction of CTA.

The neuron as a population of ion channels – the emergence of stochastic and history dependent behavior

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The classic view of a neuron as a point element, combining a large number of small synaptic currents, and comparing the sum to a fixed threshold, is becoming more difficult to sustain given the plethora of non-linear regenerative processes known to take place in the soma, axon and even the dendritic tree. Since a common source for the complexity in the input, soma and output is the behavior of ionic channels, we propose a view of a neuron as a population of channels. Analyzing the stochastic nature of ion channels using recently developed mathematical model, we provide a rather general characterization of the input output relation of the neuron, which admits a surprising level of analytic tractability. The view developed provides a clear quantitative explanation to history-dependent effects in neurons and of irregular firing pattern recently observed in single

neurons, isolated from any synaptic activity, under periodic pulse stimulation. Specifically, we were able to reproduce the observed modes of neuronal response, derive an input-output relation for the neuron's mean firing rate, and a complete probabilistic state space description for the neuron's firing patterns. Though only a few approximations were made in this model, we were able to use only a small number of biophysically measurable parameters, and include the stochastic and history-dependent nature of the channels. The results suggest a new way through which neurons can perform complex spatio-temporal computations on their inputs, on a large range of timescales, and with low sensitivity to the temporal precision of input spikes.

Asaf Gal, Yariv Kafri, Shimon Marom, Avner Wallach

The lateral habenula and the etiology of depression in Parkinson's disease

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Introduction: Although a high percentage of Parkinson's disease (PD) patients suffer from depression in addition to their motor disabilities, the etiology of this depression is unknown. Within the framework of the monoamine deficiency hypothesis of depression and viewing depression as a system disorder, we present a neuronal circuitry, centered in the lateral habenula (LHb) that is hypothesized to account for depression in PD.

Method: Unilateral 6-hydroxydopamine (6-OHDA) injected rats (A PD model) were compared to sham injected rats. Manganese enhanced MRI (MEMRI) with intra cranial injection to compare dorsal raphe nuclei (DRN) afferent connectivity, and the novelty suppressed feeding and the force swim tests for behavioral assessments, were used. Measurements were performed with and without dopamine replacement therapy and before and after functional suppression of LHb activity by electrical lesion.

Results: Depression-like behavior of the 6-OHDA rats demonstrates their suitability to study depression in PD. MEMRI demonstrates reduced afferent connectivity of the DRN, in 6-OHDA rats, to various sites including the dentate gyrus of the hippocampus and the LHb. Dopamine replacement therapy partially reversed this reduction as well as normalized rat's behavior. Bilateral electric lesion of the LHb of 6-OHDA rats normalized their behavior.

Conclusion: Dopamine deficiency, DRN connectivity and depressed-like behavior are all connected through the LHb. Our hypothesis that DA deficiency causes GPi and LHb hyperactivity, which in turn down-regulates DRN excitability and connectivity leading to depression, was validated in the 6-OHDA rat model. A physiological explanation for depression in PD patients is thus suggested.

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Learn to be fast: speed gains accuracy

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Our recent neurophysiological findings provided evidence for collinear facilitation in detecting Gabor patches (GPs) and for abolishment of collinear interactions by backward masking (BM). It was suggested that suppression induced by BM eliminates collinear facilitation. Moreover, we showed that training on BM task improved processing speed. Here we applied perceptual learning (10 days) in order to study whether reinforced facilitatory interactions can overcome BM. Event-Related Potentials (ERPs) were recorded before and after training. Low-contrast, foveal target GP was simultaneously flanked by two collinear high-contrast GPs. For BM, another identical mask was presented at different time-intervals (ISIs). Before training, BM induced suppression of target detection for ISI of 50 ms. This ISI coincides with the active time-window of lateral interactions. After training, remarkable improvement in all behavioral measurements occurred, including percent correct, sensitivity (d'), reaction time (RT) and decision criterion for this ISI. ERP results show that before training, BM abolished facilitation at the same ISI, measured as the amplitude of negative N1 ERP peak (latency of 260 ms). After training, sensory representation, reflected by P1 peak, has not changed, consistent with unchanged physical parameters of stimuli. Instead, shorter latency (by 20 ms, latency of 240 ms) and increased amplitude of N1 indicate development of facilitatory lateral interactions between the target and the collinear flankers. Thus, previously effective BM became ineffective in disrupting collinear facilitation. Moreover, robust correlation between RT and high-amplitude later "Response" peak (latency of 620-660 ms) was significantly decreased by training, suggesting evolvement of processing mechanisms that are less dependent on later stages of processing. Overall, we suggest that perceptual learning strengthening collinear facilitation results in faster and more automatic processing.

The National Institute for Psychobiology in Israel

Do purkinje cells remember?

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It is now well established that Purkinje cells exhibit bi-stability of membrane potential and spike rates. Transitions between the membrane potential states can be triggered by an input. We investigate the responses of cells to current injections of both polarities, delivered at different times after a state transition. Essentially, we question whether Purkinje cells have memory of state duration.

Activity of Purkinje cells was recorded in a whole-cell configuration, using cerebellar sagittal slices. State transitions were readily observed. Positive and negative current pulses were delivered at different times, and the transitions induced by these pulses were monitored. We define the memory trace parameter (MT) calculated as the difference between the probability of inducing a transition by injection of current and the probability of spontaneous transition, as a function of time spent in the present state.

We found that MT changes as function of time. It seems that neither the polarity nor the intensity of the current affect the behavior of MT. We conclude that Purkinje cells do remember how long they spent in their present state. This supports the hypothesis idea that the Purkinje cell is a state reporter rather than an event detector.

Axonal versus dendritic excitaiton: what do we excite?

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Primary hippocampal neuronal cultures were shown in our lab to be excited by time varying magnetic fields (Rotem A, Moses E. Magnetic stimulation of curved nerves, IEEE Trans Biomed Eng. 2006 Mar;53(3):414-20) and by electrical fields. In this work we show that excitation in neuronal cultures occurs in the axons for short duration magnetic and electric fields , and is therefore strongly dependent on axonal directions, while for longer duration fields it occurs in the dendrites and is therefore isotropic.

We used 2-dimensional and 1-dimensional primary neuronal cultures. The 1-dimensional cultures is a method developed in the lab to grow cultures of neurons with most axons directed along pre-defined patterns (Feinerman O, Segal M, Moses E. Signal Propagation along Unidimensional Neuronal Networks. J Neurophysiol. 94: 3406-3416 (2005)). We stimulated these cultures by rotating fields and constant fields with different pulse durations.

The 2D cultures were much more easily excited by rotating fields (less than half the pulse duration or less than half the amplitude). The rotating fields integrate excited neurons grown in all directions in the culture. In the 1D cultures about half of the amplitude or pulse duration were needed to excite the culture when the electrical field (either by direct applied external voltage or induced by time varying magnetic field) was parallel to the direction of axonal growth.

We conclude that when applying a short stimulating field the axons in the direction of the electrical field will produce an action potential. Long pulses will also excite the dendrites. This is due to the different physical characteristics of the axons and dendrites.

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Learning to read by “seeing with sound”: a case study of sensory substitution

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Braille reading is known to activate the ventral visual cortex of the blind, despite use of the tactile rather than the visual modality. But can this multisensory convergence of reading be generalized to the auditory modality? Specifically, can the blind learn to read using a sensory substitution artificial vision algorithm which utilizes the auditory, rather than tactile modality? If so, will it activate the ventral visual cortex similarly to visual and Braille reading? We looked into reading using the vOICe sensory substitution device, which translates visual images to sounds, enabling the blind to "see", and in this case read, with their ears. We examined a unique congenitally blind individual who was literate in reading Braille but analphabetic to the "sighted" letters. We scanned her, using fMRI, before and after she learned, for the first time, the shape of the "sighted" alphabet using the vOICe. We show that only following training, in which the participant learn to associate a phonological value to the heard sounds, reading with sounds activated the ventral 'visual' cortex, similarly to reading Braille. Therefore, reading activates the visual cortex in an a-modal, or metamodal, fashion. This suggests that the visual cortex can be trained to process reading via 'vision' using sensory substitution, even without visual experience and in a new sensory modality.

Perceptual vs. semantic mechanisms for multisensory responses in Penfield's homunculi

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Semantic knowledge of words meaning was suggested to be represented in a category-specific manner. This hypothesis was supported by recent findings demonstrating somatotopic representation of action-related words along the motor and premotor cortex. Here, we set fMRI experiment aiming to explore for the first time the involvement of somatosensory and motor areas in responses to passive perception of body parts names and to test whether body parts names are represented semantically in the sensorimotor cortex. We show that in addition to auditory cortex activation, passive perception of auditory list of body parts names elicited significant activations in the left ventral somatosensory and motor cortices. The evoked responses were restricted to the ventral areas in the sensory and motor homunculi, regardless of the body part name that was heard, and were specific to the lip and tongue representations in Penfield's homunculi. The lack of somatotopic organization indicates that the sensorimotor cortex activation during body parts

names perception reflects a more general multisensory processing which is specific for speech articulators without semantic representation.

The role of brain-derived neurotrophic factor in the antidepressant effect of desipramine and electroconvulsive treatment

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Administration of different antidepressant drugs or electroconvulsive treatment (ECT) causes an increase in brain-derived neurotrophic factor (BDNF) levels in the hippocampus. However, opposing roles were suggested for BDNF in the hippocampus and the ventral tegmental area (VTA), despite the interaction between these regions. Previously, we found that a reduction in BDNF expression, using RNA interference and lentiviral vectors (LVs) injected into the rat's dentate gyrus (but not the CA3) of the hippocampus precipitates depressive-like behavior. On the other hand, another study found that a selective ablation of the BDNF gene from the VTA induced antidepressant-like effect in the social defeat stress paradigm. Here, we tested whether elevation in hippocampal BDNF expression, or reduction of VTA BDNF expression are essential for the behavioral effects of the antidepressant treatments desipramine and ECT. In order to do so, we sought to knockdown or over-express BDNF in specific brain regions and then test whether it alter the behavioral effects of desipramine and ECT. BDNF knockdown within the hippocampus of rats blocked the behavioral effect of desipramine, but not ECT, as was observed at the forced swim test (FST) paradigm. In addition, ECT, but not desipramine, reduced BDNF expression levels significantly in the VTA of the rats, regardless to whether they were or were not subjected to hippocampal BDNF knockdown. Therefore, we over-expressed BDNF within the VTA of the rat brain and tested whether it alter the behavioral effect of ECT. Indeed, VTA BDNF over-expression blocked the behavioral effect of ECT at the FST. Theses findings suggest that the mechanism of desipramine action is dependent on elevation of hippocampal BDNF expression, while the mechanism of ECT action is dependent on reduction of VTA BDNF expression. These findings may explain individual differences in resistance to specific antidepressant treatments.

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Visuomotor neurons in the human parahippocampal gyrus

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Indirect manipulation of objects using intermediate devices, for example during Wii gaming, operation of industrial robots or during computerized digital drawing, requires the brain to coordinate the visual information about an object with goal movements. This study investigates the representation of visuomotor coordination in the human temporal and frontal lobes by recording single unit activity from 15 patients with pharmacologically intractable epilepsy undergoing invasive monitoring with intracranial depth electrodes to identify the seizure focus for potential surgical treatment. Participants performed the classic center-out task to control a cursor.

We show that the firing rate of neurons in the human parahippocampal gyrus is correlated with the speed, acceleration and direction of movement of the controlled cursor. This correlation disappears when the cursor is visualized but not under the control of the hand, or when the same hand movements are performed without visual feedback. We suggest that these activations are part of a visuomotor control loop, and are responsible for translation of the visual information into an actual motor plan.

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Novel histone deacetylase inhibitors protect astrocytes against doxorubicin induced oxidative damage

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Background: Oxidative-stress is a major cause for many neurodegenerative diseases; it is also a major factor in cognitive-dysfunction found among cancer survivors after receiving cancer therapy. Since histone deacetylase inhibitors (HDACIs) have been described as neuroprotective agents, we synthesized novel HDACIs prodrugs of butyric (BA) and valproic (VPA) acids and examined their neuroprotective activity.

Methods: The neuroprotective effect of the HDACIs against oxidative damage induced by doxorubicin (Dox) was evaluated in cultures of astrocytes. For viability test the cultures were labeled with propidium iodide and annexin FITC, and for detection of ROS production, they were labelled with DCF-DA. Cell analysis was performed by FACS. Histone deacetylase (HDAC) activity was measured using a fluorometric assay kit. Results: Treatment of astrocytes with the HDACIs as single agents, did not affect the viability or their HDAC activity; moreover, it attenuated Dox-induced mortality. In contrast, these HDACI prodrugs reduced the viability and the HDAC activity as well as augmented Dox induced death of U251 glioblastoma cells. Dox dramatically increased ROS production, whereas the prodrugs induced ROS only in cancer cells but not in

astrocytes. Additionally in astrocytes, the prodrugs abrogated ROS production by Dox. The antioxidant N-acetylcysteine (NAC) was less effective than the prodrugs in protecting astrocytes from Dox toxicity. Additionally,the HDACI prodrugs selectively affected genes expression, were found to be orally bioavailable, crossed the BBB and possessed low systemic toxicity.

Conclusions: The HDACI prodrugs protected astrocytes from oxidative damage by Dox and at the same time enhanced its anticancer activity. Since a correlation was found between reduction of cell viability and inhibition of HDAC activity, this inhibition plays a key role in the specificity of the prodrugs. The therapeutic potential of the prodrugs for treatment of neurodegenerative diseases merits further investigations.

Synchronized neuronal activity in social behavior-associated brain areas during the formation of social recognition memory in behaving rats

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The ability of an animal to recognize a familiar individual is critical for many aspects of mammalian social behavior. Most mammals rely primarily on olfactory cues for social recognition. A meeting between two unfamiliar rats or mice usually starts with a period of intensive olfactory investigation, which precedes further social interactions. Based on the natural tendency of rats to closely investigate novel individuals, a simple laboratory test to investigate social recognition memory was developed. In this test, a juvenile is introduced into the cage of a resident adult rat for a period of five minutes and the time spent by the adult rat on investigation of the juvenile is measured. Then, this procedure is repeated several times with the same juvenile, until the adult displays a very short investigation time. This short-term social recognition memory was found to be specifically dependent upon release of the neurohormone oxytocin in the medial amygdala (MeA), which receives convergent inputs from the main (MOB) and accessory (AOB) olfactory bulbs, hence is a major candidate to regulate pheromones-mediated behaviors. In this study we used local field potential (LFP) measurements in behaving rats to follow synchronized neuronal activity in few brain areas assumed to be involved in social recognition memory, including the MOB, AOB and MeA, during the behavioral paradigm. A power-spectrum analysis of the recorded LFP signals revealed a peak around 8 Hz (theta rhythm) which is most prominent during investigation of a novel animal and gradually declines during repeated investigations of the same animals. Thus, the strength of the theta rhythm in these brain areas correlates with the time of investigation, which serves as a measure for the social recognition memory. We conclude that social investigation behavior evokes synchronized neuronal activity which is proportional to the novelty of the social stimulus, in a dispersed neuronal network.

What makes us human : short term synaptic depression in the human neocortex

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Synaptic transmission in the cortex, responsible for coding and transmission of information is dynamic in nature. The postsynaptic responses carry information about the temporal structure of the presynaptic input. Findings on laboratory animals and theoretical studies have extensively characterized the rate of depression which depends on the probability of neurotransmitter release and governs the extent to which rate and temporal structure of firing of action potentials from the presynaptic neurons are signaled to the postsynaptic population. It is unknown whether short term plasticity also exists in human synapses and if similar rules also hold true for the human brain. Here, we directly tested in human slices cut from neocortex tissue removed for surgical treatment of deeper brain structures in drug-resistant epilepsy patients, whether adult human synapses can modulate responses in a short time scale, we applied and quantified this changes as given by the Tsodyks-Markram model for dynamic synapses. In contrast to values reported on rodent neocortical synapses the time constant for recovery from depression differed significantly (~550 ms in rodents and ~140 in humans). This numbers not only show that short term synaptic depression occurs, but also reveals the capacity for higher bandwidth signal processing of the human cortex.

Selective COX2 ihibition results in persistently favorable outcome and induces gliogenesis following traumatic brain injury

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Background and Objectives: Non-steroidal anti inflammatory drugs (NSAID) are used for the treatment of pain, fever and inflammation. Traumatic brain injury (TBI) is a condition which involves acute and chronic inflammatory processes. Therefore, we aimed to study whether NSAID, with special emphasis on COX2 selective inhibitor would improve outcome after TBI.

Methods: TBI was induced in Sabra male mice that were then treated with vehicle or carprofen, NASID, for 7 days. Functional outcome was evaluated with the neurological

severity score (NSS). Mice were given BrdU to label newborn cells for 10 days. The animals were killed 24 days post TBI to evaluate edema (as percent water content) and 90 days post TBI to evaluate lesion size, as well as newborn cell fates.

Results: Carprofen significantly reduced lesion size ($p=0.002$) and edema formation ($p=0.03$) and also led to significantly larger improvements in functional outcome ($p\leq0.008$). Administration of carprofen resulted in a significant decrease in the number of activated microglia in the lesioned hemisphere. Carprofen also induced a 3.5 fold increase in the proliferation of new progenitors cells in the peri-lesion area ($p\leq0.002$) but newborn cells differentiated mainly into glia cells in both groups.

Conclusions: Carprofen is neuroprotective and induces cell proliferation and neurogenesis after TBI. Treatment with carprofen is associated with better functional motor outcome. Our results imply that COX2 selective inhibitor may represent novel therapeutic options for TBI.

Differential brain activation patterns for item recognition and inter-temporal associations: a MEG study

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Background: Context effects (CEs) on recognition memory provide important insights into associative memory processes. Associations yielding CEs are not limited to items that are processed simultaneously, but can also take place when items are processed in temporal proximity.

Method: We conducted a MEG study (N=40) of memory for pairs of items encoded and retrieved sequentially, to identify neural activity associated with the retrieval of inter-temporal associations. Participants studied pairs of successive objects pictures, and were asked to make old-new judgments for each pair member, under 5 different retrieval conditions: 1) Repeat: target old, context old – same. 2) Re-pair: target old, context old – different. 3) Target old, context new. 4) Target new, context old. 5) Target new, context new.

Results: We identified four time ranges of increased activation, at ~100, ~200, ~400, and~700 post-stimulus onsets. Activation patterns at ~100 ms, ~400 ms, and ~700 ms were associated with item recognition, producing higher activation for old, compared to new items. Activation patterns at ~100 ms, ~200 ms, and ~400 ms were further modulated by temporal associations, with stronger activation for probes in the Repeat condition (in which probes were accompanied by their original inter-temporal contextual stimuli) compared to the Re-pair condition (in which probes were accompanied by familiar stimuli which were not their inter-temporal study contexts).

Conclusions: These results show dissociable modulations of event-related magnetic fields associated with item recognition and temporal binding. Beamformer analysis of the MEG data is expected to reveal distinct activation patterns related to different levels of associative binding.

Microarray study of lithium-treated mice and knockout mice with lithium-like behavior reveals a common effect on mitochondrial function

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Background: The molecular mechanism of lithium (Li)'s mood-stabilizing action is not yet unraveled. Previous studies have shown alteration in gene expression following mood stabilizing drug treatment in a variety of genes, including genes involved in inositol metabolism.

Inositol-monophosphatase (IMPA) 1 is inhibited by therapeutically-relevant Li concentrations, possibly resulting in decreased inositol, subsequent down regulation of the phosphatidylinositol cycle and dampening of assumed hyperactive neurotransmission through this pathway. Li was also shown to down-regulate the expression of sodium myo-inositol co-transporter (SMIT) 1, responsible for the uptake of myo-inositol from extracellular fluids.

Both IMPA1 and SMIT1 homozygote knockout mice exhibit lithium-like behavior in the forced-swim test and the pilocarpine-induced seizures paradigm. We aimed to identify gene networks and pathways similarly affected in homozygote IMPA1 and SMIT1 knockout mice and in Li-treated mice compared with wildtype (WT) untreated mice. Since our results of differentially expressed genes culminated in mitochondrial function, we used the oxidative phosphorylation inhibitor rotenone to evaluate behavioral reversal of Li effects.

Results: The analysis of the microarrays revealed that oxidative phosphorylation and mitochondrial function are the only statistically significant pathways commonly affected in the frontal cortex of SMIT1 and IMPA1 knockout mice and in Li-treated mice. Administration of rotenone augmented the hyperlocomotion response to d-amphetamine, an effect that was attenuated by Li treatment.

Conclusions: Our results corroborate previous findings in bipolar patients and suggest that improvement of mitochondrial dysfunction mediated by inositol depletion might underlie the therapeutic effect of Li.

Modeling network phenomena in the Inferior Olive

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Output spikes of the Inferior Olive (IO) are of great importance to cerebellar function because they directly trigger complex spikes in the Purkinje cells. There is ample evidence that the exact timing of IO output relates to underlying sub-threshold oscillations. One feature of those sub-threshold oscillations is that they are not always synchronized and often phase-locked; this is remarkable given the fact that IO neurons are wired together by gap-junctions only. In this modeling study we investigated the networks dynamics in the IO and in particular the occurrence of waves of activity in the IO

We built minimal single neuron models being able to reproduce characteristic membrane dynamics expected to be of importance in generating sub-threshold oscillations. Then, we devised a larger network consisting of 995 model neurons coupled by gap junctions and added limited inhibitory inputs, mimicking inputs coming from the deep cerebellar nuclei.

By simulating these network over different parameter regimes and by changing the type of electrical coupling, we could reproduce important experimental results. Preliminary analysis indicate that the the distance over which neurons are gap-junction coupled, the asymmetry of the gap-junctions, and the time constants of the electrical coupling affect the network dynamics. We discuss relevant experimental and modeling issues.

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The role of Parkinson's disease gene DJ-1 in microglia activity

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Background: Parkinson's disease (PD) is a progressive neurodegenerative disorder affecting more than 1% of individuals over 55-year-old and more than 3% of those over age 75. PD is characterized by motor disturbances, appearance of lewy bodies and dopaminergic neuronal death. Impairment in mitochondrial activity has been linked to neurodegeneration in PD. To date mitochondrial genes, such as DJ-1 were linked to PD, and 10 to 25 percent of all those genes correlate with early-onset (before age 50) PD. Activation of glial cells in the CNS is the first defense mechanism against pathological abnormalities that occur in neurodegenerative diseases. Recently we and others have discovered that microglia dysfunction may lead to stress conditions resulting in neuronal death. We postulate that mutations found in PD genes, such as DJ-1 affect microglia cells activation.

Methods: Based on the literature the mutations in DJ-1 are loss of function mutations, and therefore knockdown of the genes using shRNA can be used to evaluate the role of the mutation in cell culture. Microglial cell line was transfected with shRNA against DJ-1 or with non target shRNA used as control, and cell activity was evaluated by of gene expression and protein levels and cell activity.

Results and conclusions: We found that knocking down DJ-1 by shRNA reduced microglia activity as shown by gene expression levels of cytokines, such as IL-6, and degradation enzymes, such as insulin degrading enzyme (IDE) and scavenger receptor A (SRA) that are important for maintaining the homeostasis of a healthy brain. Furthermore, we have also demonstrated that DJ-1 impairment results in a significant reduction in the microglia migration ability. We suggest that DJ-1 is essential for microglia cell activation and dysfunction might result in impairment in microglia activity in PD.

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Large-scale cognitive map in a flying mammal

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The ability to navigate is crucial for animals, yet navigational mechanisms are poorly understood, especially in mammals. Here we report the first GPS-tracking of bats in the wild. Egyptian fruit bats commuted from their cave to a remote fruit-tree in high, fast and very straight flights, and returned to the same individual feeding-tree night after night. Bats that were displaced 44-km south homed to one of two goal locations – cave or feeding-tree – which allowed ruling out navigation based on beaconing, route-following, or path-integration mechanisms, and suggested instead map-based navigation. Bats released within a deep natural crater, 84 km south of their cave, exhibited severe disorientation, while bats released atop crater-edge homed well – indicating navigation by the geometric configuration of distal visual landmarks. Taken together, these results provide the first evidence for large-scale cognitive map in mammals.

Locus coeruleus urocortin 2 conditional over-expression enhances cued but not contextual fear conditioning

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Background: The salience of emotionally loaded events is amygdala dependant and involves activation of the locus cerelious -norepinephrine (LC-NE) system. The LC-NE

system modulates the amygdala, hippocampus and neocortex based neurocircuits, and is characterized by a dynamic bi-phasic mode of action, that is regulated to promote and maintain arousal to suit environmental conditions. Under challenging conditions the LC-NE system shifts towards a mode of action that promotes increased arousal, scanning attention and sampling of behaviors. This shift is known to involve release of corticotropin releasing factor (CRF) and activation of its type 1 receptor (CRFR1) in the LC, while increases in NE release in stress-related limbic structures are known to regulate CRF release in the LC. Yet, the CRF family of peptides includes also three urocortin peptides and the LC is a major site of neurons expressing urocortin 2 (Ucn2), which binds selectively to the type 2 CRF receptor (CRFR2). However LC Ucn2 functional role is poorly understood. Methodology: The current study established a novel Ucn2 site-directed genetic mouse model and utilized it to examine the effects of LC-Ucn2 conditional over-expression (LC-Ucn2COE) on aversive memories utilizing the auditory fear conditioning paradigm.

Results: LC-Ucn2COE specifically affected behaviors that were previously associated with pharmacologically increasing NE levels in the tail suspension and modified swim test, yet it did not affect anxiety like behaviors and general locomotion. Furthermore, LC-Ucn2COE increased the freezing response to the cue, but not the context, in the fear conditioning retention tests.

Conclusions: Collectively these findings suggest a role for the Ucn2-CRFR2 system in modulating LC-NE enhancement of aversive memories that may relate to stress associated alterations in memory formation.

Short-term learning induced plasticity and behavior prediction- a diffusion tensor imaging (DTI) study

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Background: Learning-induced plasticity in the adult brain is commonly attributed to functional plasticity (e.g. LTP) while structural plasticity is restricted to neurogenesis in the hippocampus. Nonetheless, other brain regions and other elements (e.g. macroglia) are gradually gaining a vast interest. Diffusion tensor imaging (DTI) is well established for microstructural characterization of the brain. However, most of the DTI studies focus on pathology and aging. Few MRI studies deal with plasticity induced by long-term learning. We use the apparent diffusion coefficient (ADC) and fractional anisotropy (FA) parameters to differentiate between gray and white matter changes. Our aims are to detect short-term structural plasticity in rats, to locate the origin of memory processing and to predict behavior performance- using DTI.

Methods: Rats underwent two DTI scans before and after they perform a one-day version of the MWM task, which includes reference and working memory paradigms. Two voxel-wise analyses were done on the DTI indices (ADC and FA): 1. Parametric comparison before and after the task, for assessing the learning-induced plasticity. 2. Correlation between the 1st scan and the following MWM performance, which contributes to the prediction approach. Rat were perfused one day after the second scan and brain sections were stained with the immunofluorescent markers GFAP (anti glial fibrillary acidic protein) and NF (neurofilament) at relevant regions.

Results and discussion: Comparison revealed FA increase in hippocampus-related white matter (cingulum bundle), implies more organized fiber system. ADC and FA decrease in striatum gray matter, suggests denser and less organized tissue (astrocytes hypertrophy and NF dynamics by histology), respectively. Correlations between FA and the following behavior performance were observed in related regions. All above findings correspond to previous related studies, thus validate our methodological approach.

HIF1aplha is required for heat acclimation mediated neuroprotection

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Heat acclimation (HA, 4 weeks at 34±1 C) is a well studied preconditioning model which offers cross tolerance against various stressors, including traumatic brain injury (TBI). We have previously found that one of the main characteristics of HA phenotype is a basal as well as post injury elevation of HIF1alpha. HIF1alpha is the regulatory subunit of HIF1, a transcription factor that is associated with many cellular pathways triggered by signals such as cell stress. The current study was designed to examine whether HIF1alpha is required for heat acclimation mediated neuroprotection. To establish that, we have used acriflavine- a recently discovered inhibitor of HIF1 subunit dimerization. HA or normothermic control mice were injected with 15mcg/kg acriflavine or equiviliant volume of saline, immediately after they were subjected to TBI, and another similar dose was injected one hour later. By using neurological severity score (NSS), core body temperature measurements and TTC staining, outcome measures of the injured mice were evaluated following the inhibition of HIF1 and its downstream pathways. Results show that acriflavine treated HA mice demonstrated significant increase in lesion volume accompanied with functional deterioration 48 h post injury as compared with saline treated HA mice, hence abolished HA mediated neuroprotection. On the other hand, acriflavine treated normo-

thermic mice demonstrated no significant difference in functional recovery or lesion volume from saline treated normothermic group. Interestingly, core body temperature measurements revealed that while all acriflavine treated mice were hypothermic, only the HA mice showed dramatic hypothermia up to 48 h post injury We conclude that HIF1has a key role in dynamic processes leading to neuroprotection establishment in HA mice after TBI.

Differential effect of antidepressants on body mass regulation, food intake and metabolic hormones in rats exposed to chronic mild stress as compared to unstressed.

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Background: several classes of antidepressants are widely used for the treatment of depression. Weight gain is a common side effect of treatment with many antidepressants. Weight gain often leads to obesity which is associated with an increased incidence of insulin resistance, diabetes and metabolic syndrome. Little is known about the pathphysiology of the metabolic changes induced by these drugs including production of cytokines like TNF-α and adipokines like Leptin.

Methods: Male SD rats were exposed to 8 weeks of unpredictable chronic mild stress (UCMS) or to normal conditions (unstressed). Animals (8/group) were treated daily with vehicle, reboxetine (NRI); paroxetine (SSRI); or bupropion (NDRI) (5, 5 and 20 mg/kg ip respectively). Body weight and food intake were followed weekly. After sacrificing, trunk blood was collected for Insulin, Leptin, TNF-α and Grhelin determination. Brains were dissected for p-ERK /ERK protein determination using western blot analysis.

Results: Body weight gain was significantly suppressed in all the UCMS groups as compared to unstressed rats. In the stressed group, paroxetine showed impaired body weight gain. Whereas, in the unstressed rats, food intake and body weight gain was significantly suppressed only by bupropion. Bupropion treatment in the unstressed group increased Grhelin levels and decreased TNF-α and leptin levels. Paroxetine increased insulin levels in the unstressed group and decreased Leptin levels in both UCMS and unstressed rats.

Conclusion: UCMS caused a marked decrease in body weight gain and food intake in the rats. Antidepressants acted differentially on body mass regulation. Bupropion inhibited appetite and weight gain and decreased plasma Leptin levels in unstressed conditions, supporting its use for the therapy of obesity and hyperphagia in man. Only paroxetine induced insulin resistance in the unstressed animals, an effect that might underlie the SSRIs-induced increased body weight in humans.

Intranasal administration of arginine vasopressin selectively reduces empathy

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In the symposium: Mirror mechanisms in humans and their involvement in social cognition

The nonapeptide arginine vasopressin (AVP) is a key regulator of social behavior from voles to humans. In humans, acute intranasal administration (INA) of AVP modulates perception of facial expressions. Empathy is the ability to perceive, recognize and react to emotional stimuli and it is crucial to all social processes. The current report uses a pharmacological strategy to assess the role of INA of AVP in modulating empathy.

Participants filled out the Interpersonal Reactivity Index (IRI), a measure of trait empathy. Later, in a between-subject double-blind design, 20 IU of AVP or placebo (P) was self-administered to 39 male subjects (age 25±2.2). Empathy was measured using the Eyes Test 45 min after INA. For each photo in the test, the participant chooses one of four words which best suits the emotion displayed.

Empathy was significantly decreased in participants who received INA AVP ($t=-2.2$, $p=.03$) so that the AVP group had made more errors than the P (AVP=12.05, P=9.74). In addition, a regression was performed using the number of errors in RMET as the predicted variable and Treatment, IRI and Interaction as predictors. This analysis revealed a complex picture of the effect of exogenous AVP. IRI and the Interaction were significant predictors (T: $b=.75$, $p=.51$; IRI: $b=-.17$, $p=.01$; Interaction: $b=-.27$, $p=.04$). The correlation between trait empathy and RMET was significant in the AVP group only (AVP: $r=-.59$, $p=.01$, P: $r=-.11$, $p=.67$). The current report is the first to test the effect of INA of AVP on empathy and its relationship to trait empathy. Understanding the underlying biological basis of empathy is an important avenue of research given the prevalence of disorders characterized by dysfunctional social communication. This report provides us with a first glimpse into the complex nature of AVP's effects on empathy.

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The 18 kDa mitochondrial Translocator Protein (TSPO) degrades protoporphyrin IX. A TSPO knockdown study

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Activation of the 18 kDa mitochondrial translocator protein (TSPO) results in cell death induction in cancer cell lines,

including apoptosis. Thus, we assumed that the putative endogenous TSPO ligand protoporphyrin IX (PPIX) may contribute to cell death induction of cancer cells. For our study we used U118MG TSPO knockdown cells (TSPO siRNA) and their control cells (Scrambled siRNA). U118MG is a glioblastoma cell line. We exposed those cells to PPIX and measured cell death as well as PPIX accumulation in whole cells and in isolated mitochondria under dark and light conditions, using fluorescence microscopy and fluorescence assisted cell sorting (FACS). We found that cell death and PPIX levels in TSPO knockdown cells were significantly higher than in control cells after treatment with PPIX in light condition. Thus, TSPO – PPIX interactions did not appear to contribute to cell death. We also found that omission of light exposure abolished the cell death we observed after PPIX exposure. Thus, in our paradigm, PPIX by itself did not induce cell death. Interestingly, accumulation of PPIX in TSPO knockdwon cells after treatment with PPIX in complete dark was higher than in combination with light exposure. Thus, TSPO appeared to reduce PPIX levels, an effect that was enhanced by light exposure. Heme levels were not increased in control cells, but did increase in PPIX treated TSPO knockdown cells. Thus, conversion of PPIX to heme was not part of the mechanism whereby TSPO can prevent accumulation of PPIX. We also found that adding the ROS scavenger glutathione (GSH) to PPIX treatment caused an increase in accumulation of PPIX compared to cells that were treated only with PPIX. This was reminiscent of the results with TSPO knockdown cells compared to control cells. Thus, our study shows that the TSPO prevents accumulation of PPIX and heme, apparently due to PPIX degradation dependent on ROS generation resulting from TSPO activation.

"Feeling by seeing": Haptic sensing induced by non-attentive visual stimuli

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Effectiveness of minimally invasive surgery robots is limited by surgeon's lack of haptic sensation while remotely operating the robot. Thus, reconstruction of haptic sensation has become an important research goal. Here we report an experiment in which visual stimuli successfully evoked haptic sensation.

Participants tracked pre-defined paths on silicon surfaces, while maintaining constant stylus pressure. Visual feedback on pressure was provided as a color signal (color performance-lines displayed on the task screen) and as a frequency signal (pulsating ellipses displayed on a unique "Haptic Sense Display", HSD developed for this study). The HSD was positioned peripherally at a 400 visual angle, and a secondary "Landolt C" detection task at stylus tip, ensured that HSD was unattended.

Comparing acquisition phase performance with trials (HSD-only, color-line-only, and no-feedback conditions), pressure was efficiently maintained in the color-line-only condition, as expected, and in the HSD-only condition. Performance significantly declined in the no-feedback condition.

Further test phases utilizing virtual surfaces (no contact between stylus and tracking surface), yielded similar results and subjective haptic sensation reports. Our results indicate a cross-modality processing of haptic sensation, induced by a non-attended peripheral-visual stimulus.

Epigenetic regulation of the Oxytocin receptor expression in the mouse brain.

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Oxytocin (OT) is a nanopeptide that is produced in the brain and released via the pituitary gland into the blood. In addition to its well known peripheral actions, it also plays a vital role in the modulation of mammalian social behavior through its secretion within the brain.

A recent study showed that hypermethylation of several CpG sites within the human Oxytocin receptor (OTR) was associated with decreased levels of the OTR mRNA in the temporal cortex tissues from individuals with Autistic Spectrum Disorder (ASD) as compared to age-matched control. This study suggests an association between DNA methylation of the OTR promoter and the level of the OTR expression.

The OTR expression profile is brain-region specific, sex specific, influenced by gonadal steroids and markedly different in between species.

In this study we hypothesize that DNA methylation is involved in the brain region and sex specific differential expression of the mouse OTR. In order to challenge our hypothesis, we compared the pattern of methylation of the OTR promoter sequence, between two brain regions; the Olfactory Bulb (OB) and the Cerebellum (Cer), of male and female mice and correlated it with the OTR expression levels in both regions.

Our results indicated that the levels of OTR expression are significantly higher (>X10) in the OB than in the Cer. By using the bisulfite sequencing analysis method, we examined the methylation pattern of seven CpG sites within the

OTR promoter region. We found that in the first CpG site, higher levels of methylation were detected in the Cer compared to the OB. Interestingly, this CpG site is located within a binding site for the Estrogen Receptor alpha transcription factor. These results suggest an association between the level of methylation in the OTR promoter region and the expression levels of the OTR within the brain, which could be regulated by the accessibility of transcription factors.

On line measurment of neuronal threshold using the Response Clamp

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Responses of individual neurons to ongoing input are highly variable, reflecting complex threshold dynamics. Experimental access to these threshold dynamics is required in order to fully characterize neuronal input-output relationships. The challenge is practically intractable using present day experimental paradigms due to the cumulative, nonlinear interactions involved. Here we introduce the Neuronal Response Clamp, a closed-loop technique enabling control over the instantaneous response probability of the neuron. The potential of the technique is demonstrated by showing direct access to threshold dynamics over timescales ranging from seconds to many hours. Moreover, the method allowed us to expose the sensitivity of threshold dynamics to spontaneous input from the network in which the neuron is embedded. The Response Clamp technique follows the rationale of the voltage-clamp and dynamic-clamp approaches, extending it to the neuron's spiking behavior. The general framework offered here is applicable in the study of other neural systems, beyond the single neuron level.

Possible contribution of satellite glial cells to chemotherapy-induced neuropathic pain

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Chemotherapy induced peripheral neuropathy (CIPN) is a dose limiting side effect, which can lead to cessation of treatment. A major manifestation of CIPN is chronic pain. Currently there is no preventative strategy or effective treatment for CIPN. Oxaliplatin is a common anti-cancer drug that induces CIPN in a high percentage of patients. We have reported that augmented gap junction mediated coupling among satellite glial cells (SGCs) in dorsal root ganglia (DRG) may contribute to chronic pain. Here we investigated the possibility that increased SGC coupling plays a role in a mouse model of CIPN.

Methods: Mice aged 3-4 months received two injections of oxaliplatin (4 mg/kg) IP, 3 days apart. Von Frey behavioral analysis was used to measure pain threshold prior to oxaliplatin treatment and 7 and 14 days after the first injection. SGCs in isolated L4,5 DRG were injected with the fluorescent dye Lucifer yellow and the incidence of coupling among SGCs surrounding different neurons was quantified. We also investigated the effect of gap junction blockers on pain behavior.

Results: Oxaliplatin-injected mice showed a significant reduction in pain threshold from 0.68 g in controls to 0.22 g at day 7 and 0.28 g at day 14 after the first injection. Coupling among SGCs was significantly increased in oxaliplatin-injected mice from 7.7% (controls) to 41% 1 week after the first injection, and 26% after 2 weeks. Administration of the gap junction blocker carbenoxolone to oxaliplatin-injected mice at day 7 in a different series increased the pain threshold significantly from 0.30 g to 0.98 g.

Conclusion: The results show that oxaliplatin reduced pain threshold and increased coupling among SGCs in mouse DRG. Gap junction blockade reduced this pain. We propose that increased coupling among SGCs contributes to the reduced pain threshold in oxaliplatin-injected animals and that gap junction blockers have a potential in CIPN therapy.

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A new role of feedback: Facilitating stabilization of perceptual learning after training

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A number of studies have systematically examined the role of response feedback (informing an observer of performance accuracy) during training in perceptual learning and found that feedback facilitates performance gain and therefore perceptual learning (e.g., Herzog and Fahle, 1998, 1999). Here we found a new role of feedback: feedback stabilizes perceptual learning to be more resilient against deterioration/adaptation due to an excessive amount of training (e.g., Mednick et al, 2005, Censor et al, 2009). In the first experiment, 12 subjects were trained on a 2IFC motion detection task. Subjects were trained on two randomly interleaved motion directions, 90º apart. One direction was always paired with response feedback, while the other was not. Training occurred for consecutive 3 days. Performance gradually increased in the time course of training for the two directions. Before and after training, pre-test and post-test stages were conducted. Unlike training, performance was measured not only for the two

trained directions but also a spread of eight other directions ±48º away from these directions in increments of 12º, for a total of 18 exposed directions. There were 30 trials for each direction. No feedback was given in any trial. Performance changes after training were calculated for the first half (early) trials and second half (late) trials of the test stages for each direction. For the direction trained with feedback and its vicinity, significant degrees of learning were observed in both the early and late trials. On the other hand, for the direction trained without feedback and its vicinity, a significant degree of learning was observed only for the early trials, but this learning effect completely disappeared in the late trials. In the control experiment, a longer 7-day training regimin was used, and no feedback was provided for either direction. Although the degree of learning for both trained directions was comparable to that in the condition with no feedback in the first experiment, learning effect was observed only for the early trials of the post-test stage. This result indicates that the destabilization of learning for feedback-absent directions in the late trials of the post-test stage is not due to the small magnitude of learning. Putting these results together, we conclude that the role of feedback is not only to increase the magnitude of learning but also to stabilize learning to be resilient to deterioration or adaptation accumulated due to excessive amount of trials (e.g., Mednick et al, 2005, Censor et al, 2009).

Neuroprotective capabilities of the major metabolite of rasagiline, 1-(R)-aminoindan, in 6-OHDA- and lactacystin-induced dopaminergic neuronal degeneration

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The anti-Parkinsonian, monoamine oxidase-B inhibitor, rasagiline (Azilect; N-propargyl-1-(R)-aminoindan) is primarily metabolized by hepatic cytochrome P450 isoenzyme 1A2-mediated N-dealkylation to form its major metabolite, 1-(R)-aminoindan. Recent studies have shown that 1-(R)-aminoindan possesses neuroprotective activities in vitro against several insults applicable to various neurodegenerative diseases. Here we show, for the first time, that 1-(R)-aminoindan reversed behavioral asymmetry and restored striatal catecholamine levels in two rat models of Parkinson's disease: the unilateral 6-hydroxydopamine (6-OHDA) lesion and lactacystin-induced neuronal degeneration. In vitro, using human SH-SY5Y neuroblastoma and rat primary cortical cells, 1-(R)-aminoindan significantly protected neurons from hydrogen peroxide (H2O2)-induced oxidative stress (OS), associated with increased catalase activity and markedly up-regulated mRNA levels of phase II detoxifying enzymes. These neuroprotective effects of the metabolite 1-(R)-aminoindan, implicated in 6-OHDA- and lactacystin-induced dopaminergic neuronal degeneration in vivo and against OS in vitro may contribute to the neuroprotective/neurorescue activities of the parental compound, rasagiline.

Teva Pharmaceutical Netanya Industries, Ltd. (Israel) and H. Lundbeck A/S (Denmark)

Ladostigil prevents oxidative-nitrative stress, glial activation and memory loss in ageing rats

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Background: Ladostigil (N-propargyl-3R-aminoindan-5yl)-ethyl methyl carbamate) was designed as a pseudo-reversible inhibitor of acetyl (AChE) and butyryl (BuChE) cholinesterase (AChE) and an irreversible inhibitor of monoamine oxidase (MAO)-A and B for the treatment of Alzheimer's disease (AD) co-morbid with depression. Its AChE inhibitory activity results from metabolites, MCPAI and CAI formed in the liver and the brain-selective MAO inhibition, from the formation of HPAI through hydrolysis of the carbamate by cholinesterase. The brains of subjects with mild cognitive impairment (MCI) many of whom develop AD show evidence of oxidative stress and glial activation. In concentrations too low to inhibit either enzyme, ladostigil and its metabolites protect against cytotoxicity induced by oxidative and nitrative stress in cell cultures by preventing the opening of the mitochondrial transition pore and reducing apoptosis. They also they reduce the release of nitric oxide (NO), TNF-alpha and IL-1beta from microglia stimulated by lipolysaccaride.

Results: When administered for 6 months to 16 month old rats, ladostigil (1 mg/kg/day) prevented the increase in glial activation in the hippocampus, fornix and parietal cortex and elevated pro-NGF immunoreactivity in the hippocampus towards the levels in young rats. It also decreased nitrotyrosine immunoreactivity (a measure of oxidative-nitrative stress) in the parietal cortex and hippocampus in association with its prevention of loss of recognition and spatial memory.

Conclusion: The ability of ladostigil treatment to reduce oxidative stress, apoptosis and neuroinflammation could enable it to slow the progression of MCI to AD more effectively than AChE inhibitors in current use.

TGF-β1 affect endothelial cells cross-talk with peripheral immune response and leads to cerebrovascular amyloidosis

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Background: Astrocyte-endothelial cells (EC) interaction plays a major role in the function of the neurovascular unit. Dysfunction in their interaction may lead to amyloid accumulation on blood vessels and cause microhemorrhage and cognitive impairment. Transforming growth factor-β1 (TGF-β1) expression levels correlate positively with the degree of cerebrovascular amyloid in Alzheimer's disease (AD) cases. Furthermore, expression of TGF-β1 under GFAP promoter in mice leads to an age-related deposition of amyloid, such as β-amyloid (Aβ), around cerebral blood vessels. Recently, it was reported a physiological role of macrophages in the regulation and clearing of cerebrovascular amyloid in AD mice. We speculate that TGF- β1 may affect EC interaction with phagocytosis peripheral cells, such as macrophage, resulting in vascular amyloid deposition. Methods: We investigate the effect of pre-incubation of EC with TGF-β1 on T-cell and macrophage activity as shown by cytokines levels, migration ability and degradation of vascular amyloid deposition from AD animal model. **Results and conclusions:** Here we demonstrated that TGF-b1 affects EC and inflammation cross talk, leading to a reduction in macrophage activity as measured by protein levels and migration ability. Changes in EC secreted factors following TGF-β1 stimulation also affects Th1 T-cell activation as shown in reduction in the levels of IFN-g. Moreover, while medium from EC stimulated macrophage to clear insoluble cerebrovascular amyloid from an AD mouse brain, pre incubation of EC with TGF-b1 prevent EC ability to affect macrophage activity. Our findings support the importance of EC, macrophage and T-cells cross talk in preventing cerebrovascular amyloid deposition. Understanding EC-immune system interactions may pave the way to a new therapeutic approach in cerebrovascular amyloidosis disease such as AD.

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The interplay of phonological, orthographic and morphological information in reading Hebrew words by adult dyslexic and skilled readers

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Background: It is well established across languages that deficits in phonological processes are considered the primary source of dyslexia, while the role of morphological processing, across languages, in dyslexia is less clear. The dual version of Hebrew script (pointed and un-pointed) and the unique Hebrew rich morphology provides an opportunity to learn more about the effect of orthographic depth, and morphological richness on reading processes among good and impaired readers. Different behavioral studies examined the effects of phonological, morphological or orthographic information on reading rate and accuracy in Hebrew. Most of these studies focused on each type of information separately, but the interactions between these processes, especially in individuals with reading difficulties have yet to be studied. The goal of this study was to look at interaction effects between all those factors in an oral naming task in normal and impaired adult readers.

Methods: A group of compensated adult dyslexic students was compared to age matched normal readers in an oral reading task. Stimuli consist of 248 Hebrew nouns with 2-3 syllables, in several conditions: 3 vs. 4 consonants, with/without diacritic, with/without vowel letter, with or without morphological structure (root+pattern).

Results: Diacritic marks interfered with the Dyslexics reading rate in the absence of morphological structure, or when a vowel letter was added. In addition Dyslexics benefited from the morphological structure (only when reading pointed words). No such effects were found in normal readers.

Conclusions: Normal adult readers have sufficiently effective reading and are not influenced by adding phonological or morphological information. In contrast Dyslexic Hebrew readers, having difficulty with phonological decoding of pointed words may compensate by relying on morphological decomposition. These interpretations are currently investigated using fMRI.

Albumin-induced model of mesial temporal lobe epilepsy in mice

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The temporal lobe, the most epileptogenic region of the brain frequently gives rise to seizures and epilepsy (namely Temporal lobe Epilepsy (TLE)) following insults such as trauma, ischemia, tumor or infection. Such insults are often associated with breakdown of the blood-brain barrier (BBB). Recent animal studies have shown that in the neocortex disruption of the BBB or direct application of the predominant blood protein albumin leads to the development of epileptiform activity(Friedman et al., 2009). Furthermore, in the pilocarpine model of TLE, a relation between BBB breakdown and the number of seizures was reported(van Vliet et al., 2007). We thus tested the hypothesis that prolonged exposure of medial temporal lobe structures to serum albumin will result in spontaneous

seizures. To this end, we implanted mice with an osmotic pump for continuous, one week intraventricular perfusion of bovine serum albumin (BSA) in artificial cerebrospinal fluid (ACSF). Control mice were perfused with ACSF. We report uptake of BSA into specific cell populations, mostly glia, within the hippocampus, temporal cortex and white matter, followed by prominent and long-lasting astro-glyial activation without apparent neuronal cell loss or hippocampal sclerosis. Using continuous Video-ECoG telemetric recordings from treated behaving mice we ruled out status epilepticus or acute seizures in BSA-treated animals; In most treated mice spontaneous seizures were recorded within 4-7 days, persisting for at least one month after treatment. Our results suggest that prolonged BBB dysfunction and exposure of temporal lobe structures to serum albumin is sufficient to induce TLE and offers a new non status epilepticus induced model for the disease.

Expertise reduces neural cost but does not modulate repetition suppression

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The extent to which repetition suppression is modulated by expertise is currently unknown. We used event-related fMRI to test whether architecture students would respond faster to building stimuli and would exhibit stronger repetition suppression in the fusiform gyrus (FG) and parahippocampal cortex (PHC) than students from other disciplines. Our subjects performed a working memory task with buildings from Barcelona and Tel Aviv. In each trial, a behaviorally relevant target and task-irrelevant distracter were repeated twice among novel distracters. Behaviorally, we found shorter response latencies with target repetition in all subjects. Moreover, the repetition of targets and distracters was associated with decreased neural responses in the FG and PHC in all subjects. Interestingly, in control, but not in architecture students, reaction times during the first repetition of the target were correlated with activation in multiple brain regions (cuneus, lingual gyrus, inferior parietal lobule, insula, and anterior cingulate cortex). Thus, despite the similar behavioral and neural responses observed in all subjects, the non-experts had to recruit additional regions in order to perform the task. Our findings suggest that as a result of their expertise, architecture students were able to encode and detect building stimuli at a lower neural cost.

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Monoaminergic control of locomotion

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Background: Monoamines released onto spinal cord networks are critical for the expression and control of locomotion. In contrast with the other monoamines, the role of dopamine (DA) in controlling spinal locomotor circuits has been largely neglected in the mammal. What we do know is that DA is released within the spinal cord during stepping activity, increases motor output, and modulates sensory transmission. DAergic neurons that project to the spinal cord are clustered in area 11 of the diencephalon. In this presentation we will examine the effects of DA on spinal locomotor networks and neuronal synaptic and intrinsic properties.
Methods: We use an isolated spinal cord preparation dissected from neonatal mice. This allows us to record locomotor-like activity from exposed ventral roots or peripheral nerves. Locomotion was elicited by stimulating sacral afferents, or ventral roots. Activity was also evoked pharmacologically by adding serotonin, NMDA and or dopamine (or dopamine agonists) to the bath. Neurons were identified for intracellular recordings using either dye or GFP labeling approaches. In addition, we are currently using a decerebrate mouse preparation that allows us to test the effects of DA in the adult animal.
Results: Our data show that DA, acting through D1 receptors modulates several network properties, including cycle period and pattern. DA contributes to a rostrocaudal gradient of excitability that may act to stabilize network function. By examining intrinsic and synaptic properties we show that DA acts on several ion channels to increase excitability. Some of these include the SKCa channel, IA, and AMPA channels.
Conclusions: Our research illustrates how DA optimizes specific circuits and cells within the spinal cord in relation to locomotion. Most work on DA has concentrated on its role in the brain. Our work has uncovered an important role for DA in the control of spinal circuits that generate locomotion

Suppression of cortical response to auditory stimuli during sleep

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Sleep is a reversible state in which a person is perceptually disengaged from the external environment. Conflicting evidence exists regarding the extent to which the brain can process sensory information during this unique state of consciousness. In this study, modulation in auditory and

language processing was explored during sleep. Neutral auditory stimuli with varying levels of intelligibility were played to 10 healthy subjects during wakefulness and sleep. Functional magnetic resonance imaging was recorded from both cortical and sub-cortical areas, while independent physiological measures (electroencephalogram (EEG), and pulse rate) were simultaneously recorded and used for sleep staging. During wakefulness, our results demonstrated activity in bilateral superior temporal gyrus and thalamus in response to auditory stimuli. Additionally, left inferior frontal gyrus and bilateral superior temporal sulcus, corresponding to language processing regions Broca and Wernicke, were activated more by intelligible stimuli than by noise. By contrast, during sleep, a significant decrease in activation of the auditory cortex was observed compared to wakefulness(1.1±0.1 percent signal change in wakefulness, 0.6±0.1 in sleep, $p<0.001$). In addition, there was a loss of differentiation between speech and unintelligible noise in language related cortical regions during sleep (p 0.3). We thus conclude that auditory and semantic processing of neutral stimuli is diminished during sleep, due to functional disconnection from thalamic processing which stays constant.

Brain metastasizing melanoma cells: cross-talk with the brain microenvironment

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Non-tumor cells in the tumor microenvironment such as lymphocytes, macrophages, fibroblasts and endothelial cells as well as their soluble products shape the malignancy phenotype of the tumor and drive its progression towards metastasis. This presentation deals with interactions of the brain microenvironment with brain metastasizing melanoma cells. Brain metastasis confers upon melanoma patients an extremely bad prognosis. The mechanisms underlying homing to and survival of metastatic melanoma cells in the brain are unknown. Our working hypothesis is that interactions of melanoma cells with the brain microenvironment control site specific metastasis to this organ. Variants that form either local cutaneous tumors or brain metastasis in xenografted nude mice were generated from single human melanomas. As these variants have identical genetic backgrounds, any molecular differences between them reflect, most probably, alterations associated with the ability to form brain metastasis. These variants are being utilized to establish a specific molecular signature of melanoma brain metastasis and to study melanoma-brain interactions. Gene expression profiling of the cutaneous and the brain-metastasizing melanoma variants revealed a set of genes differentially expressed in local and metastatic variants. These variants also differed in their adhesive capacity to various substrates, in transendothelial migration, in proteolytic activity and in other functions. Most importantly, the two types of variants react differently to signals delivered by the brain microenvironment. The differential response of the brain-metastasizing and of the local melanoma variants to brain-derived signals may account for the propensity of the former variants to specifically metastasize to this organ site.

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Enhancing and disrupting perceptual learning by combining practice with periods of additional sensory stimulation

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We recently reported that exposure to an acoustic stimulus can facilitate learning when encountered near in time to practice on a perceptual task. This enhancement appears to result from an interaction between the influences of practice on the task to be learned and the additional stimulation. Here we explored the possibility that this interaction aids learning because one portion of the training (task performance or additional exposures) serves to amplify the internal representation of the stimulus and this amplification then remains during the other portion. If this is the case, learning should be disrupted if the stimulus representation is instead suppressed during one portion of the training, because that suppression should also spread to the other portion. To test this idea, we trained listeners on a non-native speech categorization task using regimens in which periods of task performance alternated with periods of additional stimulus exposure. We manipulated the extent to which listeners presumably suppressed the additional auditory exposures by varying the attentional demands of a visual task performed during their presentation. The periods of task performance alone yielded learning. As in our previous investigation, this learning was enhanced by additional stimulation that occurred during periods of low attentional demand. However, as the attentional demand during these periods increased, learning decreased and then stopped entirely. Learning was not disrupted when the demanding visual task was performed in quiet or performed while auditory stimuli not related to the categorization task were presented. Thus, it seems that the learning was blocked by the suppression of the specific auditory stimulus associated with the task to be learned and the spread of that suppression to the periods of performance of that task. We conclude that the magnitude of the internal stimulus representation affects learning and that changes in this magnitude can spread beyond the time in which they are induced to promote or interfere with learning [Supported by NIH].

Searching for a Universal Reactivator of OP Nerve Agent-Inhibited Acetylcholinesterase

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The antidotal treatment for organophosphorus (OP) nerve agent (NA) intoxication consists of an oxime that reactivates OP-inhibited acetylcholinesterase (AChE), atropine that serves as cholinergic muscarinic antagonist and an anti-convulsant drug to control seizures. So far, hundreds of oxime derivatives have been synthesized of which only few were developed as antidotal drugs for human use. It is assumed that in vitro reactivation potency of oximes toward a specific OP NA is correlated with their antidotal efficacy in vivo. We have studied the kinetics of in vitro reactivation of the following quaternary oximes: HI-6, HLo-7, MMB-4, TMB-4, Toxogonin and 2-PAM toward human AChE inhibited by the OP NA's sarin, VX, cyclosarin, soman and tabun. The time-course of reactivation of OP-inhibited AChE was measured by first inhibiting AChE up to 90-97% followed by 50-fold dilution either in phosphate buffer (pH=7.4, 23°C) or oxime solution. Soman-inhibited AChE was prepared at pH=9, 4°C to reduce the rate of acid catalyzed aging.. The following bimolecular rate constants of reactivation (k_r, $x10^3$, $M^{-1}min^{-1}$) of sarin-, VX- and cyclosarin-inhibited AChE were obtained for HI-6: 8.0, 2.0, 120, HLo-7: 15, 2,1,10, MMB-4 3.2, 1.5, 5.1, TMB-4: 0.17, 3.5, 0.7, Toxogonin: 0.15, 3.9, 1 and 2-PAM: 0.1, 0.06, 0.025 respectively: Only HLo-7, HI-6 and MMB-4 could reactivate non-aged somanyl-AChE with kr=,9.2, 4.7 and $0.9x10^3$ $M^{-1}min^{-1}$, respectively. Interestingly, the highest k_r values were obtained for oximes with pKa smaller than 8.0. The most efficacious and universal oximes found in our study are the bisquaternary oximes HLo-7 and HI-6 that also display high antidotal efficacy against most NA's. The weighted ranking order of all oximes as reactivators of NA-inhibited AChE is: HI-6~HLo-7>MMB-4>toxogonin~ TMB-4>2-PAM. These kinetic data may assist in the decision making process for selection of the appropriate oxime as an antidote for clinical use.

PolyADP-ribosylation of PARP-1 in the central amygdala is a prerequisite for cocaine-induced place preference

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Reward-related memory is arguably a factor in cocaine addiction. Activation of poly (ADP-ribose) polymerase-1 (PARP-1) was recently proposed as a necessary signaling mechanism for long-term memory formation. Using Pavlovian conditioned place preference (CPP), in which animals learn to associate drug effects with a distinct locality; we investigated PARP-1 participation in cocaine-induced CPP. Activation of PARP-1 in the central amygdala (CeA) was significantly more pronounced in rats expressing cocaine-CPP than in saline-conditioned rats. Infusion of the potent PARP inhibitor PJ-34 into the CeA before CPP testing abolished preference for the cocaine compartment up to 14 days. Results of locomotor and object-recognition tests in cocaine-conditioned rats ruled out the possibility that PARP-1 inhibition had impaired locomotion or formation of short-term or long-term memory. These findings suggest that PARP-1 activation in the CeA possibly resulting in poly (ADP-ribosylation)-induced modifications in memory retrieval and reconsolidation, mediates the response to environmental cues previously associated with cocaine.

The hormone receptors Hr51 and E75 regulate axon re-extension following developmental pruning

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It is well established that adult neurons in the CNS undergo little or no regeneration while developing neurons are capable of extensive growth and reorganization. Understanding the molecular mechanisms underlying developmental neuronal plasticity may therefore provide insights into the mechanisms that restrict regeneration of adult neurons. Neuronal remodeling of the developing Drosophila mushroom body (MB) is initiated by axon pruning of γ-neurons, followed by developmental regeneration to form adult specific connections. Our current knowledge of the underlying molecular mechanisms remains fragmentary. Only the γ-neurons in the developing MB undergo remodeling, offering a unique system in which developmental regeneration can be distinguished from axon growth per se. A mosaic forward genetic screen has identified the orphan nuclear receptor, hormone receptor 51 (Hr51/unf), as required for developmental regeneration. Mosaic analysis has shown that γ-neurons homozygous mutant for Hr51 extend axons normally in larvae and undergo axon pruning at early pupa, yet fail to re-extend their axons to the adult specific connection. Later born neurons extend axons normally, indicating that the mutation affects developmental regeneration and not axon growth per se. Genetic in vivo interaction experiments revealed that Hr51 can repress the expression of the nuclear receptor EcRB1, a known regulator of axon pruning. We also found that the nuclear receptor E75, which is regulated by EcRB1, is required for axon re-extension. Because the mammalian orthologs of

Hr51 and E75 (NR2E3 and NR1D1, respectively) were shown to function together, our data suggests that E75 and Hr51 may work as heterodimers to induce regeneration following pruning. Our study demonstrates that Hr51 and E75 may play a role in switching the growth status of axons from degeneration to regeneration and that dynamic interactions between nuclear receptors may regulate different steps of neuronal remodeling.

Activation of putative tonically active neurons in ventral and dorsolateral striatum during a two choice alternative associative learning task

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The striatum consists of GABAergic projection neurons and various types of interneurons. Despite their relative scarcity, these interneurons play a key role in information processing in the striatum. One such class of interneurons is the TANs, cholinergic tonically active neurons . In the dorsal striatum, TANs are traditionally considered to be responsive to events of motivational significance such as conditioned stimuli predictive of reward. However, in recent years, studies have suggested that TANs are not exclusively related to reward and reward-predicting stimuli, but may contribute to other processes, including responses to aversive stimuli, detecting spatial location of stimuli and generating movement. Currently there is little data concerning changes in TAN activity in the ventral striatum. We simultaneously recorded neurons in the ventral and the dorsolateral regions of the striatum while animals performed a two choice alternative association task. A large percentage of the putative TANs in both regions tended to respond around movement initiation and execution with dorsal TANs exhibiting strong directional selectivity relative to ventral TANs. Moreover, the firing rate of dorsal TANS increased in the preferred direction and decreased in the non-preferred direction whereas ventral TANs increased activity in both directions even when exhibiting directional selectivity. The time course of selectivity evolvement relative to movement initiation was similar in both regions. Our findings suggest that coding of movement by TANs in both regions overlaps to a larger degree than previously assumed, considering the segregation in the cortex-basal ganglia- thalamus-cortex circuits, yet the differences in response patterns support the notion that the TANs in the dorsal and ventral striatum have distinct functions in associative tasks.

Sensitivity to stimulus statistics in rat auditory cortex: beyond the oddball paradigm

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Neural activity in auditory cortex is sensitive to stimulus-probability – neurons respond more weakly to common than to rare sounds. However, it is unclear to what extent the neural activity in auditory cortex is sensitive to finer details of the statistical structure of the stimulus stream. We studied sensitivity to stimulus statistics in the auditory cortex of halothane-anesthetized Rats, using a variation on the oddball paradigms we used in earlier experiments. we contrasted responses in a random sequence of tones where one tone is common and the other rare (the type of sequence used previously in this kind of studies) with sequences that had a fixed order, in that the number of common tones between successive rare ones was fixed. We found that the responses to the common tone when the order is random were significantly larger than the responses to the same tone in a fixed sequence, even when the probability of the rare tone was as low as 5% (so that it 19 common tones occurred between successive rare ones). These effects were evident in LFP and multi unit activity from extracellular recordings, and in membrane potentials and spiking activity from intracellular recordings.
These results demonstrate a significant dependence of the neural responses on the precise structure of the stimulation sequence, and therefore the existence of a fine-grained analysis of the statistics of the sound sequence already at the level of primary auditory cortex, even in anesthetized animals.

Grid cells without theta oscillation in the medial entorhinal cortex of bats

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The entorhinal cortex plays a major role in spatial representation of the environment in the brain. This region contains 'grid cells', neurons which are activated when the animal's position coincides with a vertex of a hexagonal grid. To date,all electrophysiological data on grid cells were obtained from rodents navigating in either one or two-dimensional environments. As a result, all computational models trying to account for the grid formation relied on rodent data. These models can be generally divided into two major classes: (1) Network models relying on attractor dynamics; and (2) Single-neuron oscillatory interference models, which rely on the existence of a continuous theta-band oscillation.Because neurons in the bat hippocampus exhibit sharply tuned place fields in the absence of a continuous theta oscillation, we hypothesized that grid cells in the bat entorhinal cortex might exhibit hexagonal grid fields in the absence of theta rhythm. We thus seeked to

causally test the class of oscillatory interference models of grid formation.

To this end, we conducted the first electrophysiological recordings from a novel animal model – the Egyptian fruit bat navigating in a rat-style 2-D environment. These recordings demonstrated the existence of grid cells in the entorhinal cortex of this bat species. These grid cells were found to be very similar in many respects to the grid cells previously reported in rodents, but also to differ in others. The most intriguing difference was the existence of finely tuned hexagonal grid fields in the absence of continuous theta oscillation. Our results thus provide the first evidence for the existence of grid cells (as well as other spatial cell types) in the entorhinal cortex of a non-rodent mammalian species;and more importantly, these data contradict the class of computational models that rely on theta oscillation to explain the grid-cell phenomenon.

Visuo-motor error-related potentials during planar reaching movements

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Error related potentials (ErrP) in EEG signals are the focus of major research efforts, both for understanding error processing and for providing a basis for early error detection and correction by Brain-Computer Interfaces. Most studies concentrate on cognitive errors, involved in incorrect choices, improper sequences of events, or erroneous discrete movements. Recently, a number of studies reported the presence of potentials related to visuo-motor errors during continuous motion in visuo-motor rotation or tracking tasks. The purpose of this study is to establish the presence and characterize the potentials evoked in response to visuo-motor errors in continuous reaching movements. Our experimental paradigm is unique in generating controlled visuo-motor errors, which are well localized temporally, so synchronized averaging provides a well defined error-related potential. Furthermore, we varied the size of the visuo-motor error, and investigated its effect on the error-related potentials. Our results show error-locked negative and positive components, which peak between 180–280 msec, and 360-520 msec, respectively. The amplitudes of both components vary with the size of the visuo-motor error. Source localization showed systematic activation in Brodmann areas (BA) 6, 5 and 7, with occasional activity in areas BA 3, 4, 8, and 24. These results demonstrate the presence of detectable visuo-motor error-related potentials (VMErrP) and their sources. These potentials can be used for early error detection and provide a new tool for Brain-Computer Interfaces.

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Binocular conflict prevents learning

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Here we ask whether adaptation to optical distortions is possible with two eyes exposed to different distortions. Cylindrical lenses (1D) were mounted in front the eyes to create anisotropic distortions in the retinal image, using dot lattice stimuli. The vertical/horizontal spacings between the dots were varied to introduce directional bias in perception based on proximity grouping. Three conditions were used: (1) baseline: no distortion; (2) monocular distortion: cylinder to one eye; (3) dichoptic distortion: the two eyes were presented with orthogonal lenses; In each conditions, perceived bias was measured for each eye separately (monocular, the other eye presented with blank stimulus, gray) and for both (binocular) with all trials mixed in a single testing session.

Baseline measurement (1) showed equal perceived bias in monocular and binocular conditions (~5%). Monocular distortions (2) produced stronger biased perception in the distorted eye (~15%) with the other eye showing an opposite bias (-5%). Binocular testing showed a slight (nonsignificant) bias toward in the direction of the distortion. Dichoptic distortions (3) produced even stronger monocular biases (>20%) in the direction of distortion, with binocular stimulation showing no bias. Reaction time (RT) varied between conditions, depending on stimulus ambiguity, showing, surprisingly, slower RT to ambiguous binocular stimulation.

Our results suggest that inter-ocular conflicts enhance monocular distortions, possibly preventing, or slowing down, adaptation to the presented distortion. The slowing down of RT in ambiguous binocular conditions suggests a monocular site for the perceived perceptual organization. A binocular site of the adaptation process is implicated, with adaptation averaging over time information from both eyes. Additional experiments show long term adaptation and learning in such monoptic conditions but not in dichoptic (Yehezkel et al 2010).

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Immune modulation of learning, memory, neural plasticity and neurogenesis

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Over the past two decades it became evident that the immune system plays a central role in modulating learning,

memory and neural plasticity. Under normal quiescent conditions, immune mechanisms are activated by environmental/psychological stimuli and positively regulate the remodeling of neural circuits, promoting memory consolidation, hippocampal long-term potentiation (LTP) and neurogenesis. These beneficial effects of the immune system are mediated by complex interactions among brain cells with immune functions (particularly microglia and astrocytes), peripheral immune cells (particularly T cells and macrophages), neurons, and neural precursor cells. These interactions involve the responsiveness of non-neuronal cells to classical neurotransmitters (e.g., glutamate and monoamines) and hormones (e.g., glucocorticoids), as well as the secretion and responsiveness of neurons and glia to low levels of inflammatory cytokines, such as interleukin (IL)-1, IL-6, and TNFα, as well as other mediators, such as prostaglandins and neurotrophins. In conditions under which the immune system is strongly activated by infection or injury, as well as by severe or chronic stressful conditions, glia and other brain immune cells change their morphology and functioning and secrete high levels of pro-inflammatory cytokines and prostaglandins. The production of these inflammatory mediators disrupt the delicate balance needed for the neurophysiological actions of immune processes and produces direct detrimental effects on memory, neural plasticity and neurogenesis. These effects are mediated by inflammation-induced neuronal hyper-excitability and adrenocortical stimulation, followed by reduced production of neurotrophins and other plasticity-related molecules, facilitating many forms of neuropathology associated with normal aging as well as neurodegenerative and neuropsychiatric diseases.

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Why no win for Alzheimer's disease with present therapeutics

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Alzheimer's Disease (AD) has a complex pathology with predisposition to depression and 40 % suffer from extrapyramidal symptoms (Lewy body disease).Furthermore the process of cholinergic degeneration involves a cascade of neurotoxic events, including deposition of iron , increasd monoamine oxidase B, toxic aggregated Abeta peptide amylyoid, glutaminergic excitotoxicity and oxidative stress. These features lead us to develop non-toxic, lipophilic propargylamine, brain permeable multifunctional compounds with iron chelation, possessing cholinesterase and monoamine oxidase inhibitory moieties properties for AD. We investigated the neuropharmacology, neuroprotective and neurorescue effects of M30 animal models of Parkinson's disease and in transgenic APP/PS1 (Tg) mice model of AD, including its regulatory on Ab aggregation and plaque areas, holo-APP expression levels and APP-processing mechanisms and cognitive abilities, since the 5' UTR region of APP mRNA has a functional iron-responsive element. Comprehensive behavioral batteries determined at 10 month of age revealed that transgenic APPswe/PS1 mice given M30 during that period were protected from cognitive impairments in a verity of tasks of spatial learning and memory retention, working memory. Non treated transgenic mice remained impaired in all of these cognitive tasks/domains. M30 markedly reduced the levels of holo- APP and Beta-CTF in the frontal cortex, hippocampus and parietal cortex of APP/PS1 treated mice compared to non-treated animals. Coordinately, the levels of cerebral amyloidogenic Abeta peptide in soluble and insoluble fractions and the number of Aβ plaques and dimeric Abeta contents in the frontal cortex, hippocampus and parietal cortex were decreased in M30-Tg mice as compared to non-treated animals. Our findings provide support for long-term M30 therapy as primary strategy for treatment of AD.

3.5 unsolved mysteries in bat echolocation

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Echolocating bats emit the energy with which they sense their surroundings. Bat echolocation is therefore one of the most tightly controlled sensory systems. By modifying their sensory acquisition, bats can control many aspects of the information they acquire, such as its temporal flow, tempo-spectral resolution and spatial filtering. The echolocating bat thus serves as an excellent animal model for studying active sensing and perception.

I will present three and a half major open questions in bat echolocation that have wide implications on general topics in active sensing and cognition:

1) How can bats avoid being jammed by other bats when flying in swarms with many (sometimes thousands of) other conspecifics?
2) How do bats use active sensing to code auditory space? New data suggests that bats can actively change their head-related transfer function to code auditory space.
3) What is the importance of vocal learning in bats? In the past it was commonly accepted that only humans and songbirds show a real ability for vocal learning. Preliminary evidence suggests that this might not be true. Bats could be an ideal model to study vocal learning in a non-human mammalian animal.

3.5) Finally, I will present some new leads regarding the level of innateness of natural object representation in the bat brain.

Generation of internal representations in the thalamocortical somatosensory system of the rat

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Whether internal representations of external objects are formed by an open-loop series of neuronal transformations or via a closed-loop convergence process is not yet known. Using single-unit recordings in artificially-whisking anesthetized rats we identified four classes of neuronal codes (temporal, rate, labeled-line, and windowed labeled line) for object position that were distributed across the entire thalamocortical system. Thalamocortical responses converged on stable representations within several (~4) whisking cycles, involving fast bottom-up and slow top-down processes via the thalamus and somatosensory cortices (S1 and S2). During the convergence process, responses shifted from being dependent on the anatomical (thalamus-cortex) level to being dependent on the pathway (lemniscal-paralemniscal). The distribution patterns of the basic codes plus a temporal&rate combination code suggest that, consistent with previous results, phase-detection is computed in layer 4 of S1 and threshold operation is implemented in layer 2/3 of S1. We postulate that the observed reentrant-like convergence mechanism is a key component in motor-sensory convergence processes that underlie perception of object location.

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Neural responses to pop-out visual targets in the optic tectum of the barn owl

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In humans and primates, a target embedded in a uniform background is perceived as highly salient if it is different from its background (oddball target). It is not clear if this so called pop-out effect governs saliency perception in non-primates as well. In this study we searched for neural-correlates of pop-out perception in neurons from the optic tectum (OT, a mid-brain area involved in gaze control) of the barn owl. For each neuron, we first mapped the visual receptive field and then studied the responses to a target inside the VRF in three conditions: when the target was alone in the scene, surrounded by similar distracters and surrounded by different distracters. A pop-out effect was quantified as the normalized difference between the response to the target when it was different from the distracters and the response to the same target when it was similar to the distracters. This experiment and analysis was performed for three visual features: 1) The horizontal direction of motion, 2) the orientation of the bar and 3) looming versus shrinking. We report a clear pop-out effect for the horizontal direction of motion, i.e., if the direction of motion of the target was different from its surround the neurons responded to the target stronger compared to when the distracters moved to the same direction. No pop-out effects were observed to the orientation of the bar. In this case, the neural responses to the target were strongly inhibited by the distracters, independent of the orientation difference between the target and the distracters. In the looming paradigm we observed a strong preference of the neural responses to the looming stimuli compared to the shrinking stimuli but no pop-out effects. Our results suggest a neural-correlate of motion pop-out in the OT of the barn owl. The results cannot be explained by a global lateral inhibition model and require an additional, yet unknown, mechanism.

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Axonal transport as an efficient way for distribution of molecules within neurons

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Axonal transport is a critical process for supplying necessary constituents to different parts of a neuron and maintaining normal neuronal function. Different organelles such as mitochondria, cytoskeletal polymers and vesicles are being transported along the microtubules in the axon by the motor proteins Kinesin and Dynein. This transport can be divided to anterograde (by Kinesin) and retrograde (by Dynein), and further divided to fast and slow transport, whereas the anterograde transport rate is 1.5 times higher than the retrograde one. Axonal transport is impractical for transportation of small molecules, especially when needed in large concentrations. Diffusion as well, cannot yield the needed transport through axonal length scales.

We suggest that active movement of organelles exerts a drag force on the surrounding medium, which induces hydrodynamic flow. This flow facilitates directed movement of soluble materials along the axon. As was shown by others for the case of plant cells, the direction of this movement is the same as that of the transported organelles and with proportional velocities. In addition, since axonal transport is much faster in large cells, so does the movement of the soluble materials in the cytoplasmic medium. In this theoretical work we demonstrate that the

hydrodynamic flow is faster than diffusion and provides better distribution of molecules in the cell. By using the theoretical values for the velocities and drag forces of the fast anterograde transport, and by assuming that the velocity of the fluid is proportional to the drag force and independent of the distance from the motor, due to the axon small diameter, the velocity of the fluid induced by one motor protein is assumed to be 0.76 micron/sec. We present our calculation and our preliminary experimental system aimed to measure this effect. The system is based on microinjection of quantum dots for analysis of single cells within the neuronal network of leeches.

Somatotopy and deactivation in the primary motor cortex

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In the primary motor cortex (M1), several movement parameters are encoded in parallel. One of the most fundamental properties encoded is somatotopy. The somatotopic organization in M1 is evident both in the level of the single neuron and in the level of the whole homunculus. In this study we tried to characterize the spread of somatotopic information in M1 which allows an accurate movement encoding by investigating the activation-deactivation balance that creates the accurate pattern of information.

In order to address these questions, we designed a periodic experiment in which subjects performed bilateral, synchronized movements using highly practiced movement sequence of 20 different organs which were moved consecutively inside the fMRI scanner.

We demonstrated for the first time the somatotopic organization of 20 organs in M1 using advanced analysis methods. We also demonstrated the existence of deactivation in M1, which is organized in a somatotopic manner, forming a deactivation 'homunculus', in which somatotopic areas are deactivated when organs that are not under their control are moving.

We were also able to characterize the complete population somatotopic tuning curve in different parts of M1.

The overall unique pattern of activation and deactivation and of overlap and segregation in representation in M1 might facilitate the control over synchronized movement on the one hand, and avoidance of moving unwanted muscles, on the other hand. This excitation-inhibition balance, might be disrupted in several diseases such as dystonia and spastic diplegia as well as in conditions such as amputation and post-stroke processes. A better understanding of those mechanisms might benefit our understanding of those conditions.

Carbachol dependent persistent activity in the rat somatosensory cortex

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Cholinergic systems have been associated with a wide range of cognitive and behavioral activities. Cholinergic input mediates the brain's ability to select specific stimuli and preserve them for extended processing (Sarter and Bruno, 1997). Bistable neurons, which display a persistent state of firing along with a state of quiescence, are found throughout the cortex and are often dependent on cholinergic inputs (Schwindt, 1988; Fraser and MacVicar, 1996; Haj-Dahmane and Andrade, 1996, 1997, 1998; Klink and Alonso 1997). Using calcium imaging and whole cell recordings accompanied by pharmacological agents, we explored persistent activity in the rat somatosensory cortex. This activity is dependent on carbachol (CCh), an acetylcholine receptor agonist. Bath application of 20 μM CCh depolarizes pyramidal neurons by 7.72±3.63 mV, increases the input resistance by 34.5±26.1 MΩ, and in 60% of cells recorded (48/80), primes them for seconds long after-depolarizing potentials that outlast stimulation with depolarizing current pulses. This activity is independent of the surrounding network as it can be induced even under complete blockade of synaptic activity. Furthermore, we characterize the stimulus-response relationship that leads to persistent activity. The persistent activity is likely induced with a stimulus that exceeds 5 action potentials at a frequency of 5 Hz. Calcium imaging shows that in the presence of CCh, there is an increased accumulation of spike induced calcium. While this increase is not sufficient to cause persistent activity, the use of BAPTA, removal of external calcium, and the addition of flufenamic acid, a specific blocker of I_{CAN} conductance, all prevent the appearance of persistent activity, thus showing calcium to be necessary. These results show somatosensory, layer V pyramidal neurons are capable of a transient, non-synaptic 'memory' of excitation, which may play a crucial role in the computational processing of the cortex.

The comorbidity of depression and drug addiction: who is the chicken and who is the egg?

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Major depressive disorder (MDD) is one of the world's greatest health problems, and it is often accompanied by a comorbid substance abuse disorder (SUD). There are a few suggested mechanisms for this phenomenon, but the full set of features, especially the directionality of the comorbidity (i.e. which disorder preceded and/or caused the other), are not completely understood.

In the following study, we have investigated the effects of depressive-inducing manipulations on features of drug addiction and on the other hand, the effects of repeated drug exposure on measurements of depression-like symptoms in rats.
Our results indicate that induction of a depression-like state using chronic mild stress (CMS) elevated the levels of electric current rats would endure for the cocaine self administration, suggesting stronger addiction. Moreover, CMS strengthened a preference of heroin over a natural reward in a conditioned place preference paradigm.
As for the effects of drug exposure on depression measurements, cocaine sub-chronic administration caused rats to display lower motivation in the forced swim test. However, cocaine exposure caused elevation in the number of the center visits during the exploration test, which suggests lower anxiety. These results are in line with previous research performed in our lab, where cocaine administration impaired motivation for a natural reward, but only under conditions of stress.

Long and short term effects of juvenile stress on the hippocampal local circuit activity and plasticity

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Genetic disposition and child maltreatment and abuse have been identified as main determinants in the development of posttraumatic stress disorder and major depression. A novel animal model for anxiety and affective disorders exposes juvenile rats to stress, which induces a predisposition for the development of anxiety or depressive symptoms following an emotional trauma in adulthood. Emotional stress affects neural activity and plasticity in the hippocampus. These modifications not only take place at the level of the principal cells, but also alterations in local circuit activity in the hippocampus have been found, due to affected interneurons. Juvenile stress causes long-term changes in hippocampal GABA interneurons: it was found that fear conditioning or juvenile stress can reduce the expression of the GABA synthesizing enzymes, glutamic acid decarboxylase(GAD)65 and GAD67. Also alterations in GABA-A receptor subunits in the amygdala and hippocampus were observed in adulthood following juvenile stress. Furthermore, it was shown that a genetically induced deficiency in GAD65 predisposes for increased fear and anxiety. These alterations sensitize the organism to later stressful stimuli and underlie the development of posttraumatic stress disorder. In this study the juvenile stress model will be used to explore the functional role of GABAergic neurons in emotional stress and in the predisposition for the development of posttraumatic stress and posttraumatic depression in adulthood. Changes in postsynaptic GABAergic function in the hippocampus following juvenile stress will be characterized in vivo both at juvenile age and at adult age using electrophysiological techniques. This information will be used to find strategies and tools for intervention with stress-induced dysfunction in this model system.

First spike latency code for interaural phase difference and binaural correlation discrimination in the guinea pig inferior colliculus

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Certain computations in the brain, such as identifying the direction of an approaching predator, must be completed fast and reliably. However, traditional neural coding theory focused on rate codes that extract information from the neural spike count over long periods of time. Recently, it was suggested that first spike latency is a feature of the neural response that enables fast transmission of information in the brain. Here we study a latency based readout model that allows for fast computation of sound source location in the guinea pig auditory system. The accuracy of the latency model for discrimination between different interaural phase differences and binaural correlation values was compared with a conventional rate-based model and found to improve response speed at small cost to the decision accuracy. We find that the spontaneous firing of neurons limits the capacity of the latency model to accumulate information from large populations. We study two possible solutions that allow the latency model to overcome the detrimental effect of spontaneous firing and achieve fast and reliable readout. To utilize a latency based model, the brain must first identify stimulus onset. We demonstrate how stimulus onset time can be estimated from the responses of neurons that are less selective to the interaural phase difference of the stimulus and study the accuracy of this scheme. Combining the onset estimation and the latency models improves the accuracy of the model, especially for readouts based on neurons with high spontaneous firing rate. We conclude that use of latency codes has the potential to increase processing speed and decrease transmission time, with very little detrimental effect on processing accuracy.

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Electrophysiological correlates of metamemory judgments: retrieval of semantic knowledge using musical stimuli

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"Tip-of-the-Tongue" (TOT) refers to unsuccessful recall attempt accompanied by a feeling of imminent success. Indeed, TOTs are usually resolved with high degree of accuracy. Compared to successful retrieval which reaches un-delayed resolution both retrieval types are hypothesized to commence with high levels of cue familiarity and be accompanied by a high degree of access to related information. Previous electromagnetic research suggests early differences (as early as 300 ms post-stimulus onset) between TOT and successful retrieval (Know; K). We sought to examine these retrieval states experienced in response to musical cues, and to compare them to unsuccessful retrieval not accompanied by a strong prediction of future success (Don't Know; DK), in order to assess the current interpretation of the documented early difference between K and TOT. We conducted an EEG study designed to obtain early ERP correlates of the abovementioned states. Names of commonly known popular songs were queried using short initial song segments (3 sec). EEG was recorded while subjects were asked to indicate by button press their retrieval state, choosing between four options: successful retrieval (K), Tip-of-the-Tongue, Feeling-of-Knowing and Don't Know. Knowledge claims were confirmed off-line following the recording session. EEG data were analyzed for stimulus-locked epochs to calculated ERPs. Analysis revealed a difference between the TOT and K conditions in the early time interval of 300-550 ms post-stimulus onset, prominent at left fronto-central electrodes. Post-hoc analysis revealed a difference at the same time window and electrodes between TOT and DK. Based on our results we suggest an alternative theoretical account of the memory related FN400 ERP component, which is putatively a familiarity-related component. We propose that patterns of activity observed in our study may reflect an early indication of the degree of informativity of familiarity, rather than familiarity strength.

Persistent activity in the accessory olfactory bulb mitral cells is Ca2+ sensitive and mGluR dependent

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The accessory olfactory bulb (AOB) is the first relay of sensory information originating from the vomeronasal organ (VNO), where pheromones are detected by vomeronasal receptors. VNO neurons project to the glomerular layer of the AOB, providing the main input to the AOB mitral cells. Using whole-cell patch-clamp recordings in an acute slice preparation, we measured the responses of AOB mitral cells to a stimulation of VNO sensory fibers. A brief (1 ms) electrical stimulation evoked a persistent spiking activity lasting up to 100 s. Blocking the action potentials, either by hyperpolarizing the membrane potential or by applying QX314, unraveled a long-lasting depolarization (LLD) that seemed to underlie the persistent spiking activity.

Both the persistent activity and the LLD were blocked by mGluR1a antagonist (AIDA 100 mM). In contrast, blocking ionotropic glutamate receptors (AMPA, NMDA) had no effect on the LLD. Furthermore, in the presence of mGluR1 agonist (DHPG 20 mM) LLDs as well as persistent activity could be evoked by a train of action potentials. The LLD was also significantly reduced by a bath application of flufenamic acid (FFA), a blocker of calcium-activated non-selective cation current (I_{can}), or by adding BAPTA, a calcium chelator, to the intracellular solution. These findings suggest that the LLD is produced by I_{can}, which is Ca^{2+} sensitive and mGluR dependent.

The persistent activation of AOB mitral cells reported here may imply that the accessory olfactory system serves as a gating system, which modulates the responses of higher brain centers to pheromonal stimuli.