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Motor control of regenerated arm of the octopus

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The octopus arm lacks any rigid skeleton and has virtually an infinite number of degrees of freedom (DOFs). Movements of the octopus arm are studied to understand the motor control of this hyper-redundant system. Previous studies showed that the octopus uses stereotypic reaching movements which reduce the number of control parameters to only 3 (one for the velocity of the bend point propagation and two for the orientation of the proximal part of the arm). We compared movements of a regenerative arm (half the size of normal arms) to those of normal arms in simultaneous reaching movements (both arms reach at the same time, SMs) and individual reaching movements (the arms reach independently, IMs). For IMs, the distance that the bend point moved and the time of movement for the regenerative arm was half of those of the normal arms. The tangential velocity profiles had a stereotypic bell shape characterization. Simulations of IMs by a dynamic model of the arms yielded similar results (the command was a constant velocity wave of muscle activation that took half the time to travel along the arm for the smaller arm). In contrast to IMs, no significant differences were found in the distance that the bend point moved and in the time of reaching between the regenerative arm to the normal arms in SMs. The time and the distance of the reaching movements of the regenerative arm were significantly larger in SMs than in IMs. The standard deviation of the maximal velocity of both arm types was smaller in the SMs than in the IMs. Tangential velocity profiles didn't have the bell shape characterization in SMs. Our hypothesis is that in SMs there is one motor command that coordinates the muscle activation wave which propels the bend.

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Peptide Nucleic Acid (PNA) based antisence molecules for treatment of CNS disorders.

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Recent advances in neuroscience have led an increasing number of gene targets for treatment of brain tumors and degenerative CNS diseases. A new and promising therapeutic approach has evolved based on antisense molecules. These are small strands of DNA (oligodeoxynucleotides, ODN) designed to bind to an mRNA target, thus inhibiting transcription of encoded protein. The advantage of antisence based treatment is higher selectivity towards a desired target. Polyamide (peptide) nucleic acids (PNA) are the third generation of antisense chemistry. They represent a novel concept as they have improved nucleic acid properties and peptide-like chemistry, enabling implantation of peptide biology into the nucleic acid field. Recent studies suggest that PNA cross the BBB and are internalized into neurons. PNA uptake properties were studied in vitro and in vivo in endothelial, glial and neuronal models. In primary tissue culture models we could demonstrate selective uptake of PNA into neuronal, glial and endothelial cells. FACS sorting analysis of fluorescence labeled PNA uptake into NMB, C6 and ENDB3 cell lines (models for neuronal, glial and endothelial components, respectively) showed uptake of PNA by neuronal cells but not by glial or endothelial cells. Intracellular PNA uptake into NMB cells was found to be temperature sensitive. In low concentration there is a marked difference between uptake into neuronal cells as compared to uptake into glial and endothelial cells this may suggest the existence of a transport mechanism. PNA intracellular accumulation has a punctuated pattern, an indication of endosomal/lysosomal trapping. Long term incubation of cells with high concentration of PNA was not accompanied by cellular toxicity. Following direct administration of PNAs into the brain we show selective uptake of PNAs into neuronal cells. No signs of cellular toxicity could be demonstrated as opposed to other ODN that are known to be toxic in high concentration.

ATP dependence of the non specific ion channel in Torpedo synaptic vesicles

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Synaptic vesicles of Torpedo electromotor neurons contain, in addition to the neurotransmitter acetylcholine, also a high concentration of ATP. The concentration of total ATP is around 120 mM, while the free [ATP] is about 5-6 mM. We examined the effect of the ATP concentration on the opening of the non-specific ion channel in Torpedo synaptic vesicle membrane. We found that the non-specific ion channel is closed when the ATP concentration is 60, 30, 10 and 5 mM but it opens very frequently at the concentrations of 1 and 0 mM ATP. The single channel conductance did not change significantly with ATP concentration. We assert that these results have significance in two different directions. First, they may take part in the post fusion control of transmitter release. Upon fusion of the vesicle with the surface membrane, the ATP leaks from the vesicle to the extracellular medium and thus the probability of the opening of the non-specific ion channel is increased, which in turn may lead to ion exchange and to release of transmitter. The second possible consequence of these results is that during metabolic stress and reduction of the intravesicular ATP concentration, the non-specific ion channel can open and dissipate the ion gradients in the vesicle membrane. This in turn may affect substantially transmitter release and synaptic transmission.

GABAA agonist facilitates extinction of conditioned fear in the infralimbic prefrontal cortex and the basolateral amygdala

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In fear conditioning, repeated presentation of the tone in the absence of the shock causes previously acquired fear responses to gradually decline. Most studies examined experimental extinction processes in either the infralimbic prefrontal cortex (IL) or the basolateral amygdala (BLA), both implicated in extinction of fear. Here, we focused on the kinetics of fear extinction in both structures, while using the same paradigm and temporal parameters of drug infusion. Hence, we microinfused the ã-aminobutyric acid (GABA)A agonist muscimol into the IL or BLA to examine its effect on the extinction of fear conditioning. Muscimol infused to IL before extinction training (but not after either short- or long extinction training), resulted in long-term facilitation of extinction. Infusion of muscimol to the BLA, following a short training session, transiently facilitated extinction. The differences in the temporal parameters of the effects of muscimol in the IL or BLA, suggest differential involvement of these structures in long-term extinction of fear memory. We propose that consolidation of extinction of fear may dependent on both the amygdala and IL, and concurrently the information is further consolidated and stored in the IL. Understanding the interaction between the amygdala and the prefrontal cortex in extinction of fearful experiences is of major interest, since these brain regions are closely related to the persistence of maladaptive fear seen in anxiety disorders such as post-traumatic stress disorder (PTSD) and phobia.

Bifunctional compounds eliciting non-steroidal anti inflammatory and cholinergic up-regulation as treatment for CNS inflammation

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It was previously noted that vagus nerve activation could suppress significantly the release of macrophage pro-inflammatory agents attenuating systemic inflammatory processes. This "cholinergic anti-inflammatory pathway" is mediated by the alpha7 nicotinic ACh receptor in macrophages. Therefore, we examined the in vivo anti-neuroinflammatory efficacy of bifunctional compounds containing the NSAID ibuprofen (IBU) or diclofenac (DICLO) and a ChE inhibitor Pyridostigmine Octyl (PO) or Decyl (PD). IBU-PO caused a significant reduction in rat paw and brain edema induced by carrageenan. IBU-PO, IBU-PD reduced significantly the soman-induced (1.2LD50) brain edema in mice. Pre-treatment with IBU-PO, IBU-PD, or DICLO-PD 4-5 hours before soman challenge (2.2-2.3 LD50) combined with antidotal treatment (atropine and 2-PAM-Cl), afforded higher survival rate than with PYR. DICLO-PD displayed 70% survival at 24h compared to 17% with PYR. IBU-PO and IBU-PD were examined in experimental autoimmune encephalomyelitis (EAE), a model used for studying human Multiple Sclerosis. These compounds ameliorated by 40-50% the neurological score (1 and 0.1mg/kg, ip, respectively). T cells derived from IBU-PO-treated EAE animals displayed decreased reactivity in response to the myelin oligodendrocyte glycoprotein (MOG) and also to the mitogen PHA, indicating reduced activity of MOG-specific T- cells. In addition, IBU-PO at micromolar levels down regulated LPS-induced nitric oxide (NO) and PGE2 production in rat brain astrocytes. T-cell proliferation, NO and PGE2 production in astrocytes was mildly inhibited by IBU and none by PO alone, but was significantly reduced by IBU-PO. In addition, human T-cells proliferation was significantly reduced by IBU-Octyl-Cytisine (1-5uM) that consists of NSAID and a nicotinic agonist. Our data indicate that molecular combination of NSAID with cholinergic up-regulation may be a novel approach for the treatment of CNS inflammation and demyelinating disorders.

Clinical and immunological amelioration of chronic experimental autoimmune myasthenia gravis by antisense oligonucleotide treatment

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Myasthenia gravis is an antibody-mediated, autoimmune neuromuscular disease in which the nicotinic acetylcholine receptor (AChR) is the major autoantigen. The typical neuromuscular junction symptoms can be transiently alleviated by acetylcholinesterase (AChE) inhibitors (such as pyridostigmine). Previously we found that long-term treatment of experimental autoimmune myasthenia gravis (EAMG) rats with antisense oligodeoxynucleotides suppressing AChE biosynthesis (EN101), improved muscle activity as well as clinical symptoms of the disease. In the present study we focused on the effect of EN101 treatment on the typical immunological processes occurring in EAMG. Repeated oral administration of EN101 for a month reduced the anti-rat AChR antibody level by 50%. In addition, incubation of T-cells with EN101 resulted in reduction in the proliferation rate and induction of apoptosis. EN101 also lowered total IgG antibody production by spleen cells. Our results show the beneficial effect of oral EN101 treatment on EAMG immunological parameters and highlight the potential advantage of gene-targeted drug therapy.

Ligand-induced activation of G-proteins is differentially regulated by leucine of the CB1 helix 8 domain

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The majority of physiological actions of marijuana in the CNS are mediated by activation of G-protein coupled CB1 receptors located on neurons. Modeling studies have identified the 404-414 segment of CB1 receptor to be an intracellular helical extension of the TMH7 domain, so called helix8 (Hx8) domain. The peptide of CB1 401-417 can directly activated Gao/Gai3, but not Gai1/2 proteins. We tested the hypothesis that activation of CB1 releases Hx8 such that it can interact with G proteins, and that differences in this association may contribute to constitutive activity. We hypothesized that replacing the L7.60 to the bulkier Ile residue will make the Hx8 more mobile whereas the aromatic Phe will make the Hx8 less mobile than the wild-type human CB1 receptor (WT hCB1) thus constitutive activity will be increased or decreased, respectively. HEK293 cells were transfected with WT hCB1, L7.60I or L7.60F mutant receptors. Saturation binding analysis with [3H]CP-55,940 and [3H]SR141617A showed that ligand affinity and receptor levels of the mutant receptors were similar to that of the WT hCB1. [35S]GTPγS binding analysis was performed with structurally different cannabinoid agonists. The mutations did not alter the basal stimulation levels but reduced the maximal stimulation (Emax). The L7.60I mutation significantly reduced the Emax for CP-55,940>WIN55,212-2>HU-210. In addition, the L7.60I mutation completely abolished [35S]GTPgS binding with SR141617A. These results suggest that Leu residue of the Hx8 domain does not significantly contribute to the constitutive activity of the hCB1 receptor in this model system but is important for activation of specific G-proteins. The differential stimulation obtained with the different ligands suggests that although SR141716A and CP-55,940 binding pockets are not related these ligands exclusively activate Gai3/Gao through L7.60 whereas HU-210 and WIN55212-2 can still activate the hCB1 probably by docking the IL3 domain to Gai1/Gai2.

Dopamine modulates the intrinsic properties of layer II stellate cells in entorhinal cortex

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In entorhinal cortex, axons of the Layer II spiny stellate cells travel in the perforant path to terminate directly on dentate granule and CA1 pyramidal cells. These neurons, which are essential elements in cortex-hippocampus interaction, have distinctive electrophysiological properties, including very prominent, hyperpolarization-activated cation current (Ih) and TTX-sensitive persistent sodium current (INaP). Because neuromodulation of these currents must affect the neurons' integration properties, we studied the effects of dopamine on INaP and Ih using patch clamp whole-cell recordings in rat EC horizontal slices. INaP was manifest as a TTX-sensitive current elicited by a slow depolarizing voltage ramp (40 mV/s) in the presence of Cs+1, 4-AP, TEA, and Cd+2. Bath application of dopamine (.02-.1 mM) induced a significant leftward shift in the instantaneous I-V curve, and a concurrent decrease in the peak of the current. The D1/D5 dopamine receptor agonist SKF 81297 (.005-.025 mM), but not the D2 receptor agonist quinpirole (.025 mM), mimicked these effects. Dopamine receptors are positively coupled to adenylyl cyclase and the production of cAMP and protein kinase. As expected, the membrane-permeant cAMP analog, 8-Bromo-cAMP (.1 mM), mimicked the response of dopamine. Moreover, a specific blocker of PKA, KT 5720 (.001 mM), inhibited the modulation. Ih was manifest in current clamp recordings as a prominent, time-dependent depolarizing sag during hyperpolarizing current pulses. Dopamine reversibly led to a significant decrease in the amplitude of the sag. These effects of dopamine on the intrinsic properties of such pivotal neurons in the

parahippocampal circuitry may underlie, in part, the role of dopamine in neurological and psychiatric syndromes which involve defects in this circuitry, such as epilepsy and schizophrenia.

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'Virtual histology' of human white matter by diffusion MR imaging

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Neuroscience in general and neuroimaging in particular has evolved tremendously since the introduction of dynamic functional brain mapping. Despite the ability to follow task related brain activity, the structural network connecting these regions was only hypothesized from histological databases. Few years ago, the concept of diffusion tensor imaging (DTI) based fiber-tracking was introduced. This method is based on the anisotropic nature of water diffusion in white matter. Parallel to the fibers the diffusion appears to be 'free' while perpendicular to them it appears disturbed. This quantity of white matter diffusion enables 3D mapping of large homogeneous fiber bundles. However, DTI suffers from inherent artifacts in areas of heterogeneous white matter (crossing white matter bundles) and white matter fanning into gray matter. Recently we developed an experimental and theoretical framework to describe white matter diffusion even in areas of complicated white matter structures. The composite hindered and restricted model of diffusion (CHARMED) enables extraction of physical components of neuronal structure based on their diffusion characteristics. CHARMED assumes that the diffusion within the neuronal fibers is restricted while elsewhere is only hindered. With the distinction between restricted and hindered water diffusion it is possible to examine the microstructure of neuronal white matter tissue. For example, parameters such axonal volume fraction, extra-axonal volume fraction, extra-axonal diffusivity and axonal diameter distribution can be extracted with CHARMED. Moreover CHARMED enables separation between heterogeneous white matter systems where more than one fiber-bundle passes and hence may enhance the fiber-tracking abilities. CHARMED based parameters help to obtain microstructural information that limits virtual histology and provide a new tool to follow neuronal degeneration as well as white matter connectivity and integrity.

The Insulin-like growth factor mRNA binding-protein IMP-1 and the Ras-regulatory protein G3BP associate with tau mRNA and HuD protein in differentiated P19 neuronal cells

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Tau mRNA is axonally localized mRNA that is found in developing neurons and targeted by an axonal localization signal (ALS) that is located in the 3'UTR of the message. The tau mRNA is trafficked in an RNA-protein complex (RNP) from the neuronal cell body to the distal parts of the axon, reaching as far as the growth cone. This movement is microtubule-dependent and is observed as granules that contain tau mRNA and additional proteins. A major protein contained in the granule is HuD, an Elav protein family-member, which has an identified mRNA binding site on the tau 3'UTR and stabilizes the tau message and several axonally targeted mRNAs. Using GST-HuD fusion protein as bait, we have identified four proteins contained within the tau RNP, in differentiated P19 neuronal cells. In this work, we studied two of the identified proteins i.e. IGF-II mRNA binding protein 1 (IMP-1), the orthologue of chick ß-actin binding protein-ZBP1, and RAS-GAP SH3 domain binding protein (G3BP). We show that IMP-1 associates with HuD and G3BP-1 proteins in an RNA-dependent manner and binds directly to tau mRNA. We also show an RNA-dependent association between G3BP-1 and HuD proteins. These associations are investigated in relation to the neuronal differentiation of P19 cells.

Dual effect of CD4+CD25+ regulatory T cells in neurodegeneration: Pro- and anti inflammatory cytokines determine microglial activity

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Autoimmune CD4+T cells can mediate the ability to withstand neurodegenerative conditions. Here we show that the ability to spontaneously manifest a T cell-dependent protective response is restricted by naturally occurring CD4+CD25+ regulatory T cells (Treg); depletion of Treg was beneficial in two mouse strains (C57BL/6J and BALB/c/OLA) differing in their spontaneous T cell dependent ability to withstand the consequences of optic nerve injury. Passive transfer of exogenous Treg was destructive in BALB/c/OLA mice (which can spontaneously manifest a T cell dependent protective anti-self response to injury) but beneficial in C57BL/6J mice (which have only limited ability to manifest such a response). This dichotomy was resolved by the finding that, in severe combined immunodeficient mice, a beneficial effect is obtained by passive transfer of either Treg-free CD4+ T cells (Teff) or Treg alone, indicating that neuroprotection can be achieved by either Treg or Teff in the absence of the other. We attribute these disparate effects of Treg to their differential interaction (in part via IL-10) with local innate immune cells (microglia) in the presence and in the absence of effector T cells. Activation of microglia by pro and anti inflammatory cytokines in suitably controlled amounts might trigger different signal transduction pathways, each of which induces a neuroprotective microglial phenotype. These results suggest that, under neurodegenerative conditions, the effects of Treg, and possibly also of other regulatory T cells, might not be uniform, and that their expression in different individuals might be genetically determined. Therefore, therapeutic intervention based on induction of regulatory T cells might have limitations.

A Spiking Neural Network Model with High Memory Capacity.

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A balanced network leads to contradictory constraints on memory models, as exemplified in previous work on accommodation of synfire chains. Here we show that these constraints can be overcome by introducing a 'shadow' inhibitory pattern for each excitatory pattern of the model. This is interpreted as a double-balance principle, whereby there exists both global balance between average excitatory and inhibitory currents and local balance between the currents carrying coherent activity at any given time frame. This principle can be applied to networks with Hebbian cell assemblies, leading to a high capacity of the associative memory. The number of possible patterns is limited by a combinatorial constraint that turns out to be P=0.06N within the specific model that we employ. This limit is reached by the Hebbian cell assembly network. To the best of our knowledge this is the first time that such high memory capacities are demonstrated in the asynchronous state of models of spiking neurons.

Autoimmune T cells play a role in short- and long-term plasticity

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Considering the previously observed role of mature T cells in neuronal survival and repair, we hypothesized that a similar function can be attributed to such T cells in the context of neural plasticity. We examined this hypothesis in the dentate gyrus (DG; in-vivo) and in stratum radiatum of the CA1 region (in-vitro) of transgenic mice congenic to wild-type (WT) leading to the phenotype of absence of mature T cells (nude mice). In-vivo, we found that the reactivity to afferent stimulation had the same fEPSP and population spike (PS) size in the nude and WT control mice. In addition, the nude mice showed enhanced paired-

pulse inhibition at 30 msec inter-stimulus-interval (ISI), which was reversed to a minor facilitation at 60 msec ISI. Surprisingly, only short-term but not long-term potentiation (LTP) was detected in the nude mice. In-vitro, the dynamic range of the fEPSPs was similar in slices taken from nude mice compared with controls. Moreover, both the control and the nude mice showed similar paired-pulse facilitation across 4 different ISIs. Strikingly, nude mice expressed short term but not long term potentiation of fEPSP. These results suggest that adaptive immunity is involved not only in neuronal survival but also in the maintenance of neuronal plasticity, and thus might shed light on the role of the immune system in brain learning and memory processes.

The metabotropic Glutamate receptor 1 (mGluR1) is voltage sensitive

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It is common knowledge that voltage – gated ionic channels are voltage sensors and also part of ligand –gated channels show voltage sensitivity ,although much weaker. In contrast, G-protein coupled receptors (GPCRs) involved in the majority of signal transduction processes are not considered to be voltage sensitive, although they are transmembranal and could potentially be modulated by membrane potential. In an earlier study (Ben-Chaim et al., 2003) it was shown that two GPCRs, the m2 (m2R) and the m1 (m1R) muscarinic receptors ,known to modulate neurotransmitter release, are voltage sensitive; their affinity toward the agonist is affected by membrane potential. Another type of GPCRs, the type 3 metabotropic glutamate receptor (mGluR3) was also shown to exhibit voltage sensitivity . Here we examine whether the type 1a metabotropic glutamate receptor (mGluR1a), member of group mGluRs ,exhibit voltage sensitivity. Using Xenopus oocytes we show that the type 1a metabotropic glutamate receptor (mGluR1a), known to participate in LTD, is voltage – sensitive. The mGluR1a mediated endogenous chloride channel currents were used to assay the activity of mGluR1a. We found that the apparent affinity of mGluR1a toward glutamate (Glu) was increased upon depolarization.

Endocannabinoids Affect Neurological and Cognitive Function in Thioacetamide-induced Hepatic Encephalopathy in Mice.

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Background/Aims: The pathogenesis of hepatic encephalopathy involves functional changes in neurotransmitter systems. Endocannabinoids function as neurotransmitters and neuromodulators in the central nervous system via specific receptors. Recently the endocannabinoid system was found to be involved in the vasodilated state associated with cirrhosis. We hypothesized that the endocannabinoid system might also have a role in the pathogenesis of hepatic encephalopathy in an experimental model of fulminant hepatic failure. Methods: Fulminant hepatic failure in mice was induced by thioacetamide. Neurological performance was assessed by a ten point scale, by activity and by cognitive function. Levels of brain 2-arachidonoyl glycerol were analyzed by GC-MS. Results: The CNS levels of 2-arachidonyl-glycerol were elevated in mice with thioacetamide-induced hepatic encephalopathy. Encephalopathic mice treated with the CB1 antagonist, SR141716A, demonstrated a dose-response improvement in the neurological score. Activation of the CB2 receptor with a selective agonist, HU308, caused a similar effect. Activity in the open field and cognitive function also improved after administration of SR141716A or 2-AG while HU308 did not cause any effect. Conclusions: The endocannabinoid system may have an important role in the pathogenesis of hepatic encephalopathy. Modulation of this system, either by specific antagonists to the CB1 cannabinoid receptor, or by exogenous endocannabinoid agonists for the CB2 receptor may have therapeutic potential in hepatic encephalopathy.

Molecular mechanisms of neurorescue, neurodifferentiation and regulation of APP/ A –beta peptide processing by M30, a novel bifucntional iron chelator-monoamine oxidase inhibitor.

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Accumulation of iron at sites where neurons degenerate in Parkinson's (PD) and Alzheimer's (AD) diseases is thought to play a major role in the process of neurodegeneration. The brain permeable iron chelator, VK-28, as well as the propargylamine moiety of rasagiline, exert neuroprotective activities in cell culture models and in vivo against a variety of insults. We developed, a novel bifunctional drug, M30, possessing these components. M30 (1-10 microM) decreased apoptosis of SH-SY5Y neuroblastoma (NB) cells in a neurorescue, serum deprivation model, via multiple protection mechanisms, including: reduction of the pro-apoptotic Bad and Bax; reduction of apoptosis-associated Ser139 phosphorylated H2A.X; induction of the anti-apoptotic Bcl-2; inhibition of the cleavage and activation of caspase-3. Moreover, M30 promoted morphological changes resulting in axonal growth- associated protein- 43 (GAP-43) implicating neuronal differentiation. VK-28 did not show any significant effect on cell differentiation. M30 markedly reduced holo- amyloid precursor protein (APP), C-terminal fragment (CTF) -beta levels and the amyloidogenic A-beta peptide, in NB cells and in Chinese Hamster Ovary (CHO) cells stably transfected with APP "Swedish" mutation, the in cell media and the, in a dose dependent manner. In correlation, the non- amyloidogenic soluble APPa levels were elevated as well as the levels of CTF-alpha in cell lysate. These results compliment the presence of an iron-responsive element (IRE) in the 5'-untranslated region (5'UTR) of the APP and the iron chelator properties of the drug. The bifunctional drug, M30 possesses neurorescue, neurodifferentiation and APP processing, resulting in a substantial reduction in A-beta levels, might be a novel drug for the treatment of AD.

Central Control of Bone Mass

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In vertebrates, bone mass is maintained constant between the end of linear skeletal growth and gonadal failure by a continuous destruction/formation process termed bone remodeling, which occurs simultaneously in multiple foci. It consists of a resorption phase of pre-existing bone by a specific cell type, the osteoclast, followed by a phase of bone formation by another bone-specific cell type, the osteoblast. Although different foci present different phases of the cycle, the overall net effect is that of a balance between bone destruction and formation. The physiologic importance of bone remodeling is best illustrated in osteoporosis, the most common degenerative disease in developed countries, which results from an impaired remodeling balance that leads to bone loss and increased fracture risk. Several lines of evidence suggest that bone remodeling is centrally controlled: 1) Bones are densely innervated by the sympathetic nervous system as well as by sensory nerve fibers containing calcitonin gene-related peptide, substance P and tyrosine hydroxylase. 2) Bone cells express receptors for these and other neurotransmitters, suggesting the occurrence in bone of a non-synaptic, diffuse, and slow neurotransmitter signaling which regulates bone cell differentiation and activity. 3) Clinically, obesity protects against bone loss induced by the cessation of gonadal function. 4) Perhaps the most direct evidence for the central control of at least bone formation is the consistent clinical observation of heterotopic ossification and enhanced fracture healing in patients with traumatic brain injury. 5) Stress and depression in humans and experimental animals are associated with significant decreases in bone mass attributable to activation of the HPA-axis and perhaps other, non-sympathetic processes. It thus appears that the central control of bone remodeling is mediated by multiple pathways.

Central Interleukin-1 Receptor Signaling Regulates Bone Mass

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The pro-inflammatory cytokine IL-1, acting via the hypothalamic IL-1 receptor type 1 (IL-1R1), activates pathways associated with the restrain of bone formation such as the hypothalamo pituitary-adrenocortical (HPA) axis and the sympathetic nervous system. In addition, IL-1 has been implicated as a mediator of the bone loss induced by sex hormone depletion. To address more specifically the skeletal regulatory role of central IL-1R1 signaling, we characterized the bone phenotype of young IL-1R1-/- mice and mice with astrocyte-targeted overexpression of the human IL-1 receptor antagonist, under the control of the murine glial fibrillary acidic protein promoter (IL-1raTG). The genetically manipulated mice showed normal body weight and food consumption. Although a previous histomorphometric study reported a normal bone mass in the IL-1R1-/- micc, a present micro-computed tomographic analysis demonstrated impaired femoral elongation and radial growth in these animals as well as in the IL-1raTG mice. Moreover, the trabecular bone density in the distal femoral metaphysis and lumbar vertebrae in both mutant mouse lines was markedly lower as compared to their WT controls. Similar decreases were also seen in the trabecular thickness, number and connectivity. The process leading to the low bone mass (LBM) phenotype in the IL-1raTG mice involves high turnover bone loss, characterized by doubling the osteoclast number with substantially smaller increases in osteoblast number and bone formation rate. The mechanism involved in the increased bone formation was not related to gonadal dysfunction, as testosterone levels in the IL-1raTG mice were markedly higher compared to the WT controls. These data demonstrate a LBM phenotype resulting from the absence of central IL-1R1 signaling. Whereas previously reported studies suggest a role for skeletal IL-1R1 signaling in bone loss, the present findings implicate the central IL-1R1 signaling as a positive regulator of bone mass accrual.

Rescue from Neuronal Death by N-Propargylamine via Regulation of Pro-survival Bcl-2 Family Proteins and Amyloid Precursor Protein (APP) Processing

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Our recent studies have provides evidence whereby activation/regulation of protein kinase C (PKC) in association with Bcl-2 protein family promotes neuronal survival by rasagiline (N-propargyl-(1R)-aminoindan), and in relation to its propargyl moiety. In the present study, we further investigated the neurorescue effects of N-propargylamine in a progressive neuronal death, induced by long term (3 days) serum deprivation in SH-SY5Y neuroblastoma cells. N-propargylamine (0.1-10 mM) dose-dependently reduced the levels of the early apoptosis-associated phosphorylation protein, H2A-X (ser 139), as well as decreased the cleavage of caspase-3 and its substrate poly ADP ribose polymerase (PARP). Long-term serum withdrawal significantly down-regulated the anti-apoptotic protein, Bcl-2, as well as up regulated the pro-apoptotic protein, Bax. These effects were markedly reversed in a dose-dependent manner by N-propargylamine. Furthermore, it reduced the levels of the pro-apoptotic proteins, Bad and Bim. Using real-time RT-PCR, we show that N-propargylamine elevated Bcl-2 and reduced Bax gene expression. In addition, serum deprivation induced an increase in protein levels of holo-APP, in consistence with pathophysiology of Alzheimer disease (AD). N-propargylamine markedly decreased holo-APP levels, accompanied by increased levels of the non-amyloidogenic a-secretase form of soluble APP (sAPPa) into the medium. Similar effects on cell survival and APP regulation/processing were demonstrated for rasagiline. These results indicate that the regulatory effects of rasagiline and N-propargylamine on APP and sAPPa levels promote a reduction in the toxic amyloidogenic pathway, involved in AD.

Do odd illusory shapes pop out? Effects of learning and expertise

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It is well documented that odd elements are easily detected when embedded in a field of distractors that are similar to each other and differ categorically from the odd element in one feature, such as color, orientation, motion direction or shape. We ask whether the relevant shape needs to be defined by real edges or do illusory contours (Kanizsa, 1979) also induce a pop-out effect, though their perception is slower, and to what extent does such a pop-out depends on illusory-contour training history. Previous studies investigated the possibility of a pop-out effect when subjects search for a set of illusory-contour inducers among a field of non-inducers (Grabowecky & Treisman, ARVO: IOVS 30s: 457, 1989, Davis & Driver, Nature 371: 791, 1994). Others studied pop-out of odd shapes where subjective contours were defined by offset gratings (Gurnsey et al., Percept & Psychophys 52: 263, 1992). We now tested subjects with different levels of training on a Kanizsa illusory contour task. Targets (which appeared in ½ of the trials) were illusory parallelograms and distractors were illusory triangles. Arrays contained 9, 16 or 25 illusory figures. We analyzed set-size effects and mean response time to determine if the classical tests for pop-out (relative set-size independence for odd element present trials) is relevant also for slowly induced percepts. A significant difference in performance as well as in learning rate was found between subjects with different levels of training. In contrast, a control experiment with real (rather than illusory) figures showed significantly less dependence on training level. These results suggest that pop-out detection of Kanizsa figures is a function of expertise.
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Quantitative analysis of Parvalbumin- and Calbindin-D28K- containing neurons in limbic brain structures and the SSC of Octodon degus after repeated early life stress

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Early adverse experience results in both physical and psychological alterations. Previous results in the trumpet-tailed rat (Octodon degus) pointed out, that early life stress leads to a variety of morphological changes including region-specific changes of spine densities. Are these changes of excitatory input accompanied by altered GABAergic modulation? To find answers to this question we analyzed the impact of early life stress on the development of inhibitory GABAergic neurons in the rodent hippocampus, amygdala, piriform cortex and the somatosensory cortex. The stressed degus showed significantly lower densities of Parvalbumin- and Calbindin-D28k-immunoreactive (-ir) neurons in this hippocampal subregion. Accordingly, the decreased excitatory input (lower spine densities) in the dentate granule cells appears to be compensated by decreased numbers of inhibitory neurons. In the CA1 region, the increased excitatory input (enhanced spine densities) appears neither to be compensated nor amplified by altered numbers of GABAergic interneurons. Thus, an overall enhanced neuronal excitability could be predicted. The stress-induced neuronal adaptation in the basolateral amygdala again differs from that observed in the hippocampal formation. Increased cell densities of Parvalbumin- and Calbindin-D28k-ir neurons were detectable in the basolateral amygdala of early stressed degus, whereas in the central amygdaloid nucleus no differences were found. Accordingly, the decreased excitatory input (decreased spine densities) which was reported for the lateral amygdala appears to be even more downregulated by increased numbers of GABAergic interneurons, from which an overall dampening of neuronal excitability could be expected. These stress-induced changes of GABAergic mediated changes appear to be more or less specific for some limbic regions, since in the piriform cortex and in the somatosensory cortex no quantitative changes were detectable.

Hippocampal sharp-wave

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Hippocampal sharp-wave ripple complexes (SPW-R) occur during slow wave sleep and behavioral immobility and are thought to represent stored information that is transferred to the cortex in a process of memory consolidation. Here we show that stimuli which induce long-term potentiation (LTP), a neurophysiological correlate of learning and memory, led to generation of SPW-R in hippocampal area CA3 that were identical to those observed spontaneously. Following repeated stratum radiatum-stimulation in area CA1 evoked SPW-R recurrently occured in area CA3 and propagated into area CA1 and the subiculum. The induction of SPW-R was dependent on activation of NMDA receptors and involved time-dependent changes in interactions between clusters of neurons in the associational network of area CA3. Furthermore the induction of SPW-R by high frequency stimulation (HFS) could be reversed by application of low frequency stimulation (LFS) which also reversed stimulus-induced LTP in area CA3. During application of low dose acetylcholine (ACh) in presence of ACh-esterase inhibitor physostigmine a facilitation of the stimulus-induction of SPW-R was observed as well as a bockade of SPW-R activity by application of a ten fold higher dose of ACh. Our data suggest a mechanism which, by inducing SPW-R in the hippocampus, can be used to explore their role in memory consolidation, as well as the rules governing network activity in areas CA3 and CA1 and, therefore, the generation of ensemble activity in this structure. Furthermore these results suggest that, under certain cognitive states, learning-induced synaptic plasticity might result in the generation of SPW-R and the propagation of information from the hippocampus to the neocortex.

Monaural and binaural fMRI activation of the brainstem auditory pathway

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Binaural processing of sound in humans is initiated within the auditory nuclei in the brainstem. An MRI study on patients with multiple sclerosis and stroke indicated that whenever the lesion overlapped the brainstem auditory pathway, some binaural performance was abnormal, while the monaural performance was normal. The purpose of the present study is to reveal the difference between binaural and monaural processing using functional MRI (fMRI) on healthy subjects. fMRI was performed on a 1.5 Tesla GE scanner. Axial, sagittal and coronal slices of 4 mm thickness and 0 gap were acquired. A GE-EPI sequence was used with TR based on the ECG and configured to every fourth heartbeat. Statistical analysis of the data was performed by using SPM2 software. The default bounding box of SPM was adjusted to include the brainstem. Since the brainstem auditory nuclei are relatively small structures, the analysis included removal of movement related artifacts. The analysis was performed only in the sub-cortical area. The auditory activation was mapped on a 3-D brainstem auditory pathway atlas. Fifteen young healthy subjects participated in the study. Subjects were stimulated by 20-30 seconds of either classical music or rock music presented binaurally or monaurally. In all subjects, binaural stimulation yielded activation in at least one brainstem nucleus. Activation was identified in the cochlear nucleus, superior olivary complex, and inferior colliculi. Both right and left auditory pathways were activated only when both ears were stimulated. The right auditory pathway was primarily activated when the left ear was stimulated and vice versa. We have demonstrated that fMRI can be used to identify the brainstem auditory pathway. Further investigation is required to explore the auditory pathway with different stimuli.

Voltage Dependent Conformational Changes in Muscarinic Receptors Affect Their Coupling to Their G-proteins

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G-protein coupled receptors (GPCRs) are involved in most signal transduction processes. Although GPCRs are transmembranal and could potentially be modulated by membrane potential, they are not considered to be, by themselves, voltage sensitive. In an earlier study (Ben-Chaim et al., 2003 J. Biol. Chem. 278(25), 22482) we showed that two GPCRs, the m2 (m2R) and the m1 (m1R) muscarinic receptors are voltage sensitive; their affinity toward the agonist is affected by membrane potential. We hypothesized that membrane potential affects the coupling of the G-protein to the receptor and thereby determines its affinity; high affinity when coupled to the G-protein and low affinity when free. This hypothesis was tested directly by measuring the voltage dependence of the agonist's affinity of chimeric m1R and m2R in which the third intracellular loops were interchanged. We show that the voltage sensitivity of both m1R and m2R crucially relies on the loop that couples the receptor to its respective G-protein.

Weaned Rats Return to Mother After Stress

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In the progression from suckling to weaning, rat pups show a reduced preference for the mother rat in a choice situation. We report here that 31- day old weaned rats who are exposed to 30-minutes of acute stress revert to an earlier mode of behavior reminiscent of the suckling stage – that of preferring the mother rat. Sprague-Dawley derived male rat pups (n=21) were tested for preference in a Y-maze, where one arm contained the dam and where one arm contained a female littermate. When the pup made a choice, the trial was terminated. Each animal was evaluated for choice 4-times at different postnatal ages, once as a suckling at 16-18 days and three times as a weanling at 30, 31, and 34 days. Prior to the choice test on day 31, pups were placed on small elevated platforms for a period of 30-minutes, a method commonly used to induce stress. They were then tested as usual for preference for the dam or littermate. In keeping with previous work, 70 % of suckling pups (16-18-days) preferred the mother as compared with only 33 % preference for the dam in weaned rats on day 30. However, immediately after the platform stress on day 31, significantly more of these weaned rats (71%) reverted back to preferring the mother much as they had done as sucklings. This stress-induced preference shift was largely reversed on the following trial on Day 34 without the stress manipulation, with only 43% of the weaned pups preferring the dam. These results suggest that stress may cause a regression to much earlier stages of socio-affective development. We speculate whether this phenomenon, observed in laboratory rats, may be related to instances of stress-induced regression or attachment reported by clinicians in humans.

Sixty-Minutes per Day of Social Interaction Reverses Isolation-Induced Aggression and Increased-Morphine Consumption

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Laboratory rats that are housed in social isolation are more aggressive and consume more morphine solution than socially housed rats. We report here that 60–min. of social interaction per day reverses these effects of isolated housing. In one series of studies, pairs of male rats were trained in a cooperation task where both animals must coordinate their behaviors to receive food reward. Following acquisition, subgroups were allocated to one of three housing conditions: 1) social housing (2-per cage); 2) social isolation (1-per cage); or partial social isolation (1-per cage with access to another male rat for 5-min, 60-min,

or 4-hours per day). After 21-days in these different housing conditions the animals were re-tested in the cooperation task. Significant deficits in re-test cooperation performance and increases in aggression were observed in animals with 0 or 5-min. per day of social interaction. No deficits were observed in subgroups that had at least 60-minutes per day of social interaction. In parallel studies, male rats were housed for 21-days in one of three housing conditions: 1) social housing (2-per cage); 2) social isolation (1-per cage); or 3) partial social isolation (1-per cage with access to another male rat for 60-min per day). Water or 0.5 mg/cc morphine sulfate consumption were measured in one-bottle or two-bottle tests. Socially isolated animals consumed significantly more morphine but not more water than those in the social housing or partial social isolation groups. There was no difference between the social housing and the partial social isolation groups indicating that 60-minutes of social contact per day is sufficient to reverse the effects of social isolation. Taken together, these studies indicate that social isolation increases aggression, disrupts a cooperation learning task, and increases morphine intake and that a short daily period of social interaction reverses these effects of social isolation.

Activity and significance of the brain ZnR

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Dynamic changes in zinc play a key physiological role in synaptic transmission, and are a leading factor in neuronal death following excitotoxic syndromes attributed to neuronal zinc rise. We propose that ZnR, an extracellular zinc sensing receptor is mediating intracellular signaling following changes in extracellular zinc concentrations. Indeed Ca^{2+} signals are monitored in acute hippocampal and neocortical slices following application of extracellular zinc, particularly strong activity was monitored in the CA3 region. Using TPEN, a membrane permeable zinc chelator, we demonstrate that the rise in the Ca^{2+} signal following ZnR activation is indeed related mostly to Ca^{2+} and not induced by Zn^{2+} permeation suggesting that important cellular signaling is triggered by extracellular Zn^{2+} and not only by its permeation in neurons. The brain ZnR-dependent calcium rise is mediated by the IP_3 pathway such rise in intracellular Ca^{2+} has been previously linked to the modulation of LTP and LTD, and neuronal apoptosis on the other hand. A major pathway that may convey the metabotropic signal to neuronal death or survival is the MAP kinase pathway. We have indeed monitored the specific phosphorylation of ERK1/2 following brain ZnR activation. The potential physiological significance of a zinc sensing mechanism is shown by the extremely wide range of zinc concentrations activating the ZnR, ranging from nanomolar to micromolar. The extremely high affinity of brain ZnR is intriguing since it is expected to be activated by minute, sub- toxic zinc concentrations, which we see released following electrical stimulation.

NMDA channels in superficial neurons of the mouse presubiculum contain NR2C subunits

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Functional NMDA receptors are made up of an NR1 and an NR2 subunit, which plays a critical role in determining the susceptibility of the receptor to Mg2+ and its single-channel conductance. NR1/NR2A and NR1/NR2B receptors have higher conductance and enhanced sensitivity to voltage-dependent Mg2+ blockade, while NR1/NR2C and NR1/NR2D receptors have lower single-channel conductance and diminished Mg2+ sensitivity, such that they are more likely to open at resting potential. Transgenic mice which express a LacZ indicator gene that is controlled by the NR2C promoter revealed that in addition to cerebellum, NR2C subunits are expressed in several forebrain regions not previously identified with in-situ hybridization. One such area is layer 4 of the barrel cortex, where we also showed functional expression of NR2C-containing receptors in whole cell and single channel recordings. The LacZ staining is also prominent in the superficial layers of the presubiculum, which is a major sources of input to the entorhinal cortex. Horizontal slices through the hippocampus were bathed in 2 mM Mg2+ and whole cell recordings were made from neurons of the superficial presubiculum. Cells held at -70 mV revealed prominent, DNQX-resistant, APV-sensitive, slowly decaying spontaneous EPSCs. NMDAR-mediated EPSPs were never seen at resting potential in neurons of the deeper presubicular layers; they were, however, prominent when the membrane was depolarized. In outside-out patches from the somas of superficial presubicular neurons, single NMDA channel currents induced by focal glutamate application were predominantly of the low-conductance class and displayed less sensitivity to Mg2+. By contrast, only high-conductance NMDA channels with a "classical Mg2+ sensitivity were found in deep presubicular neurons. It seems likely that the functional expression NR2C subunits by neurons in this restricted region has important consequences for parahippocampal circuit function.

MRI and histological imaging of migrating bone marrow stem cells transplanted into mouse brain

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Bone marrow mesenchymal stem cells (BMSc) are multipotent cells that can be induced in vitro to differentiate into a variety of cells and replace or repair tissues in the body. In our previous studies we were able to induce differentiation of mice BMSc into neuronal-like cells. The cells changed their phenotype and expressed neuronal as well as dopaminergic markers and also secreted dopamine. The present study was aimed to clarify whether the mouse BMSc can migrate into the lesion and differentiate into the neurons when transplanted into mice subjected to unilateral 6-OHDA lesion, an animal model of PD. BMSc obtained from transgenic mice (B5/EGFP) bearing the enhanced green fluorescent protein (EGFP) underwent differentiation during a period of 48 hours. The cells were also transfected with iron which allowed the stem cells to be visualized on MRI scan. Iron impregnated BMSc were then injected into left striatum of mice that were injected stereotactically with 6-OHDA, in the right hemisphere and demonstrated rotational behavior induced by amphetamine. The mice underwent an MRI scan at several time points during 45 days post transplantation. Histological studies indicated that the EGFP-BMSc, both differentiated and undifferentiated, injected into the opposite brain (non-lesioned) hemisphere were seen to migrate to and populate the 6-OHDA lesioned hemisphere. MRI could easily image the spatial distribution of small clusters of labeled cells at high spatial resolution within experimental times acceptable for in vivo investigations. This study demonstrates the capability of BMSc to be attracted and to migrate to lesioned areas in this animal model of PD and demonstrate the potential of high resolution MRI in in-vivo imaging of cells migration.

Modulation of rhythmic patterns produces in the neonatal rat spinal cord by selective activation of mu-opioid receptors in the sacrocaudal segments

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The possible involvement of sacrocaudal-afferent (SCA) pathways in activation of rhythmic motor patterns was examined in the isolated brainstem spinal cord preparation of the neonatal rat. Repetitive stimulation of SCA or the ventromedial medulla (VM) produced a locomotor like rhythm in the thoracolumbar (TL), and an alternating left-right rhythm in the sacrocaudal (SC) segments of the spinal cord. Selective application of the mu-opioid receptor agonist DAMGO to the SC segments blocked the locomotor and SC rhythm produced by SCA- but not by VM stimulation. The block could be alleviated by administration of the opioid receptor antagonist naloxone to the SC cord. Bath application of DAMGO to the TL

segments of the cord did not interfere with the rhythmic patterns produced by either SCA- or VM stimulation. These findings show that the DAMGO-induced block of the rhythms produced by SCA stimulation occurred specifically at the SC segments of the cord, and that the presence of DAMGO did not interfere with the ability of the SC and TL networks to produce organized rhythmic patterns. The capacity of opioid receptor to modulate rhythmic patterns produced by activation of nociceptive and non-nociceptive reflex pathways, and the suggested mechanisms of this modulation will be discussed.

Electrotonic coupling mediates slow synchronous oscillations in the anterior pituitary of teleost fish

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The anterior pituitary of teleost fish contains a variety of endocrine cells, which, under control from hypothalamus, release trophic hormones and thereby play a major role in reproduction, social behavior and growth. In fish, hypothalamic fibers directly innervate the pituitary. The hypothalamic hormones released from these fibers bind to membrane receptors on pituitary cells, triggering action potentials, rise in cytosolic calcium and exocytosis. It is unclear whether these activities are confined to the stimulated cell or propagate to adjacent cells. We addressed this issue using whole cell and perforated patch clamp technique in a novel, hypothalamo-pituitary slice preparation. Pituitary cells at rest generated occasional spontaneous spikes and spikelets. The latter probably represented spikes in neighboring, electrotonically coupled, cells. The presence of electrotonic communication, probably mediated by gap junctions, was further supported by the finding that Lucifer yellow diffuses between cells. To quantify this connectivity, we performed simultaneous recording from pairs of adjacent cells. Thirty-three percent of the cells exhibited strong reciprocal coupling. Coupling coefficients ranged between 0.18 and 0.31 and coupling resistances ranged between 16 and 39 GOhm. The electrical junctions were effective low-pass filters, attenuating action potentials much more than low-frequency waveforms. A transient application of GnRH elicited in anterior pituitary cells prolonged voltage oscillations (0.8-1.2 Hz) with bursts of action potentials, arising from the depolarizing edge of the waves. The oscillations were prominent in field potential recordings, indicating a high degree of regional synchrony. We conclude that electrical activities of anterior pituitary cells in teleost fish are synchronized by coupling through gap junctions. Regulation of this coupling may play a critical role in determining complex patterns of pituitary hormone secretion.

Acetylcholinesterase in Exercised Rat Muscles

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Acetylcholinesterase (AChE) plays a major role in the activity of muscles. Because fast-twitch motor units are recruited with increased motor demands while slow twitch motor units are readily and continuously active, and because synaptic AChE itself depends on neuromuscular activity, we examined the regulation of AChE in predominantly fast and slow-twitch rat muscles before and following strenuous exercise. Rats were trained by walking on motor-driven treadmill (2wks, 1h/d at a speed of 9m/min with 2min sprints of 17m/min, every 10min). Fast and slow-twitch leg muscles were isolated, AChE was extracted and its levels and isoform composition in trained and control-untrained muscles were analyzed. AChE content (per protein) increased in all examined fast-twitch muscles, but not in the slow-twitch soleus muscle. All muscles contained globular G1+2, G4 and asymmetric A12-AChE isoforms. After training the tetramer G4-AChE increased significantly (25-60%) in the fast-twitch muscles while the other AChE isoforms in both fast and slow-twitch muscles remained unchanged. To examine whether this increase may be expressed in synaptic AChE, frozen sections of junctional regions of trained and control gracilis muscles were double-labeled with Rd-α-bungarotoxin (BTX) for synaptic acetylcholine receptors (AChRs) and with biotin-fasciculin (followed by FITC-streptavidin) for AChE. Quantitative analysis of confocal fluorescence images revealed that synaptic AChE in the trained muscles increased (both intensity and area) relative to the AChRs when compared with controls. Altogether, these observations suggest that the G4-AChE might become significant at the endplates of fast-twitch fibers following exercise. The localization of this form at the endplates following exercise is examined.

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Twenty years follow-up on recovery of a case of left parietal, war brain injury: unilateral neglect, left/right errors

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In attempt to assess recovery in (M.A.), left parietal brain damage in 20 years follow-up started in year of injury (1982), late effects & compensatory strategies were revealed. Proximally to injury unilateral neglect (U.N.) was observed: inability to recognize family members present contralesional, these countable by left angular gyrus (ANG) damage. On psychophysical testing in 1994-6, of differentiating geometric forms incomplete in information, varying in degree of difficulty, orientation, local/global viewing & exposure time, M.A. displayed considerable inattention; yet like normals showed separation to "hard" & "easy", attention earmarking, thrust at hardest but with greater than normal pay off next to hardest, even small efforts with large pay off. This recovery lag suggested also supramarginal (Su.M.) injury, considering that in recovery ANG & Su.M. take over one for other. M.A. recovery was re-assessed (Pavlovskaya & Blum 2004) revealing visual search better performance contralesionally, in contrast, conjunction performance failures indicative defecit of sustaining attention, U.N contralesionally. Stimulus biasing to enhance hard decisions occured like in normals but without the normal's awareness of virtual change in stimulus, a feed back deficit (Blum 2002). Prior to injury M.A. made no writing errors, at present 20 yrs after injury left/right errors in Hebrew cursive letters mistaken one for the other, in performance, not cognitively, M.A. aware of mistake, trying to correct, may repeat error. Seemingly, M.A. deteriorated in 20 years due to delayed effect of injury; this is of clinical interest for possible prevention (FENS 2004).

Model of intracortical connectivity in the primary visual cortex

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Recent voltage-sensitive dye imaging studies on anesthetized cat area 17/18 have shown that spontaneously emerging activity patterns are dynamic and are similar to those evoked by various orientations of a moving grating stimulus [Kenet, et. al., 2003]. This suggests that orientation maps are intrinsic preferred states of the cortical network. Adopting this view, we study recurrent neural network models whose attractors are single condition orientation maps. To this aim, we first use an experimental set of 24 single condition orientation maps to construct a connectivity matrix through a modified version of the pseudo-inverse rule of the Hopfield network [Personnaz et al., 1985]. This modeling suggests that long-range connections depend on the difference in orientation preference of the connected columns and are strongly correlated with orientation selectivity of the columns. Motivated by these observations, we introduce a simple connectivity rule which depends on the selectivity and orientation preference of the interconnected columns. This rule can be viewed as an extension of the "ring model" connectivity rule for orientation preference [Ben Yishai et al., 1995] that accounts for non-uniform selectivity. An analytical analysis of a simple rate model with this connectivity rule shows conditions under which the network has a ring attractor that goes through the

continuum of single condition orientation maps. We perform computer simulations of the model based on an experimental orientation preference map to show that it can indeed lead to the spontaneous generation of realistic single condition maps. The dependence of the suggested synaptic weights on distance correlates with the pattern of correlations in the imaged spontaneous activity, further supporting the idea that intrinsic connectivity in this area underlies the activity in both spontaneous and evoked regimes.

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Weaning and social isolation are critical factors for the establishment of functional neuronal networks in prefrontal cortical brain areas

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Recent studies in rodents revealed that weaning is a critical formative period for adult behaviors. Moreover, it was found that this environmental factor acts in interaction with subsequent social environmental conditions such as social isolation, resulting in altered behavior in open-field and social-interaction tests. In the present study we wanted to clarify if the described behavioral alterations are accompanied by morphological changes in prefrontal cortical brain areas. Male Wistar rat pups were raised with their dam until 21 (early weaning) or 30 days of age (late weaning) and were subsequently reared in social isolation or in groups. We quantified dendritic spine frequencies and dendritic length of pyramidal neurons in the anterior cingulate cortex (ACd). We found changes of dendritic spine frequency and dendritic length specific for apical and basal dendritic branches. Two-Way ANOVA revealed an effect of weaning on apical dendritic spine frequency resulting in decreased spine frequencies in the late weaning groups. In contrast, basal dendrites did not undergo spine changes in response to weaning, however social isolation induced significantly enhanced spine frequencies. Dendritic length was affected on apical dendrites only, where we found an effect of weaning and social isolation and an interaction of these factors, resulting in decreased dendritic length after late weaning and increased length after social isolation. Our results provide the first evidence that the process of weaning in interaction with postnatal environmental conditions alters the development of neuronal connectivities in prefrontal cortical areas, which at least in part may underlie the observed behavioral alterations.

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Prenatal stress in rats attenuates hippocampal long-term potentiation (LTP) and induces deficits in synaptic plasticity and spatial memory

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Prenatal stress (PS) in rats has been shown to reduce hippocampal neurogenesis and cause mild deficits in spatial memory in adulthood. These changes are associated with altered programming of the fetal brain by excess levels of maternal stress hormones like corticosterone. The present study investigated the effect of PS on hippocampal long-term potentiation (LTP) and genes involved in its regulation, together with those implicated in synaptic plasticity. Pregnant Sprague-Dawley rats were subjected to variable maternal stress (restraint, saline injection and forced swim) on days 15-20 of gestation. Experiments were performed on male offspring aged 21 days. Field excitatory postsynaptic potentials were recorded in the CA1 region of hippocampal slices from 6 control and 6 prenatally stressed rats. High frequency stimulation (HFS) induced LTP (10 to 60 minutes post-HFS) in control rats, that was significantly reduced by PS. Littermates of these rats were used for gene analysis in RNA extracts of hippocampus by the Affymetrix DNA array. Hierarchal clustering showed a clear distinction between controls and PS. 3.5% of 20,000 genes represented on the array were up or down-regulated by PS. These included several implicated in neurogenesis and synaptic plasticity that were down-regulated. Among those involved in presynaptic activity were; rab3a, syntaxin 1, synapsin1, stxb1 (munc18) and RIM1a, and in postsynaptic activity; BDNF, PSD95/SAP90, Ephrin receptor, protein kinase C. The differential expression of many of these genes was confirmed by RT-PCR. This study shows for the first time that prenatal stress can affect neuronal development resulting in reduction in hippocampal plasticity, and LTP. These early changes in neuronal activity could explain the deficits in neurogenesis, learning and memory seen in adult life.

Effects of early life experience on corticosterone secretion in two animal models of depression (Wistar-Kyoto and Flinder-Sensitive Line rats)

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In light of links between parental depression and impaired functioning of the hypothalamic-pituitary-adrenocortical axis (HPA) in the offspring, we analyzed the activity of this axis in pups belonging to an animal model of depression (Wistar-Kyoto, WKY). In addition to a normal growing condition, a mild chronic stress condition (reduced bedding in postnatal days 2-9) was used in order to elucidate the possible interaction between hereditary vulnerability and early life stress. At postnatal day 17, two pups per litter were removed from the home cage, one was subjected to acute stress (exposure to an adult male rat) and the other was left undisturbed. Blood was collected and corticosterone was assayed by RIA. The results indicate that, while in normal growing conditions there were no differences between WKY and Wistar controls, WKY pups, growing in the chronic stress condition, exhibited dramatically lower corticosterone levels. The WKY pups' hypo-secretion of corticosterone echoes studies in humans indicating that early stress can lead to a hypocortisolism, a condition with possible effects on brain development, ability to handle stress and health. Next, a different genetic animal model of depression, Flinders-Sensitive Line (FSL) rats was compared to their controls (Sprague-Dawley), in the same procedure. FSL pups were more resilient to early stress (no difference in corticosterone was found as a result of the early chronic-stress). In addition, only Wistar/WKY rats showed an increase in corticosterone as a result of an acute stress, suggesting lower overall stress reactivity in the SD/FSL lines. The results provide insights into differences between the two models of depression and expand our knowledge on the interaction between hereditary factors and environmental conditions that lead to hypocortisolism in humans.

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Transformations in Odor Percept Identity as a Function of Odor Intensity

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Anecdotal evidence suggests that a select group of odorants such as indole and skatole undergo a dramatic shift in percept when sampled at high versus low concentration. This concentration-dependent transformation is not only an hedonic transformation, but also a transformation in percept identity. Here we set out to characterize these changes in odor percept, using the odorant indole. We first used a maximum-likelihood adaptive staircase to determine subjects threshold for the detection of indole diluted in mineral oil. We then provided each subject with the next-highest concentration step in the series. Each subject performed an odor quality evaluation on the sample provided using 48 descriptors from the Dravnieks Atlas of Odor Character Profiles. Following quality evaluation of this low intensity sample, each subject repeated the evaluation on a high intensity sample. Across subjects and intensities, 44 of the 48 descriptors were used at least once.

However, whereas 8 of the identity profile descriptors (almond, caramel, cedarwood, chocolate, dirty linen, leather, vanilla, wet wool) were used for the low, but not high concentration, no identity profile descriptors were used for the high but not low concentration. Upon collection of 30 subjects, principal components analysis will be used to characterize the odor space, and compare indole to other odorants.

A possible linkage between DA and mitochondrial complex I dysfunction: implications to schizophrenia

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Dopamine is suggested as a prominent etiological factor in several neuropsychiatric disorders including schizophrenia. In such dopamine-related diseases, mitochondrial dysfunction has been reported as well. In schizophrenia, mitochondrial complex I dysfunction was observed at the enzymatic level, as well as in the expression of mRNA and protein of three of its subunits, both in the periphery and in the brain. Notably, accumulating data show that dopamine can inhibit mitochondrial respiration both in vivo and in vitro. The purpose of the present study was to investigate the nature of the interaction between dopamine and mitochondria. When applied to human neuroblastoma SH-SY5Y cells, dopamine induced a reduction in ATP concentrations, which was negatively correlated to intracellular dopamine levels. Furthermore, in disrupted mitochondria, dopamine inhibited complex I activity with no effect on complexes IV and V activities. Interestingly, complex I activity was also reduced by typical as well as atypical antipsychotic drugs. However, dopamine and haloperidol had no effect on mRNA and protein expression of three of complex I subunits (24kDa, 51kDa and 75kDa). Abnormal interaction between dopamine and mitochondrial complex I was observed in platelets of schizophrenic patients. Thus, complex I activity in disrupted mitochondria isolated from platelets of schizophrenic patients was susceptible to dopamine inhibition twice as much as that of control subjects. The results of the present study further support the existence of an interaction between dopamine and mitochondrial complex I, which can contribute to the pathology of schizophrenia, and suggests complex I as a modulation target for dopamine and antipsychotics.

Wnt1 controls the development of midbrain dopaminergic neurons in vivo

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Midbrain dopaminergic neurons play a central role in the modulation of different brain functions and are associated with prevalent neurological and psychiatric disorders. Despite the importance of these cells, the molecular mechanisms controlling their development are still poorly understood. The secreted glycoprotein Wnt1 is expressed in close vicinity to developing midbrain dopaminergic neurons. To investigate its role for the generation of this neuronal population we performed a series of gain and loss of function experiments. We report that ectopic expression of Wnt1 in the rostral hindbrain of transgenic mice leads to the generation of additional dopaminergic neurons in vivo exclusively in the rhombomere 1 floor plate, without affecting other midbrain nuclei and rostral hindbrain cell populations. Mice lacking a functional Wnt1 protein fail to develop a midbrain and part of the hindbrain. Therefore, these mutants can not be used to address the question whether Wnt1 is directly required for the development of midbrain dopaminergic neurons. To circumvent this problem, we used an explant culture system and were able to show that Wnt1 is indeed necessary for the generation of midbrain dopaminergic neurons. Taken together, we provide evidence for the first time that Wnt1 has the capability to generate midbrain dopaminergic cells in vivo and that it is directly required for the generation of these cells.

Netwok hippocampal activity modified by conditioning

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While neuronal plasticity is the widely accepted model of learning and memory, standard protocols, used, for example in the study of LTP involve associating postsynaptic response with a brief electrical stimulation. The fallback of such studies is related to the artificial nature of the electrical stimulation. We used a conditioning procedure involving a transient enhanced activation of synaptic NMDA receptors in primary hippocampal cultures. This conditioning leads to a sustained potentiation of network activity, characterized by an increase in spontaneous activity, burst firing, and synchrony among neurons of the network. Dual whole cell recordings revealed that the plasticity occurred via a decrease in inhibitory synaptic connections and an increase in excitatory synaptic connections, both of which were shown to be independent of postsynaptic intracellular calcium concentration. These changes appear to occur through a presynaptic mechanism, as they were reflected in a potentiation of synaptic release. Finally, the amplitude and frequency of mEPSCs recorded in presence of TTX was increased as a result of the NMDA induced plasticity. Our results suggest that intrinsic amplification of NMDA receptor activity leads to an overall potentiation of network activity in culture through several concomitant mechanisms.

Learning-induced enhancement of neuronal excitability is mediated by ERK-dependent reduction of the after hyperpolarization

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We studied the mechanisms that mediate learning-related long lasting reduction of the post-burst after hyperpolarization (AHP) in cortical pyramidal neurons. We previously showed that pyramidal neurons in the rat piriform cortex from olfactory-discrimination trained rats have reduced post- burst AHP for three days after training completion, and that this reduction is due to decreased conductance of one or more of the PKC and calcium-dependent potassium current that mediate the medium and/or the slow AHP. In the present study we examined which potassium current is modulated by learning, and further explored the molecular mechanism that enables its long-term reduction. The small conductance (SK) channels inhibitor, apamin, reduced the AHP in neurons from trained, naïve and pseudo trained rats to a similar extent, thus maintaining the difference in AHP amplitude between neurons from trained rats and controls. The protein expression level of the SK1, SK2 and SK3 channels was also similar in all groups. Noradrenalin (NE), which was shown to enhance the IAHP while suppressing the SIAHP, enhanced the AHP in neurons from trained rats, indicating that sIAHP conductance is reduced after learning. The MEK inhibitor PD98059 increased the AHP only in neurons from trained rats, thus abolishing the differences between neurons from trained rats and controls. Accordingly, neuronal excitability was decreased in neurons from trained rats only. We suggest that learning–induced enhancement of neuronal excitability is mediated by reduction in the sIAHP and that this long-term reduction is maintained by ERKI/II activation.

Cytotoxic or neuroprotective? The context-dependent activity of microglia under neuropathological conditions

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'Protective autoimmunity' refers to a well-controlled T cell-mediated anti-self response that helps the body resist neurodegeneration. Using an in-vitro assay of hippocampal slices to assess the cytotoxic or protective effect of microglia in neural tissue we show that interferon (IFN)-gamma and especially interleukin (IL)-4, characteristic Th1 and Th2 cytokines, respectively, endow microglia with a protective phenotype. In contrast, aggregated beta-amyloid, like bacterial cell wall-derived lipopolysaccharide (LPS), evoked a cytotoxic microglial response. Cytotoxicity was correlated with a signal-transduction pathway that down-regulated MHC-II expression through the MHC II-transactivator and the invariant chain. Protection by IL-4 was attributed to down-regulation of TNF-alpha and up-regulation of insulin-like growth factor I (IGF-I). These findings suggest that beneficial or harmful expression of the local immune response in the damaged CNS depends on how microglia interpret the threat, and that a well-regulated T cell-mediated response enables microglia to alleviate rather than exacerbate stressful situations in the CNS.

Microglia activated by IL-4 support neurogenesis and oligodendrogenesis

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Cell renewal in the central nervous system (CNS) of adult mammals is limited, and is blocked in inflammatory conditions of the brain. Here we show that both neurogenesis and oligodendrogenesis from adult rat neural progenitor cells are blocked by inflammation-associated (endotoxin-activated) rat microglia. However, when activated by IL-4, a cytokine associated with helper T cells, the microglia induce and support neurogenesis and oligodendrogenesis. Blockage and support of neurogenesis were correlated with up- and down-regulation, respectively, of microglial production of TNF-alpha. Oligodendrogenesis induced by IL-4-activated microglia could be neutralized by specific anti-IGF-1 antibodies. In vivo, hippocampal neurogenesis and cortical oligodendrogenesis were significantly boosted by IL-4-activated microglia injected into the cerebral ventricles, but were blocked by microglia activated by endotoxin. These findings suggest that immune modulation, rather than anti-inflammatory treatment, is likely to promote repair and cell renewal in the adult CNS.

Neuroimaging of Genetically-Defined Incipient CJD

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Introduction: A new study has just been funded by the NIH to study CJD in Israel. We will use neuroimaging to elucidate early, and even premorbid, cerebral abnormalities of structure and function in a singular cluster of high incidence occurring among Libyan Jews living in Israel, caused by familial transmission of a mutated prion protein (PrP) gene. All subjects will have extensive neurological and neuropsychological examinations, as well as MRI, using both traditional structural imaging and newer neuroimaging methods: Diffusion-Weighted Imaging (DWI) and Magnetic Resonance Spectroscopy (MRS). Here we present the general logic and structure of the study, as well as results from the first seven subjects (4 patients and 3 relatives). Results: On clinical reading of the MRIs, all three controls were judged normal, and all four patients were considered abnormal. The most common findings were FLAIR and DWI hyperintensity in caudate (4/4), putamen (3/4), and cortical white matter (3/4). Quantitative analyses showed significant loss of grey matter and higher ADC values in cortex. Focal decreases of ADC were found in the lentiform nucleus of patients. Spectroscopic imaging demonstrated reduced NAA in the patients, with the NAA/Cho ratio lowest in cingulate gyrus, where it was also correlated with a neurological severity score. Duration of disease was correlated with this ratio in the caudate nucleus and putamen. Comment: This project is the largest neuroimaging study ever conducted in CJD, and the first to observe a genetically homogenous sample. It will provide data on the earliest stages of the disease, and on healthy mutation carriers before frank onset of symptomatology. The large sample sizes, availability of healthy mutation carriers, the noncarriers of similar environmental and cultural background, and rapid access to symptomatic patients, are all unprecedented features that should yield definitive data on the early stages of this devastating disease.

Do Magnets Affect our Neurons?

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Though many people started lately wearing static magnets as a therapeutic aid, the actual effects of these magnets on the nervous system is still an open issue. In order to investigate whether there is any neuroscientific basis for the claimed effects, we conducted preliminary experiments that were designed to check the impact of a relatively strong static magnetic field (SMF) on active neuronal networks. Hippocampal dissociated cultures were differentially exposed to 400mT magnets and monitored by calcium imaging (at 10Hz), combined with morphological comparisons of GFP transfected cells in these cultures. We checked both acute and chronic effects on network parameters such as spontaneous burst frequency (SBF), burst synchronicity, burst decay time and fluorescence dynamic range (DR = max amplitude- min base level). The acute treatment (immediate exposure to SMF while recording) showed little effect with very large variability in all parameters. The chronic treatment (11-12 days growth with the magnets) showed, on the other hand, significant effects. These exposed cultures showed a large increase in SBF, a small decline in maximal DR and synchronicity decline that was significant in the north magnetic pole treatment only. This unexpected asymmetry was even more pronounced in the effects on the dendritic trees morphology (Sholl analysis): south magnetic pole exposure reduced the branching at 100-150um distance from the soma, compared to the control, whereas north magnetic pole exposure increased the branching at the distances of 50-150um (both were insignificant in other distances). Our results suggest that a chronic exposure to a strong SMF affects the neuronal network activity as well as cell morphology. Nevertheless, further research must be done before making any conclusions regarding the impact of these effects on the mammalian nervous system and humans' in particular.

Common experimental procedures dramatically affect phosphorylation levels in Xenopus oocytes

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One of the preferred expression systems for the study of ion channels employs Xenopus oocytes. Channels mRNA is synthesized, injected to oocytes and induced ionic currents are measured by the Two Electrode Voltage Clamp (TEVC) or the patch clamp techniques. To explore channel activity, oocytes are held at various membrane potentials and exposed to a variety of external conditions. Here we studied the effects of common experimental conditions on the phosphorylation levels of membrane proteins as phosphorylation/dephosphorylation events modulate ion channels gating and cell surface expression. Two strategies were chosen to determine relative phosphorylation levels: a direct detection with a phospho-Ser/Thr PKA subsrate antibody and a functional method employing two different

leak potassium channels, as indicators. The two channels were chosen for their opposite responses to protein kinase phosphorylation: Drosophila KCNK0 channel activity is enhanced while human KCNK2 channel activity is reduced several fold following protein kinase A (PKA) activation. To eliminate possible modulation by pathways other then phosphorylation, mutants that are impaired in their PKA regulation were tested. We found that experimental conditions had a dramatic effect on the measured ionic currents: even a few minutes exposure to "physiological conditions" (4mM KCl, -80mV) decreased KCNK0 currents while increasing KCNK2 currents ~3 fold. Similarly, dramatic opposite current changes were observed while altering oocytes holding potential or bath solution ion composition, temperature, pH or osmolarity. On the contrary, mutant channels were not influenced by the same conditions. Correlating variations in phosphorylation levels were detected in un-injected oocytes by western analysis. We conclude that common experimental procedures dramatically affect phosphorylation levels in Xenopus oocytes. The use of kinases/phosphatases modulators might reduce uncontrolled effects on expressed channels.

Structure and Pathology in the Central Nervous System by q-Space Diffusion Weighted MRI

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Magnetic Resonance Imaging (MRI) is currently the most important imaging modality of the central nervous system (CNS). The main reasons for that is the non-invasiveness of the method, the many physical parameters that can be used as contrast mechanisms to construct MR images and the fact that morphological information can be coupled with biochemical information using magnetic resonance spectroscopy (MRS). Diffusion is an important contrast mechanism in MRI of the central nervous systems (CNS) with applications ranging from early detection of ischemic injury to fiber tracking. In the lecture we will describe the principle and selected applications of high b value q-space diffusion MRI in the CNS. Applications ranging from structural studies in excised spinal cord, through detection of different white matter associated pathologies of the spinal cord up to in vivo applications of this technique in MS and Dementia will be described. These examples will be used to demonstrate the potential and limitations of this technique. At the end of the lecture, if time will permit, we will highlight some new avenues of MRI in experimental neurology and neurobiology.

Autoantibodies against an extracellular peptide of the GluR3 subtype of AMPA receptors activate both homomeric and heteromeric AMPA receptor channels

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Autoimmunity may contribute to the pathology of some epilepsy syndromes as the sera of some epilepsy patients harbor specific autoantibodies to the GluR3 subtype of AMPA/glutamate receptor channel. Building on previous reports of a glutamatergic agonist activity of anti-GluR3 sera, we investigated here the ability of affinity-purified Abs directed against the GluR3B peptide (a.a 372-395) to bind and activate recombinant GluR3 receptor channels expressed by Xenopus oocytes. We found that affinity-purified anti-GluR3B Abs can by themselves activate both homomeric and heteromeric GluR3-containing channels without the requirement of neuronal, glial or blood ancillary molecules. When repetitively applied, anti-GluR3B Abs didn't cause receptor desensitization. Co-applications of anti-GluR3B Abs and glutamate displayed neither inhibitory nor synergistic effects, and pre-incubation with anti-GluR3 Abs didn't affect the subsequent response to a glutamatergic agonist. We therefore conclude that anti-GluR3B Abs can activate Glur3-containig receptors, and hypothesize that if present chronically in brain fluids, these Abs may lead to a detrimental activation of GluR3-containing AMPA receptors. These findings may have important clinical relevance to epileptic patients harboring anti-GluR3B Abs.

ERKI/II is essential for maintenance of olfactory-learning induced enhancement of synaptic transmission in the piriform cortex.

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Previous studies have shown that olfactory-discrimination learning is accompanied by reduced paired pulse facilitation (PPF) in response to stimuli applied to the intrinsic fibers, interconnecting layer II pyramidal neurons. Extracellular regulated kinases (ERKI/II) are thought to play major role in learning and memory as well as synaptic plasticity in the brain. The purpose of the present study was to determine whether ERKI/II has a role is maintaining the olfactory-learning induced reduction in PPF. Intracellular recordings from pyramidal neurons were performed in piriform cortex brain slices. ERKI/II inhibition by application of PD98059 (38 μM) had no effect on PPF values in neurons from naïve and pseudo trained rats. However, it caused a significant increase in PPF value in neurons from trained rats. Consequently, the difference in PPF values between trained and the controls was diminished (from 1.24 + 0.04, n=19 to 1.42 + 0.08, n=9 in trained, from 1.4 + 0.04, n=16 to 1.51+ 0.06, n=10 in pseudo trained, and from 1.39 + 0.07, n=18 to 1.31 + 0.07, n=18 in naive). In agreement with the electrophysiological analysis, Western blot analysis of synpatosomal fraction, showed an increased ERKI/II activation (40%) in brains from trained rats (n=5) compared with control brains (naïve n=7, pseudo trained n= 9). We conclude that ERKI/II activation is essential for maintenance of learning-induced enhanced synaptic transmission in the piriform cortex. We currently aim to identify ERKI/II's presynaptic substrates that are mediating the learning induced synaptic plasticity.

Modeling complex receptive fields of fly interneurons

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The lobula plate tangential cells in the fly consist of a set of 60 strongly interconnected large field motion sensitive interneurons. This small network of cells has shown to exhibit a number of different computations associated with precise and unique wiring. In this study we focus on a subset of these interneurons, the vertically sensitive VS cells. VS-cells were shown to have complex receptive fields extracting particular features of the optic flow that result e.g from rotational ego-motion. Based on dual recordings from VS-cells, it was suggested that neighboring VS cells are electrically coupled and distal cells inhibit each other (Haag and Borst 2004). Here, we analyze the suggested connectivity scheme using realistic compartmental modeling. Our calculations indicate that such a connectivity results in a linear decay of the signal from one cell to the other along the horizontal visual axis and can reproduce the experimental data available so far. The functional implications of this orderly arranged connectivity will be discussed.

Reference: Haag, J. & Borst, A. Nat. Neurosci. 7, 628–634 (2004).

Structure and function relationship of VIP: The importance of the N-terminus

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Accelerated neuronal death brings about cognitive as well as motor and other dysfunctions. A major neuropeptide, vasoactive intestinal peptide (VIP), has been shown to be neuroprotective (Brenneman DE and Eiden LE: Proc Natl Acad Sci 1986;83(4):1159, Gozes et al.: Proc Natl Acad Sci 1996;93(1):427). Several studies suggest that VIP could have a beneficial effect on neurological diseases such as Alzheimer's and Parkinson's disease. Hence, novel potent VIP analogs could be valuable for several therapeutic uses. VIP's effects are mediated through high affinity interaction with two receptors: VPAC1 and VPAC2. VPAC1 and VPAC2 are preferentially coupled to Gás protein that stimulates increases in adenylate cyclase. Currently, all the potent VIP antagonists synthesized have modifications in the N-terminal domain of the peptide. Thus, it is suggested that the N-terminal domain of VIP is responsible for the peptide's activity. In view of the above, we examined the effect of multiplication of the N-terminal domain of the VIP ligand, on the VIP receptor (VPAC1) binding and cAMP activation. The multiplication of the VIP N-terminal was performed through extending or branching methodology. We created several VIP analogs carrying multiplication of the N-terminal domain of VIP. Circular dichorism (CD) analysis revealed that these peptides maintained similar helicity to VIP in organic environment. The analog receptor binding and activation of HT29 cells expressing VPAC1 was examined. A VIP branched analog that was slightly more efficacious as compared to native VIP towards VPAC1 – related cAMP production was discovered. This analog could have potential therapeutic value in neurological disorders. It is concluded that two branched N-terminal VIP sequences are superior in recognizing VPAC1 as compared to two N-terminals in tandem.

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Very early frontal involvement in retrieval from working memory?

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The involvement of the frontal lobe in memory processes is long acknowledged. However, the exact role it plays is controversial. In recent years, both monkey and human studies have established the role of prefrontal cortex in maintenance of information across delays in working memory. As for retrieval of information however, it has been assumed that the frontal lobe is involved only in post-retrieval processes (i.e., assessing the outcome of retrieval). Following a hint from an fMRI experiment, we compared event related brain potentials during encoding and retrieval of faces in a delayed match to sample task. We asked 15 participants to remember a briefly presented face over a period of 2 seconds and then judge whether a second face is of the same person or not. The response was separated in time from the presentation of the second face. We found that the N170, a marker of face perception, recorded over parieto occipital scalp sites, is identical during the presentation of the first and second face. However, during the second presentation, when retrieval is required, a frontal scalp activity starts around 80 ms after the face is first presented. With the limitations of EEG measures to identify sources reliably, this suggests early recruitment of frontal lobe mechanisms in retrieval, inconsistent with a merely post-retrieval process. We propose therefore that the frontal cortex is involved with retrieval from the outset.

Encoding of Object Position in an Active-Touch System: Rat Whisker Kinematics & Somatosensory Cortex Dynamics

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Major events occurring during active vibrissal sensing, such as whisker protraction and touch, are encoded by various functional types of first-order trigeminal neurons. We examined how these events are represented in the barrel cortex, using artificial whisking in anaesthetized rats (Szwed et al., Neuron, 2003). We induced whisking by direct electrical stimulation of the facial motor nerve, while positioning an object at different horizontal locations along the path of the whiskers. Whisker trajectories were monitored using high-speed video, and various parameters were extracted from the whisker motion. We investigated both whisker kinematics and cortical neuronal responses. We found that the whisker curvature encodes object position better than the angle. In addition, we recorded neurons in the rat barrel cortex and investigated the encoding of object position. Neurons were classified according to their response at steady-state into Whisking-touch (WT) units, which responded both to the whisking and to object touch, and touch (T) units, which responded only to object touch. The T units are situated predominantly near layer IV, while WT units are mostly situated in the cortical layers above and below layer IV. The two components of the WT response can be distinguished by the fact that the W component adapts within 3-4 whisks, while the T component does not adapt. Overall, our results demonstrate that the computation of object position is carried out by a dynamical process which integrates whisking and touch information at different cortical layers.

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NAP binding to tubulin mediates cell survival

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The octapeptide NAP (NAPVSIPQ) potently protects neurons against a wide variety of insults in vivo and in vitro. NAP is the active site of the novel protein Activity-Dependent Neuroprotective Protein (ADNP), which is a VIP-responsive gene (Dev Brain Res. 2003 144,83). Here, cell survival-screening assays indicated specificity with NAP protecting against oxidative stress in a selected cell line of a neuronal lineage. Further studies utilizing affinity chromatography of brain extracts identified tubulin, the brain major protein, as the NAP-binding ligand and NAP stimulated microtubule assembly. When added to cerebral cortical astrocytes, NAP induced a rapid microtubule re-organization into distinct microtubular structures that were stained by monoclonal tubulin antibodies and visualized by confocal microscopy. Fluroresceine-labeled NAP induced a similar change and was detected in the intra-cellular milieu, even when cells were incubated at 40C or at low pH. Similar microtubule reorganization characteristics were observed in cerebral cortical neurons as well as in cell lines of neuronal lineage. The time course of microtubule re-organization was paralleled by a transient change in tau expression and an apparent decrease in the relative amount of phophorylated tau. Zinc toxicity that results in tubulin Zn-sheets formation and cell death was inhibited by NAP treatment in astrocytes (JBC 2004, 279, 28531) and in mixed neuro-glial cultures. In conclusion, the results suggest that NAP can cross the plasma membrane and interact directly with tubulin, the microtubule subunit, to induce microtubule re-organization and improved survival. As microtubules are the key component of the neuronal and glial cytoskeleton that regulates cell division, differentiation and protection, this finding may explain, in part, the breadth and efficiency of the neuroprotective capacities of NAP.

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Withdrawal from cocaine-seeking behavior by DHEA

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Drug addiction is a serious problem in the modern world. One of the most edicted drug is cocaine. One type of neurosteroid that seems to reduce the craving for cocaine in rats is Dehydroepiandesterone, (DHEA). Clinical trials have found that DHEA increases motivation and brings about a feeling of well-being. Cocaine addicts that underwent withdrawal and then relapsed to drug abuse exhibited low DHEA levels. Thus, it was hypothesized that a connection exists between mood, emotions and DHEA, and that increasing DHEA levels may assist in withdrawal from cocaine-seeking behavior. We decided to induce withdrawal from cocaine seeking behavior. So, we exposed a group of rats to cocaine using the self-administration technique. When rats achieved maintenance levels meaning they take a steady amount of drug on a daily basis, they received daily i.p injections of DHEA (2 mg/kg) for 2 weeks, 90 minutes before being placed in the self-administration chambers. We examined the possibility that DHEA treatment may have generally disrupted locomotor function in rats. Decreased motor activity could itself decrease the number in lever responses. Therefore, we tested the effect of DHEA treatment on water self-administration in water-deprived rats. There were no significant differences in the number of active lever responses or the number of water reinforcements in DHEA-injected compared to untreated control rats. In conclusion, DHEA treatment induces withdrawal from cocaine-seeking behavior without causing motor deficits. Furthermore, the combination between cocaine and DHEA treatment is not rewarding. Thus, it may be a novel treatment for cocaine addiction.

GCP170 Interacts with Serine Racemase and Regulates the Synthesis of the NMDA Receptor Coagonist D-Serine.

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D-serine is an endogenous coagonist of NMDA receptors that is synthesized from L-serine by serine racemase. In order to identify new mechanisms and pathways regulating brain D-serine synthesis, we screened for protein interactors of serine racemase by yeast two-hybrid technique. We identified that GCP170 /Golgin-160 specifically interacts with NH2-terminal region of serine racemase. GCP170 was first identified as a membrane associated protein present in the Golgi apparatus with unknown function. The interaction of GCP170 and serine racemase was confirmed by GST pull-down experiments. To further assess the specificity of the interaction, we carried-out co-immunoprecipitation experiments of serine racemase and GCP170. Accordingly, the two proteins co-immunoprecipitated from both transfected cells and brain extracts, indicating that the interaction occurs in vivo. Additionally, confocal immunofluorescence microscopy studies in HEK293 transfected cells and primary neural cultures demonstrated a high degree of colocalization in the cytosol and intracellular membranes. To evaluate the physiological role of the interaction, serine racemase was cotransfected with GCP170 in HEK293 cells and synthesis of D-serine was determined by HPLC. We found that cotransfection of GCP170 elicited a significant decrease in D-serine production by serine racemase. This indicates that GCP170 is a negative regulator of serine racemase and may physiologically modulate the synthesis of D-serine, with implications for the regulation of NMDA receptor activity.

Circulating cholinesterase isozyme activities are altered in dystrophin-deficient mutant (mdx) mice

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Proper synaptic transmission depends on accumulation and maintenance of high acetylcholine-receptor (AChR) concentration that is considerably greater than synaptic acetylcholinesterase (AChE) density. Previously, we demonstrated that in dystrophin-deficient mutant (mdx) mice, a model of Duchenne Muscular Dystrophy (DMD), junctional infolding is geometrically distorted and several AChR pathologies exist: post-synaptic distribution is "grape-like", junctional density is decreased, degradation-rate faster, and extrasynaptic concentration is elevated but low in denervated muscle. Other studies in mdx mice indicate that the muscle G4-AChE is undetectable and AChE sera-activity is elevated (Oliver et al. Neuromusc. Disord. 2:87, 1992). Since AChE and butyrylcholinesterase (BuChE) levels change during development and may reflect (or influence) muscle growth and differentiation, the present study quantifies the levels of cholinesterase (ChE) isozymes in mdx-sera. Specifically, AChE and BuChE activities in sera of mdx and control mice were assayed with acetyl- and butyryl-thiocholine as substrates, and with the selective inhibitors BW284c51 and iso-OMPA (for AChE and BuChE, respectively). We found that the total ChE activity in the mdx-sera decreased by 20% compared to control ($P<0.01$). However, while AChE levels in mdx-sera were significantly higher than control (25%, $P<0.02$), the BuChE levels were significantly lower (30-35%, $P<0.001$) than in controls. Thus, the ratio of BuChE to AChE decreased from 6:1 in control to 3:1 in mdx-sera. Because serum ChE levels are influenced by the ontogeny and endocrine regulation of the hypothalamo-pituitary-gonadal axis, it is possible that lack of dystrophin in mdx-mice may affect this regulation. Further studies are necessary to help clarify whether changes in circulating ChE reflect (or influence) the transmission processes at pathologically altered synapses.

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Motor Assessment within Virtual Environments: Distractor Interference Effects in Reaching Toward Visual Targets

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Background: Previous studies have demonstrated that the presence of irrelevant objects (distractors) in the environment may influence movement trajectory as well as reaction time and movement duration. The use of a virtual reality (VR) presentation provides a flexible and powerful method, which allows data to be efficiently collected (e.g. in contrast to positioning real objects on each trial), and a way to examine the temporal and spatial kinematics of limb movements. We have developed a VR system, which includes a 3D tracking device for measuring limb movements. The system enables the experimenter/clinician to assess the subjects' motor performance while interacting with static or dynamic virtual objects within the virtual environment. The system includes a single camera, video-capture application, known as the Gesture Xtreme (GX) VR System, and a 6 DOF magnetic tracking device. Aim: The main objective of this research is to investigate the interference effects caused by the presence of a distracting object while reaching towards virtual targets in 3D space, where the object's position and velocity (of both distractor and target) are manipulated. Method: In phase 1, the system is used to assess the motor performance of young adult healthy subjects, and focuses on the influence of the object's velocity on the attentional mechanisms underlying the planning and execution of movements in 3D space. In phase 2, the system will be used to assess the motor performance of elderly healthy subjects and patients with stroke. Phase 3 will address issues of design usability in order to demonstrate the feasibility of using such a system for rehabilitation evaluation and treatment. Conclusion: Use of the above VR system may shed light on the way in which movements are planned and executed, provide a rationale for improving current assessment measures, and lead to better diagnostic procedures for patients with neurological dysfunction.

Concept and Percept in Emotion processing: a cross-modal fMRI study

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Real-life emotion generation involves low-level perceptual processing of the physical properties of sensory information (e.g. color, form, movement etc.), and higher-level

manipulation of concepts producing emotional meaning. Isolating emotional conceptual processing is difficult since it is coupled and dependent upon the perceptual processing of the stimuli used to elicit emotions. In order to separate the conceptual from the perceptual aspects of emotional processing we applied a cross-modal paradigm. 12 sec video and audio clips were presented both alone and in combination (combo). Video clips, when presented alone, were rated as neutral, but when combined with music clips, were rated according to the valence of the music as neutral, negative or positive (n=15, p<10E-6). 12 subjects were scanned in a 3T GE system while passively viewing the various clips. All clips were pseudorandomly distributed and order balanced. Each subject viewed each video clip combined with only one type of audio clip. To test for conceptual processing in emotion, we compared the combo condition to video and audio each presented alone. Both the amygdala and the dorsolateral prefrontal cortex showed increased activation for this contrast. On the other hand, activation of high order visual areas was not augmented by the addition of audio to video irrespective of emotion. The findings of this study clearly differentiate between brain regions involved in the conceptual versus the perceptual constituents of emotional processing.

Olfactory bulb organotypic culture: an in-vitro neuronal zinc signaling model

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Zinc has long been known to play an essential role in many aspects of mammalian development and function, primarily as enzyme co-factors and as structural elements in transcription factors. In the brain, in addition to this tightly bound zinc, 'free' or loosely bound zinc ions are present in forebrain glutamate synaptic terminals. While the function of this 'synaptic' zinc is unclear, evidence now exists for yet another pool of 'intrinsic' zinc that is available to many, perhaps even all cells. We have established organotypic cultures of the combined mouse olfactory epithelium and bulb from 7 day old CD-1 mouse pups to study the regulation and function of zinc and zinc-homeostatic proteins (ZHP) under controlled conditions. One day after establishing the cultures, basic OFB architecture is intact and the vast majority of cells viable. After one week, immunohistochemical characterization of the explants included general and specific markers. Some, e.g., TH and parvalbumin, selected discrete cell populations. Expression of ZnT-1 was dramatically reduced in all layers. Periglomerular neurons that were ZnT-1 immunonegative and TH immunopositive were observed in the explants at all ages examine. This finding was not dependant upon availability of zinc in the medium or the presence of zinc-containing afferents from OE cells. MT I/II was expressed normally in astrocytes in and around the glomeruli. Connectivity of OE cells with their targets in the OFB glomeruli was demonstrated by DiI and immunolabeling with the synaptic vesicle protein synaptophysin. Finally, OFB cultures were exposed to the nitric oxide donor (DETA/NO) to determine what if any intrinsic zinc resources are maintained in these isolated slices. Explants exposed to NO for 8 hours release zinc from internal stores as seen by the zinc fluorophore, TSQ. These results demonstrate the utility of this in vitro model for the study of zinc signaling and olfaction.

Proteomic study: What is the role of ERKI/II in learning and neuronal plasticity?

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We are interested in the role of the extracellular regulated kinase I/II (ERKI/II) in the formation of long-term memory and plasticity. ERKI/II is involved in both early and late phases LTP (Rosenblum et al. J. Neuroscience [2002]). In addition, ERKI/II activity is correlated and necessary for the formation of long-term memories. In order to understand the molecular details of ERKI/II role in taste memory formation we aim to identify ERKI/II substrates in the taste cortex that are involved in taste memory formation (novel taste learning). We identify ERKI/II substrates using antibody that recognizes phosphorylated-Threonine only when followed by the amino acid Proline (the favorite phosphorylated site by MAP kinase) together with proteomics (two dimensional electrophoresis, mass spectrometry, and bioinformatics). We identified several proteins phosphorylated on Thr-Pro in synaptosomal fraction as well as total homogenates made from the insular cortex. We differ between ERKI/II substrates and other potential kinases using the systemic MEK inhibitor SL0126. Following the results obtained with the proteomics approach we use western blot analysis to reconfirm the list of proteins. Using this approach, we identified known ERKI/II substrates (e.g. synapsin1) and novel proteins that may explain the role of ERKI/II in plasticity and learning.

The large cytoplasmic loop of the Na+-Ca2+ exchanger NCX1.5 protects the protein from proteolysis

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The Na+-Ca2+ exchanger NCX1 is modeled to contain 9 TMS (transmembrane segments) that are separated by a large cytoplasmic loop between TMS 5 and 6. This loop contains the Na+ and Ca2+ regulatory sites as well as XIP and putative phosphorylation sites. Truncation of 426 amino acids from within the large cytoplasmic loop of the Na+-Ca2+ exchanger RBE-2 (NCX1.5), between I240-I666, results in expression of a mutant protein which exhibits about 76percent of the transport activity of the parent full length protein. Western Blot analysis of amino terminal FLAG tagged wild type exchanger derived from cell extracts indicated that the protein migrates as a 120 kDa band which fits its calculated molecular mass. The cytoplasmic-loop truncated mutant however revealed multiple protein bands ranging from 35 kDa to 200 kDa including a protein of 75 kDa which corresponds to its expected molecular mass. Similar protein profile was obtained when the surface expressed proteins derived from NCX1.5 were analyzed. Addition of the proteasomal inhibitor ALLN did not alter the protein profile of either the WT protein or its loop truncated mutant, except that an overall increase in amount of the exchanger protein was detected in each protein band. 5 partially truncated mutants, each one containing different subset of regulatory sites, were generated: I241deltaH479, H347deltaH513, I241deltaI395, R397deltaV667 and N490deltaR656. All the truncated mutants were surface expressed and displayed exchange activity ranging from 34 to 91 percent. Western Blot analysis of I241deltaH479 and R397deltaV667 mutant exchangers displayed protein bands of unexpectedly low molecular masses of approximately 60 kDa. R397deltaV667, having the largest loop deletion, displayed significantly reduced half life time (of 1hr) as compared to the wild type exchanger protein (around 2.5 hrs). Half life time of I240deltaI666 could not be measured due to an extremely week autoradiography signal.

Binaural Processing in Primary Auditory cortex

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We investigated the way neurons in the primary auditory cortex (A1), which have relatively wide frequency tuning curves and thus are expected to integrate information across frequency, respond to stimuli that include interaural time differences ,ITD. Interaural time differences are usually considered significant only in low frequency channels (up to 1500Hz in humans), whereas it is much easier to physiologically record from neurons with higher best frequencies. For this reason we used a special stimulus, the transposed stimulus, for our study. Transposed stimuli are composed of a low-frequency envelope rectified and low-pass filtered to simulate auditory nerve processing, multiplying a high frequency tone or noise carrier. To test lateralization, the envelope consisted of a bandpass noise centered at 4 different low frequencies, and the transposed stimulus was presented at different ITDs. In tests of binaural detection, the envelope consisted of the sum of a tone and a noise at different signal to noise ratios. The tone was added to the noise at both ears with the same phase,

simulating a diotic condition, or with inverted phases to the two ears, simulating a dichotic condition. Whereas it is commonly stated that neurons in A1 cannot follow repetition rates above 20Hz, using the transposed stimuli we observed neurons that locked to the fine structure of the envelopes even at 128Hz. Many neurons with high best frequency (6-15kHz) showed sensitivity to ITD, a result that has not been reported before. However, ITD tuning did not appear at all the envelopes configurations but was often restricted to a specific envelope and carrier types. When using an optimal stimulus configuration, ITD sensitivity was exquisitely sharp, with some ITD tuning curves showing a peak width of 200 is. Many neurons also showed binaural masking level difference, with the tone affecting the neuronal responses at substantially lower level in the dichotic condition than in the diotic condition.

Mechanisms of Chronic Mild Stress-Induced Depression and Bone-Loss in Mice

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In humans, major depression is often accompanied by osteoporosis. In mice, we have demonstrated that chronic mild stress (CMS), which triggers a depressive-like state, induces bone loss secondary to decreased bone formation and increased bone resorption. The present work was undertaken to uncover mechanisms that mediate the CMS-induced bone loss. Because hypogonadism promotes bone loss, we initially assessed the involvement of sex hormones. However, serum testosterone levels, measured by radioimmunoassay, were similar in CMS and control mice. Since depression was induced by exposing the mice to various stressors, and because glucocorticoids inhibit bone formation, CMS-induced enhancement in their serum levels could lead to bone loss. Indeed, immunoreactive corticosterone levels were almost twice as high in the CMS mice compared to controls. The anti-depressant drug imipramine, adminstered in the drinking water, reduced the depressive symptoms as well as the accompanying bone-loss in mice subjected to CMS. Concomitantly, imipramine blocked the increase in corticosterone levels in these mice. Finally, signaling via the hypothalamic leptin receptor, ObRb, has been recently implicated in the central control of bone mass. Specifically, leptin signaling is a negative regulator of bone formation. Indeed, CMS mice showed a significant increase in hypothalamic ObRb mRNA levels as measured by real-time RT-PCR. To conclude, the bone loss that accompanies the depressive-like state in mice exposed to CMS may be mediated by several mechanisms. Our results suggest corticosterone and leptin signaling, but not gonadal hormones, as possible mediators.

The Effects of Perioperative Pain Management on Recovery, HPA Axis Activation, and Brain PGE2 Levels Following Laparotomy in Rats

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Surgery is characterized by elevated levels of proinflammatory cytokines, including interleukin-1beta, and by hyperalgesia. It is also characterized by activation of the hypothalamic-pituitary-adrenal (HPA) axis, by elevated levels of adrenocorticotropin (ACTH) and corticosterone (CS), and secretion of prostaglandin E2 (PGE2) in the periphery and in the brain. Effective perioperative pain management can attenuate activation of the HPA axis and improve recovery (as assessed by body weight (BW) and food consumption (FC)). The present study examined the effects of two perioperative pain management techniques on FC and BW following laparotomy in rats. All rats received an intrathecal (i.t.) mixture of morphine plus bupivacaine before the incision. This preemptive injection was combined with one of two treatments: 1) injection of slow-release morphine at the end of the surgery, or 2) an anti-inflammatory agent, IL-1 receptor antagonist (IL-1ra), combined with the preemptive i.t. mixture. The effects of perioperative pain management on PGE2 levels in several brain regions, and on plasma levels of ACTH and CS, were also examined. A significant analgesia was achieved by both treatments. Laparotomy significantly decreased FC and BW. Both analgesic treatments resulted in faster recovery of FC and BW; this beneficial effect was more pronounced in the group receiving preemptive analgesia combined with IL-1ra, suggesting that IL-1ra contributes to a better postoperative recovery. Laparotomy elevated CS and ACTH plasma levels, and brain PGE2. Analgesic-treated rats exhibited attenuated elevation of plasma stress hormones, and of PGE2 levels, especially in the amygdala. Thus, effective preemptive analgesia improved postsurgical recovery, and attenuated surgery-induced HPA activation and elevation of brain PGE2. Since PGE2 is involved in activation of the HPA axis, the present findings may suggest a mechanism by which pain relief reduces stress response to surgery.

Neurons work for a living.

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Constant network activity is a common feature of neuronal populations throughout the CNS. This activity can be induced by afferent input, or produced spontaneously in the network, as is the case during embryonic development and sleep. While the mechanism by which too much activity damages neurons has been extensively studied, little is known about how might the lack of activity harm the cells. To study this phenomenon we used primary cortical cultures, deprived of their normal spontaneous activity by the sodium channel blocker tetrodotoxin (TTX). We found that blocking the network activity had a slow yet devastating effect on neuronal populations. Nearly all the neurons died within two weeks, unless provided with an extrinsic supply of brain derived neurotrophic factor (BDNF), which produced a partial rescue of the cells. The slow neuronal degeneration was accompanied by morphological shrinkage of the neuronal soma and dendritic arborization. On the other hand, Miniature excitatory postsynaptic currents (mEPSCs), increased after long term exposure to TTX, both in amplitude and in frequency. Surprisingly, abolishing network activity by blocking glutamate receptors did not produce any neuronal death. Furthermore, when the AMPA receptor blocker DNQX was combined with TTX treatment it dramatically diminished neuronal death. We suggest that the upscaling of mEPSCs in the absence of action potentials plays a role in the chain of events leading to neuronal death. We also suggest that a possible coupling between BDNF release and action potential discharges offers a partial rescue of the activity deprived neurons.

Regulation of the glial inflammatory response by selective agonists for somatostatin receptors.

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Chronic inflammation is involved in the pathogenesis of neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD). This chronic inflammatory response is characterized, among other things, by reactive gliosis in which astrocytes and microglial cells are activated and proliferate. Activated glial cells are a major source of inflammatory mediators such as prostaglandins (PGs) and cytokines. The aim of the present study was to investigate the role of somatostatin (SS) and selective agonists for SS receptors (sstr) in the regulation of basal and lipopolysaccharide (LPS)-induced PG production in microglia and astrocytes. Our results show that SS and octreotide, agonist for sstr 2,3,5 inhibited basal PG synthesis by 25-32% and 45-77% respectively in astrocytes. Selective agonists for sstr1, sstr2 and sstr3 reduced basal

astrocyte PG production by 35%, 32% and 19% respectively. LPS increased PG synthesis in microglia and astrocytes. SS and octreotide inhibited LPS-induced microglial PG synthesis by 80% and 62% respectively but, did not change LPS-induced PG levels in astrocytes. It is suggested that if microglial PG synthesis that is induced by inflammatory agents like LPS is significantly regulated by SS and analogues, then specific preventive and therapeutic modalities may be devised to intervene with these mechanisms.

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Biosynthesis and Degradation of D-Serine an Endogenous Coagonist of NMDA Receptor.

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Mammalian brain contains high levels of D-serine, an endogenous coagonist of N-methyl D-aspartate type of glutamate receptors. The presence of D-serine in the brain challenges the idea that only L-amino acids will be present or play a role in mammals. We now sought to understand the mechanism of biosynthesis and degradation of brain D-serine, which will shed light on several aspects of D-serine in neurobiology. D-serine is synthesized by serine racemase, a brain enriched enzyme converting L- to D-serine. Degradation of D-serine is achieved by D-amino acid oxidase, but this enzyme is not present in forebrain areas that are highly enriched in D-serine. We now report that serine racemase is a bifunctional enzyme catalyzing both the racemization and *f*N,*f*O-elimination of water from serine, producing both D-serine and pyruvate. We found that elimination of water from D-serine provides a novel mechanism for regulating intracellular D-serine levels. Robust degradation of D-serine by serine racemase was observed in transfected HEK293 cells and primary astrocyte cultures. In order to further investigate the role of elimination in regulating cellular D-serine, we generated several serine racemase mutants displaying selective impairment of elimination activity. As a result, levels of D-serine synthesized by the mutants are several fold higher than the wild-type both in vitro and in vivo. Extracellular D-serine is more stable toward elimination, likely due to physical separation from serine racemase and its elimination activity. Elimination provides a novel mechanism for the metabolism of D-serine in brain areas lacking D-amino acid oxidase, with implication for the regulation of NMDA receptor neurotransmission.

Cannabinoid receptors and "failure to thrive" in newborn mice

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We have previously suggested that a deficiency of cannabinoid CB1 receptors may underlie the enigmatic syndrome in infants 'Non-organic failure to thrive' (NOFTT). Thus we have reported that specific blockade of the CB1 receptors in one-day old mouse pups induced hypothermia, depressed ultrasonic vocalizations, prevented milk intake and resulted in death within days after birth. Similar deficiencies were found in (untreated) CB1-/- knockout pups. Aim: To further evaluate the validity and explore the mechanisms of neonatal CB1 receptor blockade as a model for NOFTT. Procedure: We compared the effects of neonatal blockade of CB1 receptors (with SR141716) in two strains of mice (ICR and Sabra). Experiment 1: Suckling-related motivation, general motor behavior and oro-motor performance were studied in pups, when exposed to an anesthetized dam. In addition, daily measurements were made of body weight, ultrasonic vocalizations and axillary temperature. Experiment 2: Control and SR141716-treated pups were warmed to 300C and developmental parameters were measured as before. Results: 1. ICR mice displayed more competent suckling than Sabra's 2. The rate of mortality induced by CB1 receptor blockade is strain-dependent 3. General motor and oro-motor behaviors are suppressed in SR141716-treated pups but motivation to suckle was not impaired 4. Increasing environmental temperature prevented hypothermia in the experimental pups, but did not prevent the suckling impairment and mortality induced by CB1 receptor blockade. Conclusions: CB1 receptors play a critical role in the ability of newborn mice to suckle milk, but genetic differences determine the rate of vulnerability of the pup to blockade of the CB1 receptor. Although CB1 receptor antagonism causes hypothermia, this does not explain the inability to nurse. CB1 receptors are involved in motor functions required for the suckling apparatus, but not in the motivation to suck.

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Central and peripheral cannabinoid receptors

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Conclusive evidence for the existence of a specific receptor for delta-9-tetrahydrocannabinol (THC), the major psychoactive constituent of marihuana, was obtained in 1988. Since then, this receptor has been cloned and detected in widespread areas in the brain, highly concentrated in the nigrostriatal system, hippocampus, cerebral cortex and cerebellum. A second receptor was cloned in 1993 in peripheral tissue, and found notably on immune cells, but also in embryonal cells, osteoblasts and osteoclasts. The centrally located receptor detected in the brain was denoted "CB1" and is mainly found presynaptically where it modulates transmitter release. The "peripheral" receptor is called "CB2"; both are G-protein-coupled. Since these discoveries, CB1 receptors have been detected in many localities outside the brain, including sympathetic ganglia, immune cells and the gastrointestinal system. Recent evidence indicates that CB2 receptors are also expressed in glial cells in the brain and have even been suggested as neuronal receptors. Phylogenetically, CB1 receptors are already present in primitive invertebrates such as leech and Hydra. Ontogenetically, CB1 and CB2 receptors are present from the embryonal preimplantation stages. In view of their widespread distribution, it is not surprising that cannabinoid receptors and their endogenous ligands the "endocannabinoids", fulfill many functions in physiological as well as in pathophysiological conditions. Their functions include feeding and appetite, pain perception, motor functions, blood pressure regulation, bone remodeling, memory and regulation of the stress response. Pharmacological data have suggested the existence of additional CB receptors which await definitive identification. Research of the "Endocannabinoid-CB-Receptor System" has greatly accelerated over the last decade. Observations ensuing from these efforts will contribute to our understanding of this newly discovered, highly important biological system.

Variability of the mesolimbic neuronal activity in a rat model of depression.

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The Flinders Sensitive Line of rats is a widely accepted and validated model of depression. These rats demonstrate abnormalities in limbic dopamine neurotransmission, suggesting disturbed neuronal activity in the ventral tegmental area. Interspike interval time-series were recorded from the ventral tegmental area of control Sprague-Dawley and Flinder sensitive line rats. These data were analyzed for the variance of interspike-interval for each group of animals. We found that FSL rats show a significant decrease of the variance of interspike intervals of the length 0.2-0.6 sec. We suggest that the interspike intervals of this range have an important role in the information encoding in the mesolimbic dopaminergic system. Impaired varience of the interspike interval length in this area can correspond to the pathophysiology of depression and can be a possible marker for the analysis of the efficiency of antidepressant treatment.

Investigating the roles of DOC2 in calcium-triggered exocytosis

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Ca+2-dependent exocytosis involves vesicle docking, priming, fusion and recycling. This process is preformed and regulated by a vast number of synaptic proteins and depends on proper protein-protein interactions and protein-lipid interactions. DOC2 are protein family that contains 3 isoforms that was found when screening DNA libraries with a C2 probe. DOC2 has 3 special domains: the Mid domain that interact with Munc13, a priming factor localized to the presynaptic membrane and two tandem C2 (designated C2A and C2B) separated by a short polar linker. C2 domains participate in Ca+2 dependent associations with phospholipids. These observations suggest that DOC2 might be involved in one of the final stages of the synaptic vesicle cycle such as priming. To investigate the role of DOC2, we overexpressed DOC2B in adrenal chromaffin cells using Semliki Forest Virus system. Using live fluorescence imaging we studied DOC2B dependence on Ca+2 and found that DOC2 translocate to the membrane at very low internal Ca+2 concentrations (~200nM) and presents a positive correlation between the internal Ca+2 concentrations and translocation. Mutation in the C2A domain that affected the Ca+2 binding site caused the protein to be constantly on the plasma membrane. Using flash photolysis of caged-Calcium, we studied the effect of DOC2B on the different kinetic components of exocytosis with capacitance measurements. Overexpression of DOC2B caused an increase in the fast burst size and a decrease in the sustained component. We also tested the physiology relevance of the mutated C2A domain and found that overexpression of the mutated DOC2B caused an increase in all 3 kinetic components of the exocytosis response in the first and the second flash. These results suggest that DOC2 is a positive regulator of exocytosis and influence exocytosis via time-dependent interaction with another priming protein.

Identification of regulatory mutations in the MECP2 gene associated with Rett Syndrome by means of quantitative RNA expression assays in peripheral blood.

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Rett syndrome (RTT) is an X-linked progressive neurodevelopmental disorder that primarily affects females. Disease-causing mutations have been identified in 80% of RTT cases predominantly in the methyl-CpG-binding protein 2 (MECP2) coding region at the CpG hot-spots. Additional 10% of the patients have been found to harbor minor or major deletions involving MECP2. In attempt to verify the role of MECP2 as a single underlying cause of RTT, we pursed the detection of additional mutations in regulatory elements of MECP2 in clinically definite RTT cases. To this end, we employed quantitative RNA expression assays in the peripheral blood lymphocytes including TaqMan probes for both known MECP2 transcripts and RNAseP and ODC1 reference genes. Within this framework, we identified several patients with lower blood MECP2 expression levels that had no previous indications of MECP2 mutation presence. By means of denatured-high-performance-liquid-chromatography (DHPLC) and direct sequencing of the non-coding MECP2 regions, we identified a novel splice site mutation in the first exon-intron junction of MECP2 that potentially leads to imbalance between the two MECP2 transcripts. We also detected several potentially meaningful elements in the intron adjacent to the alternatively spliced exon 2 of MECP2 and in the 3'UTR. These elements were highly conserved among species and were associated with RNA splicing or RNA transcription machinery in other genes. We also obtained a preliminary indication of overexpression of blood MECP2 in patients with missense mutations, which overlaps with recent findings in a controlled mouse animal model that traced overexpression of MECP2 to a neurodevelomental delay phenotype reminiscent of RTT.

Latent inhibition in schizophrenia: two poles of abnormality

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When a relatively simple stimulus such as a tone or visual shape is repeatedly presented as irrelevant, it becomes difficult for that stimulus to enter into new associations. This phenomenon, termed latent inhibition (LI), is extensively studied in animals and humans, reflects the organism's capacity to ignore irrelevant stimuli. In the clinical setting LI the results of LI studies indicate that it is disrupted during the initial stage of schizophrenia, or during an acute phase of a relapse. Thus, LI disruption is considered to model the main cognitive attribution of schizophrenia patients, namely, inability to ignore irrelevant stimuli. Based on data from animal studies Weiner (2003) proposed the 'two-headed' model of LI, pointing that the LI phenomenon could represent two extremes which characterize schizophrenia patients, the disruption of LI in the initial stages, and a persistence of LI in chronic patients. We have recently developed a new within-subject LI procedure which is based on visual recognition of letter characters. A special feature of this procedure is that it enable the testing of the two abnormal poles of the LI phenomenon in a single testing session. Application of the procedure in schizophrenia patients have confirmed the hypothesis. First, healthy volunteers have shown faster learning of the predictive value of novel compared to preexposed cues, indicating LI. In addition, in healthy subjects the LI effect was attenuated with repeated presentation of the cues. Second, first-episode patients learned the predictive values of novel and preexposed cues in a similar rate, i.e. LI disruption. Third, chronic patients have shown faster learning the predictive value of novel compared to preexposed cues, and this effect was not attenuated with repeated presentation of the cues, namely, LI perseveration. These findings are the first demonstration of the applicability of the 'two-headed' model of LI to the clinic.

Novel Bifunctional Drugs with Iron-Chelating and Monoamine-Oxidase Inhibitory Activities for the Treatment of Neurodegenerative Diseases

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One of the defining characteristics of neurodegenerative diseases, including Parkinson's disease (PD), Alzheimer's disease and amyotrophic lateral sclerosis is the abnormal accumulation of iron in the affected brain areas, which together with monoamine oxidase (MAO) contribute to the onset of oxidative stress via generation of reactive hydroxyl radical. We have developed several bifunctional iron chelators from the brain permeable iron chelator VK-28, possessing the neuroprotective propargyl-MAO inhibitory moiety of rasagiline. The bifunctional drug, M30, has been shown to be a potent iron chelator, with an IC50 value (9.21μM) comparable to that of the prototype iron chelator, desferal. It is also a potent inhibitor of brain mitochondrial MAO-A and B in-vitro (IC50A= 0.04μM, IC50B= 0.05μM). In-vivo, M30 markedly inhibits brain (striatum, hippocampus and cerebellum) MAO-A and B activities, with a greater selectivity (20-30%) for the latter at the doses (1, 2.5, 5mg/kg) examined. It has very little effect on the liver and small intestine enzymes. These results indicate that M30 has the ability to penetrate the blood brain barrier, and suggest that similar to ladostigil it would not induce the "cheese reaction" in response to tyramine. Importantly, M30 attenuates striatal dopamine depletion induced by the parkinsonian neurotoxin N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in mice and increases brain levels of dopamine, serotonin and noradrenaline. M30's ability to inhibit MAO and chelate iron, may have a great potential as a neuroprotective drug as compared to its individual components, since, recent studies have indicated that a combinations of two drugs were more effective in preventing neurodegeneration.

"That obscure object of feeling": Neural correlates of intentionality in emotional experience

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An important cognitive feature of adaptive emotion is its relatedness to an object, whether a physical object, a person or an event (i.e. intentionality). Does processing this cognitive aspect of emotion involve the limbic networks? Isolating intentionality in emotion is not possible with standard paradigms in which the emotion is directed to the stimulus that is eliciting it. To address this issue we used a cross modal approach to evoke similar emotions with and without intentionality content. In an fMRI experiment, 15 healthy subjects (F=8) were scanned in a 3T GE system while passively listening to emotional musical clips. Each clip was presented twice for 21 sec: once combined with a neutral film in the first 9sec (Film+), and once without the film (Film-). We assumed that music elicits an emotion not relating to an object; however, the film provides this abstract emotion with meaningful reference (i.e. intentionality). The musical clips were of negative, positive or neutral emotional valence and the films neutral, as validated in a preliminary behavioral study (n=15, p<10E-6). The addition of neutral film to the music did not change the rated properties of the emotion elicited. The last 6 sec of Film+ and Film- (featuring identical stimuli) were contrasted in order to find film traces in the musical emotion. Prefrontal regions were activated in both emotional and neutral conditions. No emotion-specific activations for traces were found in the amygdala. Film traces in negative music evoked the sub-callosal cingulate and right superior temporal sulcus (STS) while in positive music they evoked the left STS. This study was able to demonstrate differential cortical activation to cognitive traces in emotional experience.

Clotiapin in Schizophrenia: A Controlled Study

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Clotiapin is a neuroleptic with chemical structure similar to clozapine. Probably the patients unresponsive to other neuroleptics respond to clotiapin. However after the discovery of D-2 blockade as a mechanism of neuroleptic efficacy, this claim seemed to lack logical theoretical basis. The success of clozapine in patients unresponsive to other dopamine blockers raised hopes for the discovery of new antipsychotic drugs with new mechanisms of action. Thus the authors became interested in the fact that 40 patients in our 454 bed hospital were being treated with clotiapin and the treating physicians felt that this drug has unique antipsychotic properties in neuroleptic non-responsive patients. The Lokshin et al study (1998) suggested that clotiapin may indeed have unique properties. Clotiapin affects multiple receptors like clozapine and olanzapine. It blocks 5HT3- receptors and down-regulates cortical 5HT2-receptors like clozapine. The ratio of D2 to 5HT2 blockade by clotiapin is similar to that of clozapine. Clotiapin and clozapine share high affinity for the 5HT-6 receptor. Clotiapin shows little blockade of D-2 receptors and in the rat retinal model seems to possess D-4 blockade like clozapine, although D-4 blockade by clotiapin has not to our knowledge been evaluated directly. We are conducting a study of severe chronic active psychotic hospitalized patients with a history of non-response to at least 3 neuroleptics. The design is double-blind crossover of clotiapin vs. chlorpromazine (CPZ) as monotherapy. No washout is necessary from previous neuroleptic treatment, and flexible overlap over 2 weeks with the study medication is individualized for each patient. Patients are treated for 12 weeks with clotiapin and 12 weeks with CPZ, in random order. Medication is supplied in identical capsules of 100 mg CPZ or 40 mg of clotiapin. PANSS and Nurse's Observation Scale are rated every 2 weeks. 38 patients have completed the trial. Initial results are presented.

Depression: Novel genetic model

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Depression is among the most prevalent forms of mental illness, but the neurobiological basis of depressive behavior is poorly understood. Many of the rodent models for depression are based on the assumption that depression is a response to acute or chronic stress. Other models are based on assumption of a certain biochemical dysfunction that underlies depression, while there is no consensus on the biochemical basis of depression. The diagnostic criteria for depression include several symptoms and it has also become clear that the risk for depression is partially genetic. We were therefore encouraged to investigate genetic factors of depressive behavior by establishing a novel animal model for depression based on selective breeding for a depressive phenotype. The selective breeding is based on tests that cover the core symptoms: loss of interest or lack of motivation (using a modified swimming test), anhedonia (using the sucrose preference test) and reduced energy/fatigue by chronically screening locomotor activity (Inframot system). Additionally, we have developed a novel scoring method of the swimming test, that allow continues monitoring of different levels of the animal's activity using a joystick. This novel method shows a Gaussian distribution of scores (which is not observed in the standard scoring method) that is necessary for reliable selection of extreme cases for the purpose of our selective breeding. We found already at the second generation of descendants a significant differences between "depressed" and "motivated" rats in the swimming test, in the basal locomotor activity at young ages and in offspring quantity. At this point we find no correlation between the different tests. We expect this model to allow the study of the genetic contribution to depressive and motivated behavior and the neurochemical characterization of these behaviors.

Two discrete inactivation states with distinct pore properties coexist in a LQT mutant of KCNQ1 K+ channels

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The KCNQ potassium channels whose mutations cause cardiovascular and neurological disorders are members of the superfamily of voltage-gated K+ channels. The KCNQ1 pore-forming subunit can interact with various KCNE auxiliary subunits to form K+ channels with very different gating behaviors. Inactivation gating is a property of KCNQ1 that is susceptible to modulation. KCNQ1 inactivation is invisible macroscopically but can be revealed by a hook of the tail currents which reflects recovery from inactivation. However, KCNQ1 mutants can depart into a macroscopic inactivation mode. Here we show that in a long QT mutant of KCNQ1, L273F, two distinct inactivation states coexist, one similar to WT channels and a macroscopic inactivation whose time course and recovery are much slower compared to wild type channels. The inactivation produced by WT KCNQ1 is intrinsically voltage-independent, while that elicited by L273F is highly voltage-dependent. Interestingly, the two discrete inactivation phenotypes exhibit distinct pore properties. External protons strongly depressed WT KCNQ1 inactivation but weakly affected the macroscopic inactivation of L273F mutant. Similarly, external barium ions discriminate between the two discrete inactivation states by suppressing the wild-type and barely affecting the macroscopic one. Allowing L273F channels to populate the voltage-dependent inactivation transition, produced a considerable delay in the exit of barium ions from the pore (more than 6-fold). This result suggests that during the voltage-dependent inactivation transition, the topology of the external vestibule is such that it traps barium ions inside the deep pore. A kinetic model of the LQT channel mutant accounts for the coexistence of two distinct inactivation states.

Conducting STDP in dendrites.

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Spike timing dependent plasticity (STDP) is a synaptic learning rule operating in many neuron types. When the pre-synaptic neuron fires after the post-synaptic neuron the synapse is depressed whereas the synapse is potentiated when the pre-synaptic neuron fires before the post-synaptic neuron. The time window for this plasticity rule spans over tens of milliseconds and its dynamics varies according to neuron type. We applied STDP learning rule in a dendritic neuron model, using NEURON simulation environment. Random asynchronous synaptic inputs impinged onto the model neuron with initially uniform peak conductance for all synapses. After running the STDP rule, a bimodal synaptic conductance distribution was attained at the steady state. Some of the synapses obtained the maximal conductance change whereas the conductance of the other synapses was close to zero. The proximal synapses were the strong ones and the distal synapses were near "extinction". Indeed, STDP imposes competition among synapses over the control of the postsynaptic spike. Thus, a positive feedback loop ensues and proximal synapses, which tend to evoke larger somatic EPSPs have a better chance at generating spikes and become progressively stronger. The opposite is true for distal synapses, which generate smaller somatic EPSPs. We propose several solutions for "saving" distal dendritic synapses from extinction. First, we show that a multiplicative (rather than linear) learning rule can equalize the local conductance for all dendritic synapses. Second, we apply anti-STDP rule (Rumsey and Abbott, 2004) for gmax, the maximal conductance possible for each synapse. Consequently, the distribution of synaptic strengths at the soma is identical for all synapses, independent on their dendritic location. We also explore the effect of active dendrites on "saving" distal synapses from extinction. Finally, we consider STDP rule in different dendrites morphologies.

Visuospatial attention: How to measure effects of infrequent, unattended events in a blocked stimulus design

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This fMRI study investigates the differences between a blocked and event-related analysis in a cued target detection task, the so-called Posner paradigm, using a hybrid design. Validly and invalidly cued trials were presented intermingled in different blocks containing 50, 75, or 100 percent valid trials. Four analyses were conducted: i) An event-related analysis comparing invalid and valid trials, ii) a blocked analysis comparing blocks with 50 percent valid and invalid trials to blocks with 100 percent valid trials, iii) a blocked analysis detecting differences between block models when modelled as epochs or chains of events and iv) a blocked analysis that modelled blocks as chains of events to scale regressors equally to the event-related analysis. Irrespective of the type of analysis (blocked or event-related), significant activation of the right intraparietal sulcus was observed. A larger cluster size was evident in the blocked analysis which can be attributed to higher efficiency. In addition to this common right parietal activation, the event-related analysis revealed activations in right superior parietal cortex and left intraparietal sulcus. In contrast, the blocked analysis yielded additional activity in the right occipito-parietal junction. No influences of the block model (epoch versus chain of events) were found in regions activated in the blocked or event-related analysis, respectively. In summary, using a hybrid design and both event-related and blocked analysis techniques we show both sustained and transient neural processes underlying reorienting of visuospatial attention.

Agmatin – a naturally occuring, highly efficacious neuroprotective compound

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Agmatine [(NH2(CH2)4NH2C(NH=)NH] is a naturally occurring guanidino compound found in abundance in plants and bacteria, and recently identified in mammalian tissues. Agmatine is formed by decarboxylation of arginine, and is metabolized principally into urea and putrescine, the diamine precursor of polyamine synthesis. The compound is present in the brain and spinal cord where its synthesis, which is normally very low, is greatly increased during development and after injury. Agmatine was postulated to exert neuroprotective effects by modulating several relevant molecular targets, including: modulation of several neurotransmitter receptors and receptor ionophores (e.g., nicotine, NMDA, imidazoline, and á2-adrenoceptors), blockage of key ionic channels (e.g., ATP-sensitive K+ channels and voltage-gated Ca++ channels), inhibition of nitric oxide (NO) synthase, inhibition of ADP-ribosylation of proteins, and inhibition of advanced glycosylation end (AGE)-product formation. Treatment with agmatine results in increased insulin release, but in reduced catecholamine release. While agmatine is a cytotactic compound, preventing proliferation of certain cell types (e.g., endothelial cells and astrocytes), it is not cytotoxic. In several animal models of acute neurotrauma and ischemia, agmatine proved efficacious in preventing nerve cell death and in reducing neuropathic pain. Additionally, we now report that agmatine treatment can enhance the regeneration of cut facial nerve, a purely motor cranial nerve in rats. The cumulative evidence, therefore, indicates that agmatine acts at multiple molecular targets to enhance nerve cell survival, thus fulfilling the concept of "one drug – multiple sites of action", a concept postulated as advantageous for neuroprotective drug development strategy.

Effect of selected antidepressants on inflammatory processes associated with model of experimental autoimmune encephalomyelitis (EAE) in mice

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Multiple sclerosis (MS) is a chronic autoimmune neurological disorder targeting the white matter of the CNS. MS symptoms result from inflammatory damage to the myelin sheath, activation of TH1 cells and secretion of pro-inflammatory cytokines. Our aim was to determine the immunomodulatory effect of some antidepressants on developed motor deficits in experimental autoimmune encephalitis (EAE) model in mice and on the secretion of TH1 cytokines from activated splenocytes in-vitro. EAE was induced in C57/bl mice by immunization with rat myelin oligodendrocyte glycoprotein (MOG). Animals were divided into 4 groups (10/each) receiving saline/MOG alone or MOG and the antidepressants paroxetine, fluoxetine and clomipramine (15mg/kg x3/week i.p). Animals were followed for 24 days and manifestations of EAE were scored (scale of 1-6). MOG animals developed paralysis reaching the mean score of 1.65, all 3 antidepressants significantly protected against the induced neurological symptoms (score 0.35, 0.6 and 0.72 respectively for paroxetine, clomipramine and fluoxetine). In a 2nd experiment 4 groups of animals were treated with saline/MOG alone and MOG and paroxetine or sertraline at lower dose (5mg/kg x3/week i.p.) or dexamethasone (1mg/kg x3/week). Results showed that after 22 days of therapy dexamethasone completely inhibited the manifestations of neurological signs (0 compared to 0.9 of MOG alone). Sertraline induced a delay in paralysis manifestation appearances as well as inhibition of the total score (0.45 vs 0.9), while paroxetine did not protect the animals (total score of 0.81). In-vitro all antidepressants caused a marked inhibition of Con-A or MOG-induced splenocyte proliferation. Moreover, the antidepressants significantly suppressed the secretion of the proinflammatory cytokines IL2, INFg and TNFa resembling the effect of dexamethasone. Conclusions: We suggest that some antidepressants could be of value for the treatment of MS mainly during initial stages.

Sharp (sub-exemplar) tuning for faces revealed in human face related areas

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Although human face recognition is extremely selective, it is still un-clear how this selectivity is implemented at the neuronal level in human face-related cortical areas. In order to answer this question, we used the paradigm of functional magnetic resonance adaptation (fMR-A). Our stimuli consisted of colored face photographs (neutral expression, male, Caucasian) which were parametrically morphed to produce various degrees of facial similarity. The face stimuli were divided into four groups: (a) identical images (no variability); (b) different face images (maximum variability); (c) 1/3morph faces, i.e., images morphed at 1/3 of the morphing distance from the full identical-to-different distance (low variability), and (d) 2/3morph· - same procedure but morphed at 2/3 of the morphing distance (intermediate-to-high variability). Twelve subjects participated in a short block-design fMR-adaptation experiment and were scanned in a GE 1.5 T magnet. In order to balance task difficulty between the identical and 1/3morph conditions, a 1-back memory task was used. Examination of the activation levels of the face selective fusiform gyrus (FFA) revealed that even small facial variability (created by a slight morphing level of individual faces, 1/3morph condition) was sufficient to induce full recovery from adaptation (1/3morph activation vs. identical-face activation ($p<3*10-4$), but 1/3morph activation vs. different-face activation ($p>0.07$)). Our results demonstrate that face-selective regions are tightly tuned even to subtle shape changes at the sub-exemplar level. Such sharp tuning can provide the necessary neuronal sensitivity to allow highly selective face recognition.
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History Dependent Multiple Time Scales Dynamics in a Single Neuron Model

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History dependent time scales are a ubiquitous feature of neuronal systems, at all levels of organization. It is not clear, however, how multiple time-scale dynamics rise from one level to the next higher one. This study approaches this question by looking at the interaction between the rich channel dynamics and the dynamics of neuronal activity; we construct a single neuron model in the spirit of single channels models. The model neuron describes its activity in response to an external stimulus. The activity is a coarse grained time-averaged representative of firing and temporal details at the resolution of action potentials are intentionally neglected. Novelly, our model input/output function is nonlinear, parametrically depending on the neural excitability. Changes of this function on long time scales has been observed experimentally, but has been neglected in other neuron models. The model neuron is composed of an ensemble of ion channels that can wander in a large pool of inactive states, and their distribution registers the history of activity. The concept of neuronal excitability is used to bridge the gap between dynamics of the channels and that of the neuron: channel kinetics modulates neuronal excitability, thus affecting the neural activity; activity, in turn, enhances channel inactivation. Thus, the neural activity is both affected by excitability and determines the changes in it. In this way the multiple time scale dynamics on the channel level rise up to the next higher level, which is the neuronal dynamics. In spite of its simplicity, the model presents a rich repertoire behavior, with multiple time-scales dynamic. Moreover, the characteristic time scales of our model are history and context dependent. These results are in qualitative agreement with experimental results. It is important to note the robustness of these results, since no specific structure of the ion channel state space is required.

Prenatal "ultramild stress" protects against stress and schizophrenia and reduces cannabinoid activity in the offspring

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Prenatal stress (PS) has long-term consequences for emotional development of the offspring. The nature of PS-induced alterations vary with stress schedule and timing. Although the newly discovered cannabinoid receptors and their ligands ("endocannabinoids") have been implicated in the stress response and in schizophrenia, their possible role as substrates for PS is unknown. Here, we studied effects of daily prenatal "ultramild stress" on the stress response, sensorimotor gating as indication for schizophrenia, and on cannabinoid CB1 receptor functionality. Methods: Pregnant Sabra mice were exposed daily to 2 mild stressors (incl. tilted cage, confinement, social stress). At adulthood, offspring were divided into 3 groups: a. undisturbed, b. swim stress (2 daily 9 min exposures to a water tank) or c. one 0.1 mg/kg injection of the CB1 receptor agonist HU210. Offspring were studied for the stress response (acoustic startle response, ASR), anxiety ("plus maze") and "schizophrenia" (pre-pulse inhibition, PPI). Results: In male offspring, PS reduced anxiety and ASR, suggesting decreased sensitivity to stress. Adult swim stress increased ASR in controls and PS mice, indicating enhanced anxiety. Adult stress, but not PS, decreased PPI, suggesting a greater severity of adult stress. Adult stress did not affect PPI in PS mice, suggesting that PS protected against the deleterious effects of the adult stress. HU210 reduced ASR and PPI in controls, but not in PS males, suggesting that PS induced subsensitivity of CB1 receptors. In females, PS reduced anxiety and ASR especially after adult stress. Conclusions: 1. Prenatal daily, ultramild stress protects against stress and enhances robustness to schizophrenia in later life. 2. Stress during adulthood impairs the stress response and 3. PS seems to decrease CB1 receptor sensitivity. Assessments of endocannabinoids and CB1 receptors after PS, are currently performed.
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Radial Correlation Contrast – A functional connectivity MRI contrast to map changes in local neuronal communication

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A functional connectivity MRI method that groups neighboring voxels in relation to their degree of temporal cross-correlation between their time courses is presented. This grouping generates a vector field, which is assumed to provide insights into the local organization of neuronal activity. Application with high spatial resolution fMRI rat data subjected to electric forepaw sensory stimulation (156m•156m•1000000 m) shows a significant localized increase of the vector field amplitude in cortical layers 4 and 2/3 of the primary sensory cortex and in layer 2/3 of the primary motor cortex, suggesting a strong correlation with local neuronal communication. Vector field phases exhibit a transition with neuronal activation from random-like orientations during rest to clusters of common orientations. Cluster size is shown to be weakly dependent on the radii of the neighboring voxels with which the vector field is calculated, and shuffling voxel position within clusters generates a random-like vector orientation instead. This suggests that changes in vector orientations upon activation represent changes in the internal correlation between voxels that is interpreted as a change in the internal neuronal communication.

Perinatal enhancement of the gabaergic system impairs learning and memory - suggested mechanism.

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Antiepileptic drugs (AEDs) acting through the potentiation of GABA-ergic pathways have harmful effects on brain development. Increased risk of impaired intellectual development was reported in children born to women treated for epilepsy during pregnancy. We established an animal model for the study of the damage induced by the new AED – vigabatrin (GVG) during postnatal days 4-14, which parallel the 3rd trimester of human embryo brain development. Delayed development of sensory and motor reflexes, reduced mobility in the open field, impaired object recognition and deficient spatial learning and memory were observed. A morphological study indicates only transient changes in the hippocampus (P7) and significantly lower cell density in most layers of the M2 cerebral cortex of GVG adult mice compared to the controls ($P<0.01$). The possibility that perinatal GVG treatment impaired learning and memory in the adult mice by modifications in hippocampal synaptogenesis was examined in 16 weeks old mice by immunohistochemistry of synaptic vesicle proteins and field excitatory postsynaptic potentials (fEPSP) recording from hippocampal slices in CA1 region. We found that perinatal GVG induced long-term enhancement of Synaptotagmin I (164.8% of control mice, $P<0.01$) and VAMP II (196.2%, $P<0.01$) in the CA1 region. Over-expression of these proteins in the GVG group was associated with a significant reduction in the fEPSP efficacy, as measured by fEPSP response to stimulation at various intensities ($P<0.05$). In addition, perinatal GVG treatment induced modification in the fEPSP response to a series of 5 repeated stimuli at 50Hz, and blocked the induction of long term potentiation in response to 3 trains of 1 second at 50Hz (5 minutes inter train interval), a stimulus that induced potentiation in the control mice. Our findings suggest that the long-term deleterious effects of GVG treatment on mice behavior may be caused by altered synaptogenesis.

Mapping Human introspection using fMRI

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Conventionally it is assumed that attentive visual perception of identical stimuli engages the same perceptual mechanisms. However, attentive perception can engage at least two mental states: a. An internal, introspective state-in which the subject attends both to external stimuli and to himself as an observing agent. b. An external, extroceptive state in which the subject is exclusively engaged by the external stimuli. Here we report on brain imaging results which explored to what extent these two mental states engage different cortical regions, despite being driven by identical sensory stimuli. Five subjects performed two different tasks during a block-design fMRI scan. In a categorization task, subjects were required to categorize pictures (animal vs other). In the introspection task, subject were asked to look at the same pictures as in the first task but to attend at the same time to himself and evaluate his emotional reaction to the pictures (negative/positive vs neutral). Prior to each block, a visual cue indicated which task to perform and subject's responses were recorded. In order to discriminate task difficulty as potential confound between the 2 cognitive tasks, external categorization epochs were subdivided into "difficult" and "easy" perceptual tasks by manipulating presentation speed; "easy" epochs were identical to the introspection task, stimulus-wise. Our results show preferential activations across prefrontal cortex during "introspection" compared to the "easy categorization" task. Consistent preferential activations were found bilaterally in dorsolateral and medial aspects of prefrontal cortex, with a left hemisphere bias dorsally. The results and their relevance to broader issues such as the search for neural correlates of subjective awareness will be discussed.

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The bi-partite organization of the human caudal brain

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Recently (Hasson et al., 2004) we found that a large expanse of human cortex shows a high level of inter-subject correlation when subjects are exposed to a long segment of an audio-visual movie. While this finding reveals a wide spread level of stimulus-driven activity in the human cortex, it was also noticed that certain cortical regions consistently fail to show such inter-subject correlation. This result hints that either these regions are related to individually unique cognitive processes or their activity is dissociated from the external stimulation. To examine this issue further we mapped the cortical areas showing high correlation between repeated presentations of the same movie in each individual. Our results show that these areas still failed to show any movie-driven correlations - indicating that their activity is intrinsic and unrelated to the external sensory stimuli. Functional connectivity analysis of these "intrinsically" driven areas revealed a striking result - all the cortical regions in the caudal brain which were un-correlated to the external stimuli showed an intrinsic correlation with each other- forming a closely interlinked network. Furthermore, the two networks - i.e. the externally driven system of sensory areas and the intrinsically driven network complemented each other providing essentially complete coverage of the entire extent of the human caudal brain. A large number of experimental results in our lab and in the published literature indicated that the "intrinsic" system largely overlaps with a set of regions previously shown to be de-activated by any sensory stimulus. Thus, we would like to propose a fundamental neuroanatomical partition of the human caudal brain into two global networks of areas: those dealing with processing external sensory input, and those dealing with some, as yet not fully understood, internal cognitive function.

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GABA-B mediates frequency-dependent latency in POm thalamus analytical results and comparison with experiment

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The latency in the steady-state spiking response of POm thalamic neurons to periodic vibrissa stimulation increases with increasing stimulus frequency (Ahissar et al., Nature, 2000). In contrast, the latency of the response of neurons in VPM thalamus is essentially constant. Yet the two nuclei are inhibited by an overlapping region of reticular thalamic nucleus (RE). To provide a possible explanation for this effect, we construct a firing rate model and consider only a slow time scale, corresponding to dynamics of GABA-B synapses. We calculate the steady-state response of the system and compute its stability analytically for the case of the duty cycle of the stimulus < 0.5. Considering only a POm-RE network, we find that POm activity decreases with GABA-B conductance. If this conductance is too large, the period-1 state undergoes a period-doubling bifurcation at large enough frequencies, which is not seen experimentally. If the stimulus increases gradually, e.g., triangular stimulation, the latency increases with GABA-B conductance. The inclusion of VPM excitatory connections to the RE resolves the period doubling bifurcation and may reduce the POm response even to zero. VPM-to-RE feedforward connections are more effective in reducing POm activity and increasing POm latency than POm-RE feedback connections. If the VPM receives GABA-B inhibition, the latencies in the two nuclei are determined by the ratio of their GABA-B inhibition and the input strength. According to this explanation, the maximum latency in POm neurons is larger because they receive weaker input from the brainstem.

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Zinc Modulation of the L-type Calcium Channels.

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Zinc modulation of the L-type Calcium channels (LTCC) was studied in Xenopus oocytes expressing alpha 1, alpha2 delta and beta2 – subunits of the rabbit cardiac calcium channel. Whole cell voltage clamp experiments were carried out using Ba2+ as the charge carrier. Our results show that zinc causes a reversible inhibition of LTCC in a concentration dependent manner. Nonlinear fitting to a Michaelis Menten equation yielded an appKi of 102 micromolars and a Hill coefficient~1. The decrease in steady-state current amplitude is accompanied by a shift of the I-V relationship to more negative voltages. Similar inhibitory effect of zinc was found in the presence of the LTCC activator BayK 8644. In contrast to the inhibitory effect of extracellular zinc, no such inhibition is observed when zinc is applied intracellularly. The injection of of zinc (~80 micro molars) changed the extent and rate of current block caused by extra-cellular zinc. Hence, we concluded that intracellular zinc, although did not block LTCC, was capable of modulating other cellular functions. Zinc inhibition of LTCC developed with time, reaching maximum inhibition after 3 minutes. The inhibition was not activity dependent as similar inhibitory effect was observed when oocytes were either exposed to zinc and activated every 10 second or exposed to zinc with no stimulation and tested after 3 min Our results suggest that zinc may play an important modulatory role of LTCC in physiological concentrations. Zinc inhibits the channel's currents by acting from the extra-cellular side and its effect is not activity dependent.

Chronic Mild Stress Induces Depression and Bone Loss in Mice: Attenuation by Anti-depressant Therapy.

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In humans, osteoporosis is often accompanied by major depression. However, it is not clear whether bone loss (and the associated morbidity and incapacitation) induces depression or vice versa. To determine the cause-effect relationship in this association, we examined the bone status in mice subjected for 5 weeks to chronic mild stress (CMS), a model for depression in rodents. CMS-induced depression was confirmed by reduced sucrose consumption, an established indicator of anhedonia, and reduced social exploration. Micro-computed tomographic measurements of femora showed a marked bone loss in CMS mice, reflected by a significant decrease in overall bone mass, in particular trabecular bone volume density (30% loss). A further histomorphometric analysis showed that the mechanisms underlying this bone loss comprise a decrease in the number of osteoblasts (bone forming cells) and increased number of osteoclasts (bone resorbing cells) leading to diminished bone formation and enhanced bone resorption, respectively. The anti-depressant drug imipramine, administered in the drinking water throughout the experimental period, attenuated both the depressive symptoms and the bone loss. Further analysis of the behavioral responsiveness to imipramine revealed that mice that responded better to imipramine (as measured by increased sucrose preference) displayed no loss of trabecular bone volume following CMS. However, imipramine-treated mice that did show some residual depressive symptomotology displayed significant bone loss. These results demonstrate that CMS induces bone loss in mice, and are consistent with a causal link between depression and bone loss in human osteoporosis.

NAP (AL108): A Peptide Derived From Activity-Dependent Neuroprotective Protein (ADNP) is Poised Toward Clinical Development

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Activity-dependent neuroprotective protein (ADNP) is essential for brain formation (Dev Brain Res. 2003 144, 83). Peptide activity scanning identified NAP (NAPVSIPQ, also known as AL108) as a small active fragment of ADNP that provides neuroprotection at very low concentrations. In cell culture, protection has been demonstrated against toxicity associated with the beta amyloid peptide, excitotoxicity, electrical blockade, the envelope protein of the AIDS virus, dopamine, H2O2, nutrient starvation and zinc intoxication (JBC 2004, 279, 28531; JPET 2004 309, 1190). In animal models of apolipoprotein E deficiency, cholinergic toxicity, closed head injury, stroke, middle aged anxiety and cognitive dysfunction, NAP provided neuroprotection (Neurosci Lett. 2004, 361,128; JMN 2004, 24, 181). The structure of NAP allows cell penetration, inhibition of toxic protein beta sheet formation and stimulation of proper protein assembly. NAP binds to tubulin and facilitates microtubule polymerization leading to enhanced cellular survival that is associated with fundamental brain cell elements, the cytoskeleton. A mass spectrometry assay determined that NAP reaches the brain upon nasal administration showing a half-life of ~ 90-120 minutes in rat and dog plasma. In a battery of toxicological tests, 1 month repeated dose toxicity in rat and dog, cardiopulmonary tests in dog, and functional behavioral assays in rats, no adverse side effects were observed with NAP concentrations that were about 500-fold higher than the biological active dose. No genotoxicity was associated with NAP. At doses that are at least a 1000-fold over the biologically active dose, reversible lethargy and piloerection was observed in mice. A mass spectrometry assay has been validated for tests in human plasma (MPI Research). A first exposure of AL108 (NAP) to human subjects is now planned. *NAP is patented & licensed to Allon Therapeutics, Inc. where IG serves as CSO. Other *Supported by Gildor Chair, NICHD, NIA.*

Crossmodal Visual-Auditory Interference in Object Recognition Process

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Several studies have concentrated on resolution of spatial conflict between vision and audition, and recently the temporal domain has been also addressed. Much less is known about auditory-visual interaction in object recognition. The present research addressed this issue. The subjects were presented with bi-modal stimuli, composed of concurrently appearing pictures and voices of animals. The task was to identify either the picture or the voice by answering a forced-choice question presented after the auditory-visual presentation. In one third of the trials the picture and the voice belonged to the same animal ('congruent' trials), in another third the picture and the voice belonged to different animals ('incongruent' trials). In the remaining trials, a neutral stimulus was presented as the non-target stimulus. Performance on congruent trials was better than on incongruent trials, both in the visual and in the auditory conditions, but the effect was larger in the auditory condition. This finding indicates that task-irrelevant objects of an unattended modality are processed and even recognized and suggests an asymmetry between the two modalities in the process of object-recognition. Event related potentials were recorded in 14 subjects with similar design. Results showed that incongruent trials elicited a more negative response than congruent trials in latencies of circa 200-650 ms post stimulus onset when the target was the auditory stimuli, reminiscent of an N400 effect. In contrast, no significant incongruity effect was found when the target was the visual stimulus. Thus, visual information affects the process of auditory object recognition relatively early but the opposite interaction is much more tenuous. This is congruent with the behavioral results, and suggests that like the case of spatial conflict, but unlike the case of temporal conflict, our cognitive system relies more on visual than on auditory information, in the case of conflict in object recognition.

Atenuation of cocaine- seeking behavior by GDNF-conjugated nanoparticles in a rat

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Neurotrophic factors such as glial cell line-derived neurotrophic factor (GDNF) may have therapeutic potential for preventing and treating cocaine addiction. Previously, we found that transplantation of a GDNF-expressing astrocyte cell line into the striatum and nucleus accumbens attenuates cocaine-seeking behavior in Sprague-Dawley rats. However, as a potential treatment for humans, cell transplantation presents several technical and ethical complications. Nanoparticulate systems are a safe and effective method for introducing exogenous compounds into the brain. Binding of therapeutic drugs to nanoparticles provides the drug with long-term protection from enzymatic degradation and thereby enhances its effectiveness . Therefore, we examined the effect of GDNF-conjugated nanoparticles micro-injected into the striatum and nucleus accumbens on cocaine self-administration in rats. GDNF-conjugated nanoparticles blocked the acquisition of cocaine in self-administration compared to control treatments. This is one of the first demonstrations that drug-conjugated nanoparticles may be effective in treating brain disorders

Quantitative MRI analysis of the human fetal brain in utero

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Magnetic resonance imaging (MRI) allows for high resolution imaging of the central nervous system. We have tested the feasibility of using MRI in conjunction with quantitative image analysis to perform volumetric measurements of the brain in the developing human fetus in utero. The data base comprises 40 fetuses (gestational age 22-40 weeks) referred because of suspected infarct, hydrocephalus, asymmetry of the ventricular system, or other abnormalities. Scans were obtained using a 1.5T magnet and a single shot fast spin echo (SSFSE) T2 sequence, slice thickness of 3mm, no gap and analyzed with NIH Image software. All scans were evaluated by an expert neuroradiologist.. The intra-rater error was 5%-9% for 2 raters, while the inter-rater error was 13%. Thus, a single rater then performed all the measurements. The right and left hemisphere and lateral ventricles were identified and their area measured on all relevant slices. The volume of hemispheric parenchyma was calculated by subtracting the ventricular volume from the total hemispheric volume. Results from the first fully analyzed brains (N=5, 1 normal, 4 suspected pathologies, 25-33 weeks gestation) indicate that ventricular enlargement and asymmetry in this sample result in a proportional increase and asymmetry in the total hemispheric volume, with no effect on parenchymal volume asymmetry. However, the contribution of the ventricular volume to the total hemisphere volume gave a faithful representation of the severity of the ventricular enlargement, regardless of gestational age and absolute hemispheric or ventricular volume: the lateral ventricles represented `2% of the total hemisphere volume in the normal fetus and 4.7-38.9% in the pathological brains. These preliminary results support the use of image analysis and MRI to produce quantitative severity assessments of brain pathologies in the developing human fetus.

The attribution of gender stereotype strategy as an indicator of frontal lobe mediated Theory-of-Mind

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Introduction: Most patients with ventromedial-frontal lobe damage exhibit 'Theory-Of-Mind' (ToM) dysfunction, the inability to understand others. The current work offers a novel paradigm, enables testing ongoing non-verbal interactive ToM behavior. The study setting (iterative prisoner's dilemma - IPD game) was designed to tap participants' cooperative or competitive behavior and confidence within a dyad of same-different gender. In that context, literature review reveals that women are more cooperative and participants tend to relate women a cooperative behavior. Method: Participant plays against a simulated opponent holding a simple reactive strategy ('Tit for Tat' - the strategy chooses the same choice as the participant chose the previous trial). In this IPD game, efficient opponents' strategy deciphering, results in choosing cooperation, which has highest utility. We run 4 groups (24.3 yrs ± 2.8): man-man, woman-woman, man-woman, and woman-man. Results: As hypothesized we found overall participants, a normal learning curve (increasing cooperation probability), increased confidence in choice, and low cooperation probability on early trials - only in groups that thought they played against men and not in women and men that thought they played against woman. Conclusion: As manifested by attributing different strategies to others, and by showing a normal understanding of others' strategy, ToM is probably the core cognitive element of this paradigm. Further support is given by initial data collected from ventromedial-frontal patients.

An approach to the molecular basis of tinnitus in the rat

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Tinnitus is persistent and debilitating ringing in the ear. It is very common in the adult population. Little is known, however, about the molecular and cellular mechanisms that underlie this pathology. The understanding of these mechanisms could lead to the development of new therapeutic strategies. Further, the analysis of long-term tinnitus could unveil molecular and cellular mechanisms of persistent experience-dependent alterations in brain circuits that subserve sensory, emotional, and cognitive responses. Toward that end, we have developed a new behavioral paradigm to study tinnitus in the rat. Animals were conditioned to locate a platform, submerged in one of two arms of a water T-maze. The arm in which the platform was located depended on the presence or the absence of a tone, which was chosen to mimic salicylate- or noise-induced tinnitus. The rat had to learn to associate the tone or its absence with the platform-containing arm. Conditioning (three 15-20 min sessions of 12 trials each) led to a marked increase in the probability of correct arm choice in response to the presence or the absence of the tone, and a decrease in time to reach the platform. Memory of the tone- or no-tone-arm association was evident 15 days after training. Tinnitus was induced by sodium salicylate (300 mg/kg/day i.p. for 4 days) or by over-exposure to noise (6 kHz, 130 dB SPL, 15 min). The expectation was that animals with tinnitus would behave as though they hear a tone even in its absence. This indeed was proven to be the case: treated animals spent significantly more time in the arm associated with the tone even in silent periods. This protocol hence permits objective measure of tinnitus in the freely moving rat. Combined with inner-ear targeted or brain targeted pharmacology, it could facilitate the investigation of the molecular mechanisms of tinnitus. Preliminary results unveiled similarities of molecular mechanisms of tinnitus and neural plasticity and memory.

Anxiety associates with taste to produce conditioned taste aversion in the rat

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The interaction among experience, emotion and memory is considered to be instrumental in the ontogeny and maintenance of acquired emotional and behavioral disorders, e.g. phobias. Here were address the question whether anxiety can associate with taste to produce conditioned taste aversion (CTA). We have used an anxiogenic agent, the 5-HT2C receptor agonist meta-chlorophenylpiperazine (mCPP), to induce anxiety in rats after consumption of an unfamiliar tastant. The anxiogenic agent induced CTA. The mCPP-induced CTA could be prevented by concomitant administration of ethanol, which is known to reverse mCPP-induced anxiety, at a concentration that had no effect on CTA memory. Ethanol did not prevent, however, LiCl-induced CTA. Administration of mCPP before the consumption of the

tastant had no effect on the preference for that tastant. Taken together, our results indicate that anxiety can serve as the US in CTA training. This finding may bear relevance to the ontogeny of pathologies involving food aversion.

Adaptation in the barn owl"s inferior colliculus: a potential mechanism for generating an error signal

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The auditory space map in the barn owl's external nucleus of the inferior colliculus (ICX) is calibrated by visual input from the optic tectum (OT). When bicuculline is injected in the OT, units in the ICX respond to visual signals. When auditory and visual stimuli are presented simultaneously, visual responses are modulated by the direction of the auditory stimulus: visual responses are strongest when the light source is away from the sound source. This modulation can be explained by neural adaptation in the ICX. To test this hypothesis, we measured adaptation using sequential auditory stimuli (30ms broadband noise). We found that when the inter-stimulus interval is 30 to 320ms, the response to the second stimulus is decreased. Two lines of evidence suggest that the site of at least part of this adaptation resides in the ICX. First, adaptation was stronger in the ICX than in the central nucleus of the inferior colliculus, the major source of auditory input to the ICX. Second, the decrease in response to the second stimulus occurred even when the two stimuli were narrow-band and each centered on a different frequency. The strength of adaptation depended on the distance between the two frequencies, which corresponded with the width of the frequency tuning of the ICX unit. This tendency of ICX units to adapt may underlie the encoding of mismatch between visual and auditory representations of stimulus location. Since visual responses appear 20-120ms after responses to simultaneously presented auditory stimuli responses to visual stimuli will decrease, when the spatial representations for the two modalities align and activate the same locus in the ICX space map.

Category Learning from Equivalence Constraints

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We investigated human category learning from partial information provided by equivalence constraints. Participants learned to classify stimuli on the basis of either positive or negative equivalence constraints, that is, when informed that two exemplars belong to the same category or to different categories, respectively. Knowing that in natural contexts positive constraints are more informative than negative constraints, we suspected that participants will not use the two types of constraints in similar ways even in a setting in which the amount of objective information in the two types of constraints is identical. We discovered that when provided with positive constraints, participant categorization performance is distributed normally, but when provided with negative constraints performance distribution is not unimodal. A constrained EM algorithm was used with identical constraint information to simulate the experimental setup. Results of the EM clustering algorithm showed surprising qualitative similarity to human results, with unimodality for positive but not negative constraints. Although we can not infer from this computational simulation how the human brain computes equivalence constraints in the context of category learning, it provides us useful insights into computational aspects of this learning problem. Taken together, these results suggest that positive constraints provide information that may be used intuitively for categorization, while use of negative constraint information may require a less natural, rule-based, strategy, which most participants failed to implement. These results are consistent with the view that humans naturally use similarity-based representations (prototypes or exemplars) as opposed to rule-based strategies (e.g., strategies that use decision boundaries).
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Selective neural responses to objects of expertise in experts' ventral visual pathway

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Expert object recognition occurs when one learns through experience to identify quickly and accurately individual exemplars of a homogenous class, a process associated with qualitative changes in perceptual processing. The neural mechanisms that underlie the perceptual changes, however, are not sufficiently elaborated. Recent research to date, investigated expertise as an alternative to the putative domain-specificity of face processing (McKone and Kanwisher, in press). Thus, neuroimaging studies of expertise were limited to face-selective ROIs of the ventral visual pathway. But, selectivity for objects of expertise may not involve only face regions but may manifest as an organizational principle in ventral visual pathway, starting as early as retinotopic areas. In the present study we examined this hypothesis. Five car experts and five novices were presented with three object categories: cars, airplanes and faces, while being scanned in a 1.5T MRI scanner. A one-back memory task was performed by all subjects. Differential BOLD-fMRI responses were found in car experts in response to cars compared to car novices while equivalent responses were found to faces and airplanes. Since cars and airplanes are objects of transportation with approximately equal level of visual complexity, in absence of expertise no difference should have been expected in the distribution and level of brain activation elicited by each object category. Our preliminary results suggest that differential responses to cars can appear in various regions of the ventral visual pathway in addition to the fusiform face area, including lateral occipital areas and posterior ventral temporal areas. We conclude that expert object recognition modulates visual perception, and this modulation may be reflected by neural selectivity in the experts' visual cortex for objects of their expertise.

Neuroprotective potency of the lipophilic transition metal modulator DP-b99 against oxidative stress

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Reduction in glucose and oxygen supply, which occurs in cerebral ischemia, leads to a cascade of events resulting in neuronal death. We have synthesized a lipophilic analog of BAPTA, DP-b99, currently in Phase II clinical trials, and determined its neuroprotective potency. We have reported that following MCAO in rats DP-b99 was found to reduce infarct volume and improve neurological scores. Here we present results from several in vitro studies using different models of oxidative stress. Oxygen-glucose deprived (OGD) hippocampal slice cultures were used as a model of ischemia. OGD was induced for 1 hr followed by reperfusion. Cell death was quantified by measuring LDH release and the cellular uptake of PI. LDH release increased gradually over the 24h period following reperfusion. PI uptake increased mainly in the CA1 region but also in the CA3 and dentate gyrus following OGD. DP-b99 (30mM) reduced significantly both LDH release and PI uptake at all time points tested. Exposure of cortical neurons to 100mM H2O2 for 4h causes oxidative cell death. Pretreatment with DP-b99 or BAPTA-AM significantly protected the cells. The NMDA receptor antagonist MK801 and calpain inhibitor MDL28170 also protected against cell death. Calpain activity in H2O2-treated neurons and OGD-treated slices was determined by evaluating proteolysis of the calpain substrate a-spectrin. DP-b99 inhibited H2O2--induced calpain activity, suggesting that DP-b99 may protect, in part, through calpain inhibition. We further used the HT22 hippocampal cell line that lacks ionotropic glutamate receptors but is sensitive to glutamate-induced death via oxidative stress. DP-b99 protected the cells by ~50% when added before or up to 4hr after glutamate. Taken together, the neuroprotective potential of DP-b99 in ischemic rat models is related to its protective effect in different types of neuronal cultures demonstrating its usefulness in the treatment of cerebral ischemia.
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Fast-Same effect: implicit priming of ordinal number categories

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Humans and monkeys categorize images according to their ordinal position in a repeated list. Category assignment is assumed to be based on an abstract label (first, second, etc.), common to all images of the same ordinal category (Orlov et al., Nature 2000, Cerebral Cortex, 2002). In previous research with human subjects we measured explicit category priming. Subjects were trained with 32 images, divided into 8 quadruplets. On each trial they viewed 4 sequentially presented sample stimuli, followed by a test stimulus, consisting of the same 4 images. The task was to select the images (by mouse-click) in their correct order. Performance gradually improved. A subsequent memory test confirmed subject ordinal categorization of the stimuli. In a following priming test, we presented subjects with a prime image - to which they responded by reporting covertly the image category. Then (0.3-1s after prime presentation), they were presented with a pair of target images - to which they reported whether the targets belong to the same category or different categories. We found that explicit retrieval of the prime category shortens reaction time (RT) of the same-different judgment - if the prime was of the same category as one or both of the targets. Furthermore, there was a Fast-Same effect, i.e. an additional shortening of the RT for the pair of targets when they belonged to the same category compared to when they belonged to different categories. Both of these findings support the conclusion that subjects learn to associate the stimuli with their ordinal category. We show that the Fast-Same effect is not motor-based, but rather a truly conceptual effect.

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Adaptation Properties of Neurons in the Rat Barrel Cortex Revealed by Dual Intracellular Recordings

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Neuronal adaptation to repetitive presentation of sensory stimulus is a well known characteristic of neurons at different cortical sensory areas and has been studied using extracellular and intracellular techniques. However, the underlying mechanisms of adaptation in the somatosensory cortex are not well understood. Previous studies on this subject suggest that the main source of adaptation is depression of the thalamocortical synapses. In order to visualize the effect of repetitive stimulation in different SI neurons, dual intracellular recordings were performed with sharp electrodes in the barrel cortex of halothane anesthetized adult rats. The principal and/or adjacent whiskers were repetitively stimulated using a piezoelectric device at 10, 20, 30 and 40 Hz for 1 second. Our results show different patterns of adaptation for cells at different cortical layers, ranging from cells that were strongly depressed at 10 Hz to cells that showed a clear response at 40 Hz. Suspected layer 4 cells showed better responsiveness to high frequency stimulation than simultaneously recorded cells from supragranular and infragranular layers. In most cells adaptation was characterized by a monotonic decrease in response amplitude. However, some cells showed a beating behavior characterized by a slow periodic modulation of the response. Additionally, in few neurons, we observed alternation between clear response and absence of response from one stimulus to the next (period doubling). The differences observed in simultaneously recorded neurons and the complex dynamic of the responses suggest that the cortical network is involved in shaping the adaptation properties of neurons to repetitive stimulation.

Lack of paternal care interferes with synaptic composition in the rodent orbitofrontal cortex and amygdala

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Beyond the related endocrine and behavioral alterations found after maternal separation in various animal studies, the development of synaptic connections in limbic brain regions is modulated by early adverse emotional experiences, i.e. the separation from the parents (Poeggel et al., 2003). In the present study the effect of chronic separation from the father on the development of dendritic spines in the limbic system was analyzed. Quantitative analysis revealed region-, cell and dendrite-specific changes of spine densities in the orbitofrontal cortex, in the lateral and basomedial amygdala, hippocampal CA1 region and dentate gyrus of three week old trumpet-tailed rats. The comparison of pups which were either raised with or without their father revealed in the fatherless animals a 40% decreased spine density on apical and basal dendrites of layer II/III pyramidal neurons in the orbitofrontal cortex and up to 20% lower apical and basal spine densities in the amygdala whereas the dendritic lengths remained unchanged. No changes of spine densities and dendritic lengths were observed in the hippocampal CA1 pyramidal neurons and in the granule cells of the dentate gyrus. The lack of paternal care appears to inhibit or suppress the formation of presumably excitatory spine synapses in the limbic cortex and in the amygdala, whereas synaptic development in the hippocampus occurs independent from paternal interaction with his offspring.

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Behind the veil of a fearful face: Large scale neural integration measured by MEG and fMRI.

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Emotion can bias for enhanced visual processing. The evidence for such enhancement includes faster and greater visual detection possibly beyond awareness. This study characterized spatial-temporal aspects of large scale neural integration that underlie emotional modulation of the bias for awareness during Binocular Rivalry (BR). Fearful and neutral faces presented to one eye, competing with a house presented to the other, were studied with and without their aware percept. 40 sec periods of fused stimuli (Rivalry) were followed by same periods of distinct stimuli based on subject's response during the rivalry (Replay). 22 subjects indicated longer aware percept of faces than houses and more so for fearful faces (interaction, $p<0.05$), suggesting that fearful face biased the competition for enhanced visual processing during BR. To study the brain dynamic of this bias, high density MEG and fMRI were applied on 10 subjects. During aware fearful face more than neutral face, MEG showed increased power in beta (14-24Hz) and theta (4-8Hz) bands in estimated sources in the medial temporal sources (MedT) that include the amygdale and. However for switching from a house to a face more so for a fearful face, both MedT and inferior temporal (IT) regions showed increased power. These regions were also observed in the fMRI data when comparing rivalry vs. replay more so in the fear condition. This provides converging evidence for limbic-visual involvement in the dynamic aspect of competing visual processing of emotional stimulus. Next we applied coherence analysis to the MEG signal timecourse obtained in the from MedT and IT sources during periods of switch to- and state of- aware or unaware faces. We found that coherence in the beta and theta bands respectively probed category (face / house) and emotional (fear / neutral) aspects of the competition. This suggests that emotion mediates awareness through large scale coupling between visual and limbic regions.

Very small (10'' & 15'') face drawings generate functional imaging responses in the human "face areas"

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How do we perceive faces of ever changing sizes as we view our visual world? What are the smallest face stimuli that we can perceive? The LOC and the FFA are two face selective regions in the human extrastriate cortex. It is commonly accepted that these regions are the human homologue of the monkey IT cells. Available evidence shows that those IT "expert" cells are size invariant, have very large receptive fields and do not respond to stimuli smaller than 0.8o. If physiological properties of IT "expert" cells predict functional responses in the human homologue regions, it may be expected that visual stimuli smaller than the physiological threshold will not evoke any direct, bottom-up, response in the human face areas. To test this prediction, we conducted a study, using two functional imaging methods: fMRI with a spatial resolution of several millimeters and a temporal resolution of several seconds, and LORETA- a functional imaging method based on Event Related Potentials that gives a fair degree of spatial localization at a superior millisecond resolution. Threshold for face recognition was behaviorally established to be around 8 arc minutes. We aimed to delineate areas showing preferential activation to various size face stimuli, particularly very small ones. 15 Subjects viewed different size (18x18o, 3x3o, 1x1o, 15x15', 10x10') black and white drawings of faces. In both functional studies the smallest face stimuli (10' and 15') evoked robust responses in the "face area". These responses were comparable to those generated by larger faces. That stimuli that are much below IT cells activation threshold generated robust responses in the human homologue of the IT cortex, may indicate that these responses resulted from top-down rather than bottom-up activation.

The role of cGMP-dependent protein kinase (PKG) and the foraging gene in locust density-dependent Phase polymorphism

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Much effort has been invested in recent years into understanding how genes act on the nervous system and in response to the environment to generate behavioral plasticity. Locust phase polymorphism is an extreme example of environmentally induced behavioral variations; in response to changes in population density locusts alter their behavior. A major component of the behavioral phase differences, which is a key feature of locust biology and is central to their occasional yet catastrophic impact on humans, is the more intense flight behavior of gregarious locusts compared to solitary ones. The current is a first step in unfolding the molecular and genetic background of locusts phase polymorphism as a model for the environmental effects on animal behavior. Following previous work in the fruit fly and honeybees we focus on the role of PKG and the locust foraging gene encoding for locust PKG on flight related phase characteristics. We found the total PKG and endogenous PKG activity of gregarious locusts to be significantly higher than that of solitary ones. Flight initiation and flight duration tests confirmed that gregarious locusts demonstrate much higher flight capacity than solitary ones. Chronically treating solitary locusts with 8-Br-cGMP, increased their total PKG activity and also resulted in a significant increase in their flight performances. This could not be generated by cAMP treatment. We suggest that the locust foraging gene and its product PKG have a key role in flight-related density dependent phase differences. This is a new and one of very few examples of a single gene controlling complex behavior and behavioral variations.

Is there a monitor for the monitor? Evidence from a pilot ERP study

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When people detect their errors in a discrimination task, a negative- going waveform can be observed in scalp recorded EEG that has been coined the error-related negativity (Ne/ERN). Although far less elaborated in the ERP literature, a later occurring error positivity (Pe) also appears to be associated with response monitoring processes. Falkenstein et al (2000) proposed that the Pe may be related to additional processing that occurs after error detection, such as conscious error recognition. In a pilot study we encouraged five participants to correct themselves in a two-choice reaction-time task. Surprisingly, participants tended to produce the same correct response twice (namely, produce a double correct response) as often as they tended to correct their errors. Reaction times of the second responses were found to be longer when they were a repetition of a correct response then when they were a true correction. Although a Pe-like component was found in both response types, the ERN-like component was found only in correction responses. These findings support the conception of the Pe as associated with consciousnes awareness of the output of the monitoring process per se.

Immunochemical recognition of activity dependent neuroprotective protein (ADNP) and the active peptide NAP

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Activity dependent neuroprotective protein (ADNP, human calculated molecular mass 123,562.8 Da) is a newly discovered glial protein that it is essential for embryonic development and brain formation (Pinhasov, 2003). ADNP includes an active neuroprotective site, an eight amino acid peptide NAPSVIPQ (NAP). The current study was set out to prepare antibodies to ADNP that will recognize different sites on the molecule. Four peptides of (8-20 amino acid) that spann the ADNP molecule, including NAPVSIPQ were prepared. Peptides (containing a Cys residue attached to the N-terminal amino acid) were conjugated to Keyhole limpet hemocyanin (KLH) and injected to respective rabbits in the presence of Freund's complete adjuvant. Following five booster injections in incomplete Freund's adjuvant, the respective antisera were collected and assayed by Enzyme-Linked Immunosorbent Assay (ELISA) and purified by affinity chromatography on peptides conjugated to SulfoLink Coupling Gel (Pierce). Mouse brain proteins were prepared (4 months old) and separated into cytoplasmic and nuclear fractions. Proteins were further separated by SDS-PAGE (SDS- PolyAcrylamide Gel Electrophoresis) and transferred to nitrocellulose membranes. Membranes were then probed with the antibodies followed by a secondary antibody Horseradish Peroxidase conjugated Anti-Rabbit IgG prepared in goat and developed with ECL. All antibodies recognized intact ADNP in both cytoplasmic and nuclear fractions. This work developed antibodies against ADNP and NAP that will be utilized for further experimentations to elucidate the distribution and mechanisms of ADNP and NAP neuroprotection.

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Immunomodulation of autoimmune responses by pregnancy-related factors

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Clinical remission during the second half of pregnancy, and a tendency to postpartum relapse; have been observed in several autoimmune diseases. These phenomena can be attributed to the immunomodulating activity of several pregnancy-associated molecules such as alpha-fetoprotein (AFP), estrogens, early pregnancy factor (EPF) and placental protein 14 (PP14). In the present study, we tested recombinant human AFP (rhAFP) and estrogens/steroids

for their immunomodulating activity in vitro and in vivo in experimental autoimmune encephalomyelitis (EAE). RhAFP, delivered intraperitoneally, significantly ameliorated the clinical severity of EAE induced in mice by myelin oligodendrocyte glycoprotein (MOG). Central nervous system (CNS) inflammation and axonal degeneration were prevented by this treatment. RhAFP also inhibited T-cell activity and antibody production and down-regulated the expression of cell-surface leukocyte markers CD3, CD11b, MHC class II and CCR5. In addition, we tested estrogens and dehydroepiandosterone (DHEA), (a neurosteroid and the precursor of steroid hormones), using an in vitro model of CNS inflammation, and an encephalitogenic T-cell culture. 17âestradiol and DHEA exerted a moderate inhibitory effect on LPS-induced nitric oxide (NO) secretion. In addition, DHEA reduced MOG-induced T cell proliferation. Our observations show that several pregnancy-related proteins and hormones influence immune function and might be successful candidates alone or in combination, for therapy of autoimmune diseases.

Controlled single step conversion of human embryonic stem cells into neural precursors

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The realization of the remarkable potential of human embryonic stem (hES) cells as a model for studying human development and as an unlimited source of differentiated cells for drug discovery and transplantation is hampered by the existing limitations in directing their differentiation. Current protocols to generate populations enriched for a distinct cell type, most commonly rely on an initial spontaneous disorganized step of differentiation, co-culture, the use of undefined conditioned medium or factors with non-specific and/or poorly understood effect. Here we report the efficient, controlled, reproducible, single step conversion of hES cells into highly enriched cultures of developmentally competent proliferating neural precursors (NPs). When hES cells are cultured in defined serum-free medium, in the presence of specific soluble factors they uniformly develop into highly enriched cultures of NPs. We show that these culture conditions suppress non-neural differentiation and allow hES cells to adopt a neural fate. The NPs may be propagated for prolonged periods, and can differentiate into astrocytes, oligodendrocytes and various subtypes of neurons including mature neurons that fire action potentials and form functional synapses. During prolonged propagation of the NPs, a gradual shift from neuronal to predominantly glial fate is observed after induction of differentiation, probably reflecting the neuronal to glial developmental shift that occurs during neurogenesis in vivo. The presented controlled, single step conversion of hES cells into near homogenous cultures of NPs, is highly valuable for the study of human neurogenesis. It allows the efficient and simple creation of neural cells for drug development, and is an important step towards the potential utilization of hES cells in transplantation therapy of neurological disorders.

Abnormal K+ buffering in the epileptic blood brain-barrier disrupted cortex

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The blood brain-barrier (BBB) is a complex structure designed to maintain a unique neuronal environment and limit the penetrance of serum components to the brain. We have recently demonstrated that opening of the BBB leads to a delayed (~4 days) appearance of a long-lasting focus of epileptiform activity. This was associated with early (24 hrs) activation of astrocytes. In the present study we investigated K+ buffering in neocortical slices maintained in vitro. Extracellular recordings using ion-sensitive microelectrodes were done in treated and sham-operated cortices 1-30 days after surgery. K+ buffering was studied following tetanic and single pulse stimulation or K+ ionophoresis. In all cases buffering was found to be compromised, strongest 1 day after BBB-treatment and fully recovered within 4 weeks. To differentiate between different buffering mechanisms we applied low concentrations of BaCl (100μM) to the bath to block inward rectifier K+ channels (KIR). This was significantly less effective in augmenting K+ signals in the 24 hrs BBB-disrupted cortex. In contrast, further increase in BaCl (2mM) to block K+ leak currents was equally effective in control and treated cortex. Ouabain in concentrations of 9μM which blocks predominantly the α2/3 subunits of the Na/K-ATPase had a smaller effect on the clearing of extracellular K+ in treated slices one day after treatment, indicating a smaller activity of the enzyme. This compromised buffering showed functional significance as slow repetetive stimulation (0.33-0.67 Hz) evoked abnormal afterpotentials after the third and 5th stimulus of a train only in treated cortex which were never seen after the first stimulus. Our results show that development of epileptiform activity in BBB disrupted cortex is preceeded by activation of astrocytes and impaired K+ buffering. This could contribute to neuronal hyperexcitability and later on to the development of chronic epilepsy.

The origin of Purkinje cell simple spikes and the role of parallel fibers

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Purkinje cells can display two different suprathreshold responses: complex spikes and simple spikes. Complex spikes occur when the climbing fiber input onto a Purkinje cell is activated, while simple spikes are considered to result from granule cell inputs. Recent results raise two questions concerning the simple spike activity of Purkinje cells: 1) Do simple spikes represent intrinsic properties of Purkinje cells or granule cell inputs? 2) Are Purkinje cells more responsive to granule cells just underneath them compared with more distal ones arriving through parallel fibers (PFs)? To address these questions, we recorded in vivo Purkinje cell activity extracellularly, concurrently with voltage-sensitive dye (VSD) imaging of the surrounding cerebellar cortex. The signal was acquired from new blue VSDs at high rates (2.8-5.5 kHz) using a 464-photodiode array (amplitudes of 0.1-0.8% dF/F). To address the first question we compared responses of direct PF stimulation to responses obtained by peripheral stimulation. We found that while direct activation of PFs elicited a "beam" of activity propagating along the parallel-fiber axis, peripheral stimulation resulted in a simultaneous activation of an irregular patch-like area, exhibiting no spread along the PF axis. This suggests that Purkinje cells are more sensitive to the granule cells just underneath them, as a significant contribution from PFs would result in a beam-like response. To study the second question, we performed spike-triggered averaging of the optical signal on spontaneous Purkinje cell simple spikes. Simple spike activity was not correlated with any structured activity in the surrounding cerebellar cortex. This supports the idea that simple spikes arise spontaneously as a result of intrinsic neuronal properties, and not due to random granule cell inputs.

The BOLD signal dependence on odorant intensity in primary olfactory cortex.

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Functional magnetic resonance imaging (fMRI) of primary olfactory cortex (POC) has yielded inconsistent results. Odorant-induced POC activity is present at times and absent at others even within the same lab using the same task. Most statistical models used to analyze fMRI data rely on two assumptions: 1. a monotonic transform from stimulus magnitude to neural activity quantity, and 2. a linear transform from neural activity quantity to MR signal magnitude. Whereas the latter has been demonstrated for MR (Boynton et al 1996), the former has not been

demonstrated for POC. An equally viable alternative to a rate-encoding model is a temporal-encoding model. Models of temporal-encoding do not necessarily imply a monotonic transform from stimulus magnitude to neural activity quantity. Thus, fMRI is a potentially invalid measure of POC activity under temporal-encoding models. To address this issue we set out to quantify the stimulus magnitude dependence in POC in thirty subjects. An olfactometer generated low, medium and high concentrations of the odorants phenethyl alcohol and propionic acid in an event-related design (4T, T2* GEMS, TE=28ms, TR=1sec, 192mm FOV, 8 slices, 0.5mm skip, 3x3x3.5mm voxel, ISI=30sec, stimulus repetition=27). The initial 6 subjects of propionic acid had significant activation overall in lateral orbital fronal cortex ($p<.05$) and in POC ($F(3,20)=3.44$, $p<.03$). The relationship between increased signal and increased stimulus concentration in POC was monotonic but not linear (approximately logarithmic). We will test if this finding is the nature of POC encoding or is the consequence of another factor. For example, in several of these initial subjects the signal in POC appeared to be confounded by individual sniff dynamics. Final data analysis will include regressors based on individual sniffs to reduce this variability.

Follow-up on White Matter Changes in Stroke

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Diffusion MRI is a common diagnosis tool for stroke despite the fact that diffusion changes following acute stroke are not fully understood. In addition, Diffusion Tensor Imaging (DTI), which is more sensitive to white matter, reveals mixed effects of fractional diffusion anisotropy (FA) changes within the same subject in the acute stage without distinction of neuronal degeneration or tissue disintegration. The purpose of the present study was to estimate the outcome of areas having increased FA at the acute stage of the stroke. For that we conducted a follow-up study on seven stroke patients using diffusion MRI. The examinations were performed at two different time intervals following the stroke (less than 48 hours and more than 3 months). For data analysis, we segmented the infarcted area into 5 regions of interested (ROIs) based on their FA values and followed their condition at the chronic phase using image co-registration. The results revealed two different patterns of changes. One pattern was characterized by reduction of both the FA and ADC values at the acute phase as compared to normal controls. In the chronic stage, the FA values decreased further reflecting white matter disintegration. Severe deterioration was observed at the ROIs that correlate with the core of the lesion, while slight reduction was observed at the ROIs that correlate with the penumbra of the lesion. In the second pattern, at the acute stage, the ADC reduction, at the ROIs that correlate with the core of the lesion, was accompanied with increased FA (as compared to control values). At the chronic stage the FA values approached control values. These two different patterns of changes may reflect different mechanisms of pathology. This preliminary study suggests that higher FA values, at the acute phase following ischemic stroke, may predict good tissue recovery, while reduction in FA values at the acute stage may predict further deterioration at the chronic phase.

The balance between production and continuous delamination of neural crest progenitors.

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We have previously found that delamination of premigratory neural crest (NC) cells from the dorsal neural tube depends both upon BMP/noggin signaling and successful transition from G1 to the S-phase of the cell cycle. These two mechanisms are hierarchiclly related as BMP is upstream of Wnt1, which in turn promotes G1/S transition and NC delamination. In light of the continuous departure of NC cells from the tube upon synchronization to the S phase, we investigated the mechanism by which the premigratory pool of NC cells is replenished. Two alternative models were analyzed. First, a stem cell model implying asymmetric cell divisions in the dorsal midline, as a consequence of which, one daughter cell delaminates while the other remains in the tube to generate another round of a delaminating cell+a stem cell. The second model involves the existence of a dorsolateral source of NC cells, which translocate dorsomedially into the BMP/Wnt domain and then delaminate (Source and sink model). Our data support the second view of NC cell replenishment. These results are highly significant for our understanding of NC ontogeny as well as of the histogenesis of the CNS primordium.

Extracellular Regulated Kinase I/II (ERKI/II) as a coincident detector of neuromodulation and fast neurotransmission

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In order for a particular neural representation to become consolidated for longer periods, long lasting changes in the neural connectivity should take place, as well as other intrinsic neural changes. These changes depend upon molecular processes such as signal transduction, transcription and protein synthesis. We hypothesize that in order for an afferent ionotropic "fast" experience (N-Methyl-D-Aspartate, NMDA) to be consolidated as a long term memory, it should come in convergence with another metabotropic "slow" modulatory input (Dopamine). First, we set up to define time and dose curves of ERKII activation by Dopamine and NMDA in hippocampal slice preparation. We find that application of 10-100 uM Dopamine creates a dose dependent rise in ERKII activation. When Dopamine is applied in 100uM it raises the ERKII activation in about 50% of basal level, in a time frame maximal at 5 minutes. We also find that when NMDA is applied in different doses ranging from 10uM to 100uM it creates a dose dependent rise in ERKII activation. 100uM NMDA raises the ERKII activation in about 50% in a time frame maximal at 5 minutes. The kinetics of ERKII activation by 10uM and 100uM NMDA is different. Mutual application of NMDA and Dopamine in the same temporal phase does not cause any augmentation in ERKII activation. The results do not dismiss the hypothesis of convergence in different temporal phases.

Neuronal Synthesis and Release of D-Serine to Activate NMDA Receptors

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High concentrations of D-serine occur in central nervous system where it may play an important role in excitatory neurotransmission. D-Serine levels in the brain are a third those of L-serine and it appears to be an endogenous co-agonist of a subtype of glutamate receptor referred to as NMDA receptor. D-serine is synthesized from L-serine by the serine racemase, an enzyme previously shown to be enriched in glia. We now investigated possible localization and synthesis of D-serine in neuronal cells using new antibodies for both serine racemase and D-serine. We observed significant synthesis of D-serine and expression of serine racemase in purified neuronal cultures of cortex, hippocampus, striatum and cerebellum. Levels of D-serine and serine racemase were comparable or higher to those in purified astrocyte cultures and the synthesis of D-serine required the presence of L-serine in culture media. Immunohistochemistry experiments confirmed the expression of serine racemase in neurons in rat cerebral cortex and hippocampus. D-serine immunoreactivity was also detected in neurons of rat brain, indicating that neuronal cells play a role in synthesizing D-serine in vivo. We found the release of D-Serine from cultured neurons to be elicited by agonists of several glutamate receptor subtypes. Depletion of endogenous D-serine in cortical cultures by the enzyme D-serine dehydratase was neuroprotective against NMDA-elicited cell death. Our data indicate that regulated release of endogenous D-serine from neurons plays a role in NMDA receptor activation, with implications for the regulation of glutamatergic neurotransmission.

Separating signal from noise in contrast perception

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A basic problem in psychophysics is the independent estimate of the mean internal response and the noise amplitudes evoked by the sensory stimulus. An analysis of the two-alternative force-choice method derived from the standard detection theory, frequently applied in studies of contrast discrimination, shows that this method is not suitable for the estimation of these unknown parameters (mean and variance). To overcome this problem we used the Thurstonian scaling method of successive intervals. Three observers were tested on a visual identification task, using Gabor signals at five contrast levels as targets. In each trial one of five targets was presented to the observer and he was asked to report which one he saw, pressing the numeric keyboard button from one to five. The model parameters, namely, mean internal responses (n=5), noise amplitudes (n=5) and category boundaries (4 criteria) were found using a best least square fit to the data. In all experiments the noise amplitudes were found to be independent on the contrast. The internal responses were found to be best described by a saturating function of contrast. Surprisingly, the obtained criteria were uniformly distributed and not optimally set. The confidence intervals for the model parameters obtained from the experiments were estimated using Monte-Carlo simulations of the identification task. The results show that the known increase of contrast discrimination thresholds with contrast is due to reduced sensory gain and not due to increasing internal noise.

VAMP-2 regulates the activity of the voltage-gated K+ channels Kv2.1 and Kv2.2

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Kv2.1 has been shown to interact physically and functionally with t-SNAREs, Syntaxin 1A and SNAP-25 (Michaelevski, 2003). Also, Kv2.2, exhibiting high sequence identity with Kv2.1 throughout the N-terminus and the core transmembrane region, but has a pro-found sequence divergence at their C-termini, interacts with Syntaxin 1A and SNAP-25 (in preparation). However, the interactions of both channels differ (in preparation). Re-cently, we have shown that the Kv2.1 interacts also with VAMP-2. The central conserved domain of VAMP-2 has binding sites for both syntaxin 1A and SNAP-25 and is required for SNARE complex formation and synaptic vesicle membrane fusion. In this study we characterize the interactions of Kv2.2 with VAMP-2 and compared with those of Kv2.1. A co-immunoprecipitation analysis, using antibody against Kv2.2 and Kv2.1, reveals physical interactions of both channel proteins with VAMP-2 in Xenopus oocytes injected with the corresponding mRNAs. The functional implications of these physical interac-tions are revealed using two-electrode voltage clamp analysis performed in Xenopus oo-cytes. Thus, VAMP affects in a concentration dependent manner both steady-state activa-tion and inactivation of Kv2.1, i.e., shifting half-activation and half-inactivation poten-tials to more negative voltages without affecting the slope factor of both activation and inactivation. The same effects can be detected in Kv2.2, however, at lower VAMP-2 con-centrations. Namely, Kv2.2 is more sensitive to VAMP-2. Additionally, VAMP co-expression with ether Kv2.1 or Kv2.2 decreases the channel conductance in a dose-dependent manner. The effects of VAMP-2 were further investigated in Kv2.2. Different temporal relationship between the injection of VAMP-2 and channel mRNAs were de-tected for the different effects of VAMP-2 on Kv2.2, indicating that the reduced ampli-tudes are probably due to impaired trafficking to plasma membrane and/or synthesis.

Estimating the Portion of Shared inputs Activated by Different Sensory Pathways in the Rat Barrel Cortex

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Receptive fields of neurons in the barrel cortex are composed of several whiskers. Thalamic receptive fields however are not limited to a single whisker. Thus it is not clear if multi-whisker receptive field of cortical neurons is determined by convergence at the cortical level or by their thalamic afferents. To examine at what stage convergence occurs and to estimate the portion of common inputs arriving to a cortical neuron we used the known adapting behavior of cortical cells as a tool. Adaptation of cortical neurons is believed to result from depression of the thalamocortical and cortical synapses. Therefore reduction of response to stimulation of one whisker after adapting the cell to stimulation of another whisker is a possible evidence for cortical cross talk or shared inputs. Indeed we show, using several simultaneous extracelluar recordings, that adaptation to repetitive stimulation is strong in cortical neurons and almost absent in thalamic neurons. Average membrane potential recorded from neurons of different cortical layers. To calculate the percentage of common inputs out of the total response of one of the whiskers we used a simple linear model. We assumed that the response after depressing one pathway is an algebraic sum of the not adapted, non shared inputs and of shared inputs that were adapted by the second pathway. On average ~40% of the inputs are shared, however, we found large variability in the shared inputs across cell population. Examination of various parameters reveals that the portion of shared inputs is related to recording depth. Assumed layer IV cells showed the smallest portion of shared inputs while cells from other layers showed larger portions. Our results are in agreement with anatomical and electrophysiological studies suggesting that convergence of spatially distinct inputs occur at the stage of layer IV cells, while neurons in other layers are likely to receive inputs from different whiskers after convergence at layer IV.

Anti-P-ribosomal antibodies induce depression in mice

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There is indirect evidence that anti-P-ribosomal Abs is associated with CNS disease. Anti-P-ribosomal autoantibodies occur specifically in systemic lupus erythematosus (SLE). These antibodies are detected predominantly in patients during the active phase of the disease and are believed to correlate with CNS involvement and nephritis. The aim of study was to examine the pathogenic role of anti-P-ribosomal in animal models by intracerebroventricular (i.c.v.) injection of polyclonal anti-P-ribosomal affinity purified Abs from patients with SLE. Naïve female mice (C3H/Hej) were injected i.c.v. with 6 mg/ml anti-P-ribosomal Abs or with 6 mg/ml IVIg as control. The mice were examined for neurological dysfunction in a staircase test, cognitive swim T-maze, grip strength, Rota rod, elevated plus maze (EPM), forced swimming test (FST), and passive avoidance. Anti-P-ribosomal Abs injected mice had a significantly different behavior in the EPM and FST compared to controls. In the EPM, the mice injected with anti-P-ribosomal Abs had significantly less exploration and were less active compared to the controls. In the FST, the anti-P-ribosomal Abs injected mice were found significantly more depressed (a significantly prolonged immobility time) compared to the controls. No significant differences were found between the study and the control groups in the staircase, grip strength, Rota rod, and cognitive (swim T-maze and passive avoidance) tests. Conclusions: Anti-P-ribosomal injected mice display highly significant behavioral changes compatible with depression. No motor or cognitive effects were found in this model. This unique model may be relevant to the pathogenesis of depression in SLE patients.

Effects of controllable vs. uncontrollable stress on amygdalar neuronal activity and plasticity.

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We studied the effects of controllable versus uncontrollable stress on neuronal activity and synaptic plasticity in the amygdala, using the electrophysiological procedure of long-term potentiation (LTP) induction. Rats of the controllable stress group were presented with 100 trials of a tone followed by a foot shock in a two-way shuttle avoidance box. The controllable stress group could avoid the shock by pressing a bar during the tone, or escape the shock by passing to the opposite side of the box during the shock. From this group two sub-groups emerged: rats which learned the task well and avoided more than 50 shocks (good learners) and those which avoided less than 50 shocks (bad learners). Rats of the uncontrollable stress group could not avoid or escape the shocks which were presented according to the average performance of the good learners. A naïve group was left undisturbed until the recording commenced. Immediately after the training rats were anesthetized and prepared for stimulating the entorhinal cortex and recording in the amygdala. The neuronal activity was not significantly affected by the training. The good learners did not differ from the naïves, but the bad learners and uncontrollable stress groups showed less LTP than the naives and the good learners. There was no difference in LTP between the bad learners and the uncontrollable stress group. These results show that a strong stressor reduces amygdalar synaptic plasticity, and suggest that failure to learn the task might be emotionally perceived as uncontrollable situation.

Neuronal activity and plasticity in the amygdala, the dentate gyrus and the CA1, following controllable vs. uncontrollable stress.

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The level of controllability has been shown to modulate effects of stress on physiology and behavior. We studied the effects of controllable versus uncontrollable stress on neuronal activity and synaptic plasticity in the amygdala, the dentate gyrus (DG) and the hippocampal CA1, using the electrophysiological procedure of long-term potentiation (LTP) induction in the rat. Rats of the controllable stress group were trained in the Morris water maze to locate a hidden underwater platform, thus escaping the cold water, immediately before the recording. The uncontrollable stress group was exposed to the water for the averaged time of the controllable group, without the platform. A naïve group was left undisturbed until the recording commenced. The controllable stress group showed no difference from the naïves in any of the measures in the dentate gyrus and in the amygdala. The uncontrollable stress increased baseline activity in the amygdala, and enhanced LTP in the dentate gyrus. In the CA1, both stressors impaired LTP, but the effect of the uncontrollable stress was more robust. These findings were further verified in a second experiment in which the effects of amygdalar activation on DG and CA1 activity and plasticity were assessed. Stimulation of the amygdala increased neuronal activity in DG, but not in the CA1. Furthermore, amygdalar activation 30 s prior or after LTP induction increased LTP in DG, but decreased it in CA1. These findings show differential effects of stress, controllability and amygdalar activation on different brain regions, and suggest that the amygdala mediates some of the effects of stress on hippocampal activity and plasticity.

Constraining compartmental models using multiple voltage-recordings and evolutionary algorithms

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In the last decade there has been a significant advancement in the ability to record membrane potential and ion channels from dendrites. Compartmental models with many non-linearly dependent parameters are used to learn the physiology of such complex neurons. However, the number of loosely constrained parameters makes it impossible to construct the desired model manually. Recently, progress has been made using automated parameter search methods, such as evolutionary algorithms. These stochastic algorithms enable to construct a compartmental model of a neuron, using recorded spike trains. However, these methods are limited to somatically recorded spikes using relatively simple target functions. We've used a new fitting method based on trajectory density in a phase plane to compute a robust fitness coefficient. We exclude the time parameter by plotting the membrane potential V(t) versus its first time-derivative V'(t), in which the periodicity of the signal is reflected by a closed loop that can be geometrically analyzed, and each point of the plane can count how many times it has been hit during the entire recording. This method prevents from the algorithm to ignore the steep spikes and thus converge into a strait line. We investigated the contribution of several recording locations (soma, dendrites and axon). At each location a set of 5 currents (2 passive + 3 spike trains) was measured. We combined least square sum function for the passive currents with the trajectory density for the spiked ones. We concluded that convergence efficiency improves as more recording locations are used.

Proteolytic processing of F-spondin is required to elicit its affect on commissural axon fasciculation at the floor plate

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F-spondin, a gene expressed at the floor plate, encodes a secreted guidance protein that plays a role in patterning axonal trajectory in the spinal cord. The carboxyl half of F-spondin, which contains 6 thrombospondin type 1 repeats (TSR), is proteolytically processed. The cleaved products of F-spondin have different properties and activities: the 1-4 TSR fragment neither binds the ECM nor promotes axonal outgrowth, while the 5th and 6th TSRs bind ECM and promote outgrowth. To test the relevance of F-spondin processing in-vivo, we applied genetic tools to the chick embryo. Cell-specific expression was achieved by electroporation of DNA utilizing a floor plate specific enhancer. The activity of the specific enhancer was further amplified by the use of DNA site-specific Cre recombinase and Plox conditional constructs. The ectopically expressed 1-4 TSR domain is deposited along the membrane of floor plate cells, while the 6th TSR is found in the basement membrane underlying the floor plate, reflecting its ECM binding properties. By utilizing protein tags at the amino and carboxyl ends of the protein, we demonstrate that F-spondin is processed in vivo. Mutating the putative cleavage sites generated a non-cleavable protein, comprising the two domains, that accumulated on the surface of floor plate cells. The re-routing of the neurite outgrowth-promoting domain of F-spondin to the membrane of the floor plate cells, rather than to the basement membrane, resulted in re-directing commissural axons growth dorsally into the floor plate cells. Thus the cleavage of F-spondin is required for the deposition of the adhesive motifs at the basement membrane, which can then facilitate the fasciculation of commissural axons at the ECM below the floor plate.

Neurogenesis, long-term potentiation and learning and memory processes are impaired in immune deficient mice

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Autoimmune T cells have been shown to benefit neuronal survival after CNS injury, and hence to help maintain the equilibrium of motor and sensory functions of the brain under adverse conditions. In this study we found that T cells play a role in spatial learning and memory both under physiological and adverse conditions, e.g. neurodegeneration or dementia. We found that in mice with severe immune deficiency long-term potentiation (LTP) and learning and memory processes are impaired and adult neurogenesis is significantly reduced. Replenishment of the immune deficient mice with T cells restored hippocampal plasticity. Under adverse conditions, caused by neurotransmitter imbalance, a T cell-based vaccination was

sufficient to overcome the behavioral malfunctioning. The beneficial effect is attributed in part to brain-derived neurotrophic factor (BDNF). These findings, by suggesting that a peripheral immune deficit or a local neurotransmitter imbalance or both can lead to cognitive impairment, highlight the role of the peripheral immune system in CNS maintenance.

Trajectory control during rodent whisking

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The relative simplicity of the rodent vibrissal system facilitates a systematic study of motor control and sensorimotor loop dynamics. Multiple anatomical loops contribute to active control of the vibrissal plant during explorative behavior. We have examined motor control during exploratory and task-related whisking in rats and mice. Using high-speed video we monitored whisker trajectories and extracted various kinematic parameters from the whisker motion. We analyzed repetitive whisker movements with a forward (protraction) and a backward (retraction) phase. We found that, across tasks, the protraction phase during high-amplitude whisks is characterized by a pulsatile forward motion with relatively constant velocity. The amplitude of protraction is governed primarily by the duration of movement whereas retraction amplitude scales primarily with velocity. During protraction, object touch is followed by a rapid (~10 ms) active thrust of the ongoing movement, typically observed as an increase in whisker velocity. These observations are consistent with the notion that the protraction phase acts as the sensory acquisition stage during whisking and that rapid brain loops can process and adjust pre-planned movement trajectories in the behaving rodent.

Transgenic mice overexpressing different variants of acetylcholinesterase are hyperalgesic but have opposite reactions to the elevated plus maze.

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Mice that overexpress either the synaptic variant of acetylcholinesterase (AChE-S) or the rare readthrough variant (AChE-R) (developed by H. Soreq, Hebrew University) were tested for reactivity to pain using the hot plate paradigm and for unconditioned and learned anxiety in the elevated plus maze (EPM). Acetylcholine mediates in fear-potentiated startle, and the response to anxiety. Moreover, AChE-R is elevated following exposure to stress or to the cholinesterase inhibitor diisopropylfluorophosphate, suggesting that the two transgenic genotypes would show alterations in measures of reactivity to aversive stimuli. EPM was tested using a transparent maze with 2 open and 2 closed arms. Mice were placed in the middle of the maze and videotaped for 6 min in 2 sessions separated by 48 hours. Reactivity to pain was measured in the hot-plate test at 47o and 50o C. The AChE-S mice showed significantly less exploration than the AChE-R and FVB/N control on the second, but not the first exposure ($F=14.5$, $p<.0005$), whereas the AChE-R showed significantly more exploration ($F7.34$, $p<.01$) on the second exposure. In addition, AChE R females had more risk taking than males on the first exposure whereas, AChE-S females had more risk taking than males on the second exposure. Both AChE-S and AChE-R mice had lower latencies to paw lick on the hot plate test, suggesting hyper-reactivity to pain. These findings confirm the involvement of AChE in anxiety behaviour and suggest that AChE-R is related to a deficit in inhibitory behaviour.

Locally uncaged calcium induces rearrangement of GluR1 receptor clusters in the heads of dendritic spines of hippocampal neurons in culture

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Previous investigations have demonstrated that dendritic spines are able to regulate intracellular calcium concentrations ([Ca2+]i) independently of the adjacent dendrite such that synaptic elevation of [Ca2+]i is mainly restricted to the spine head. The spine neck is a critical regulator of communication between the dendrite and the spine head. In previous studies we have shown that spine length can affect [Ca2+]i levels in the parent dendrite by controlling the diffusion of [Ca2+]i, released by local flash photolysis from caged NP-EGTA+[Ca2+]i compound in the spine head. Diffusion of calcium varied as a function of spine size, so that only the fraction of shorter (<1.5 um) spines revealed significant calcium diffusion into the dendrite. We now extend these observations to examine the functional relevance of calcium reaching the dendrite after uncaging in the spine head by measuring changes in GluR1 receptor clusters. Cultured hippocampal neurons transfected with pDsred and GluR1GFP were preincubated with APV during 2-3 days and imaged in a confocal microscope (Pascal, Zeiss). Caged EGTA AM (7uM, Molecular Probes) was loaded into cells over 1.5 hr of incubation at room temperature. Pulses of 4ns UV laser light were directed on a spine head through a 63x water immersion objective. About 80% of APV treated spines did not express GluR1 puncta whereas almost all of control spines contained GluR1. UV flashes produced [Ca2+]i transients which peaked at 1-2 ms and decayed exponentially with time constants of 10-12 msec. Sequences of about 30-60 pulses applied at 0.2Hz on spines without GluR1, induced in 60% of cases, its slow accumulation over 10 – 20 min. Single or infrequent UV pulses were not efficient. A clear correlation between the spine length and the appearance of GluR1 puncta was found, such that only shorter spines became GluR1-positive. These results indicate that spine length may play a pivotal role in dynamic modulation of GluR1 receptor localization.

The effect of pre-challenge learning on MK801 induced psychosis-like behavior in an animal model of schizophrenia

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There is mounting evidence to support the concept of education producing a functional reserve in the brain, a process that provides some protection against the clinical manifestation of severe CNS illness. At the molecular level BDNF was suggested to mediate memory consolidation and synaptic plasticity produced by learning experience. This study aimed to examine whether pre-challenge learning prevents psychosis-like behavior in an animal model of schizophrenia, and to describe the learning-related cellular mechanisms which attenuate the course of schizophrenia. Rats were trained to distinguish between pairs of odors in an olfactory discrimination task. We examined whether such olfactory-learning induces protection against the effects of i.p. injections of MK801 in a series of behavioral tasks, the Morris water-maze, pre-pulse inhibition and elevated plus maze. Forty-eight hours after the behavioral tasks, rats were sacrificed and the frontal cortex, CA1, CA3 and dentate gyrus were dissected for BDNF measurements. MK801 caused sensory-motor disturbances, spatial learning acquisition deficit, and swimming strategy alterations in pseudo trained and naïve rats, to the point were they were unable to complete the task during the course of 4 days of training. Although MK801 strongly affected learning of rats from the olfactory-discrimination trained group, these rats performed better than the naïve and pseudo trained, and were able to complete the task. Moreover, administration of MK-801 significantly disrupted pre-pulse inhibition in the pseudo-trained and naïve groups, but not in the trained rats. In learning rats, BDNF mRNA in the frontal cortex was significantly higher compared to naïve and pseudo-learning rats. Our data support the notion that learning-induced protection against schizophrenic behavior is mediated by glutamatergic transmission and modifications in the frontal cortex, manifested as enhanced expression of BDNF mRNA levels.

Characterization of a novel brain protein –KIAA0863

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KIAA0863 belongs to a protein family, which includes activity – dependent neuroprotective protein (ADNP). Here we report a comparative expression analysis of ADNP and KIAA0863. ADNP is a protein that has protective effects on neurons (Regul Pep. 2000 96, 39) and that is involved in neurodevelopment (Dev Brain Res. 2003 14, 83). Computer analysis and sequence alignments with human ADNP identified a paralog protein, KIAA0863, with 33% identity and 46% similarity. KIAA 0863 is composed of 5 introns, 4 exons, and encodes an 1131 amino acid protein with a molecular weight of 122832 Dalton. The protein structure contains 8 zinc finger motifs and a homeobox domain, suggesting transcription factor activity and a nuclear localization. The protein is highly conserved in human, mouse and rat (with 73% and 75% identity, respectively, to a human protein), and is mapped to chromosome 18 within these species. The mRNA expression of KIAA0863 was obtained by reverse transcription-polymerase chain reaction (RT-PCR) analysis in several tissues from a normal four month old mouse. KIAA0863 is abundantly expressed in distinct normal tissues. We showed increased expression of the mRNA in the heart, brain and kidney, similar to the findings on ADNP (J Biol Chem. 2001 276,708). This study is the first description of KIAA0863 gene expression and the first step towards a better understanding of the activity and the relationship between the resembling proteins – ADNP and KIAA0863.

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Representation of tone in fluctuating maskers in the ascending auditory system

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Comodulation masking release (CMR) is a psychoacoustical phenomenon in which the perception of low-level tones is facilitated with the increase in the bandwidth of accompanied slowly-fluctuating noise. We have previously suggested a neuronal correlate of this phenomenon, the ability of low-level tones to suppress neuronal locking to the envelope of the fluctuating noise ('locking suppression'). Here we study the neuronal responses to different paradigms, which were designed to evoke CMR in human subjects, in the primary auditory cortex (A1) of halothane-anesthetized cats. We show that the locking suppression encountered in A1 is capable of explaining a large body of the CMR psychoacoustical research. In addition, we studied the responses to one CMR paradigm in three successive auditory stations: inferior colliculus (IC), medial geniculate body (MGB) and A1. While responses in IC were roughly isomorphic to the physical structure of the sounds, with only a small perturbation in their responses to the fluctuating noise following the addition of low-level tones, some neurons in MGB and all A1 neurons displayed striking suppressive effects. These neurons were hypersensitive, showing suppression already with tone levels lower than the neurons' threshold in silence, starting more than 75 ms after tone onset. Our findings demonstrate a qualitative change in the representation of tone in fluctuating noise along the IC-MGB-A1 axis, suggesting the gradual segregation of signal from noise and the representation of the signal as a separate perceptual object in A1.

Improved spatial resolution to density estimation of voltage gated potassium channel conductances distributed in a non space clamped structure

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Currents yielded from voltage-clamp recordings performed in non-isopotential structures, such as dendrites, are severely distorted due to voltage attenuation around the injecting electrode. Therefore, up till now it has been impossible to determine correctly the underlying ionic conductances of voltage-gated channels distributed in the membranes of such structures, and from them to accurately estimate channel densities. Recently, a numerical algorithm was developed by our lab, that has been shown to successfully correct such distortions in a number of simulated experiments using various neuronal structures inserted with a number of models of voltage gated potassium channels, and correctly estimate channel kinetics and conductance densities when inserting a range of homogenous densities, and even density gradients and slopes. However, one limitation of this correction algorithm is relatively poor spatial resolution, when estimating conductances in structures inserted with a step-wise varying channel density, around the abrupt conductance step. This study shows an improvement in spatial resolution achieved by performing a sequence of voltage clamp simulations in locations progressively closer to the position of the conductance step, each time utilizing the conductances estimated in the farther positions. These improvements in kinetics and density estimations were successful with various potassium channel models and a series of increasingly larger conductance density steps.

Cation Binding At The Pore of Lc-Type Ca2+ Channel Regulates Depolarization-Induced Exocytosis

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A unique coupling of voltage-gated Ca2+ channel (VGCC) with the release machinery suggests a regulatory function for the channel in depolarization-evoked exocytosis. To test this hypothesis, amperometry in chromaffin cells was used with trivalent ions that bind to VGCC but do not cross into the cytoplasm. We found that exocytosis is mediated by La3+ ions in divalent ion-free solution with no detectable change in intracellular Ca2+ concentrations. A stringent requirement of ionic radii for lanthanides activity and competition with nifedipine, verapamil and Cd2+ confirm La3+ binding at the VGCC. The time from fusion pore opening to dilation of single dense core vesicles ('foot signals') was significantly shorter in La3+ than in Ca2+, indicating different kinetics of the molecular structure that links vesicle and plasma membrane. The considerable effect of impermeant cations on foot dynamics implies that the channel participates in the fusion pore structure and controls exocytosis in a cation-dependent manner, upstream to intracellular proteins.

Quantification of synapses made by thalamocortical afferents reconsrructed in 3-D serial thin sections.

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This study focuses on synapses made by reconstructed segments of thalamocortical afferents to layer IV of barrel cortex in the adult mouse. Aims are to determine the numbers of synapses per axon length, the numbers of synapses made at axonal varicosities vs. those along cylindrically shaped regions of the axon, and the proportions of synapses formed with dendritic shafts vs. spines. Axons were labeled by the anterograde transport of lysine-fixable biotinylated dextran amine (BDA) injected in vivo into the ventrobasal thalamus. Labeled thalamic axons in the posteromedial barrel subfield were identified by light microscopy, serial thin sectioned and then reconstructed in 3-D from digital electron micrographs. All thalamocortical synapses were of the asymmetrical type. Most were formed at varicosities, however, some occurred at cylindrical regions of the afferents. Preliminary results indicate that axonal varicosities form about two synapses each, a lower value than observed in preparations where lesion induced degeneration (LID) has been used to label thalamic afferents. It may be that during degeneration, the axonal varicosities coalescence and/or 'absorb' synapses situated in adjacent, non-varicose axonal segments. The ratio of axospinous to axodendritic synapses is 4:1; this ratio has been observed for BDA labeled afferents at 11 days postnatal, and for LID and PHA-L labeled afferents in adults (White, 1989).

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Induction of alpha-Synuclein aggregates in dopaminergic neuronal cell lines as an experimental model for Parkinson's disease

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Parkinson's disease (PD) is the most common neurodegenerative movement disorder. The pathologic hallmark of PD is the appearance of intracytoplasmic inclusion bodies, named Lewy bodies. Alpha-Synuclein is a major component of these inclusions and its mutated form causes autosomal dominant PD, implicating its central role in PD. Recent evidence suggests that failure of the ubiquitin– proteasome system leading to protein accumulation contributes to degeneration of dopaminergic neurons and Lewy body formation in the substantia nigra. The aim of this study is to characterize the conditions that induce protein aggregates formation in differentiated and undifferentiated dopaminergic cell lines. We established dopaminergic SH-SY5Y and PC12 cell lines overexpressing wild-type or mutant alpha-synuclein and exposed them to various ROS generators. Neuronally differentiated SH-SY5Y and PC12 cells were established by treating the cells with retinoic acid or nerve growth factor, respectively. The cell lines were also stably transfected with pDsRed1-N1 plasmids containing WT or mutant á-synuclein fused to red fluorescent protein. The cells were treated with rotenone, SIN-I chloride and FeCl2 with or without proteasomal inhibition by lactacystin. After exposure to ROS or to proteasomal inhibition, alpha-synuclein aggregates were formed in the cytoplasm and were also immunopositive for ubiquitin and thioflavin S staining. Protesomal inhibition increased the rate of aggregates formation in response to ROS, emphasizing the synergistic effect of both insults. This cellular model is informative for our understanding of the molecular mechanisms of the disease process in PD and may help develop future therapies.

Perinatal enhancement of the GABA-ergic system modulates synaptgenesis

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Antiepileptic drugs acting through the potentiation of GABA-ergic pathways have adverse effects on brain development. Increased risk of impaired intellectual development was reported in children born to women treated for epilepsy during pregnancy. We have previously shown that vigabatrin (GVG) treatment during perinatal days (P) 4-14 delays reflex development and impairs learning and memory in adult mice. Here we examined the possibility that enhancement of the GABAergic system at early postnatal age modulates synaptogenesis, by evaluation of synaptic vesicle proteins. Perinatal GVG treatment significantly modulated the expression of synaptotagmin I (Synt I) and synaptobrevin/VAMP II but not Synt II. At the end of the GVG treatment period Synt I-immuno-reactivity (IR) was reduced in the hippocampus CA1 region (9.6 % of control, P<0.01), secondary visual cortex, V2 (0.9%, P<0.01), and a trend of decrease was observed in the frontal association cortex, FrA (17.7%, P<0.07). A week later, at P21, Synt I-IR in CA1 and V2 was equal in both groups. However, at the age of 16 weeks the GVG group showed a significant increase in Synt I-IR in CA1 (164.8%, P<0.01). Thus, the short-term suppression of Synt I-IR switched into over-expression of Synt I in the hippocampus CA1 region. When VAMP II-IR was examined, the general trend resembled that of Synt I. However, the effect of perinatal GVG treatment on VAMP II was significant mainly in the adult mice. An increase in VAMP II-IR was observed in CA1 (196.2% of control, P<0.01) and the cortical regions: FrA (204.5%, P<0.05), V2 (224.6%, P<0.01) and primary sensory cortex, S1 (218.5%, P<0.01). The association between perinatal GABA enhancement and modulation of synaptogenesis is reported here for the first time. We suggest that the short and long term modifications in Synt I and VAMP II expressions in the hippocampus and cerebral cortex may interfere with synaptic plasticity leading to impairment in learning and memory.

Homocysteine Reducing Strategies Improve Symptoms in Chronic Schizophrenic Patients with Hyperhomocysteinemia

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Elevated homocysteine is reported to be a risk factor for several diseases including Alzheimer's and schizophrenia, and can be lowered by oral folic acid, B-12 and pyridoxine. Thirty seven schizophrenic patients with plasma homocysteine above 15 Micromolar were treated with these vitamins for three months and placebo for three months in a randomized double-blind placebo controlled crossover design. In all patients except for one non-compliant subject, homocysteine levels declined significantly on vitamin therapy compared to placebo as did clinical symptoms of schizophrenia. A subgroup of schizophrenic patients with hyperhomocysteinemia may benefit from simple addition of B vitamins.

Effect of intraperitoneal Acetyl-L-carnitine (ALCAR) on anxiety-like behaviors in rats

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Acetyl-L-carnitine (ALCAR) is an acetyl derivative of carnitine, an endogenous molecule synthesized in vivo and supplemented by diet mainly from meat and dairy products. Several parallel, double blind, placebo-controlled studies have demonstrated that ALCAR treatment produces beneficial effects in geriatric depression. Since most antidepressants also have anti-anxiety effects we examined whether ALCAR shows anti-anxiety effects in a rat model of anxiety. Compared with a control group, chronic administration of ALCAR at doses of 10 and 100 mg/kg (tested 24 hours after the last dose administration) showed no effects, whereas doses of 50 and 75 mg/Kg significantly reduced anxiety-like behaviors in the elevated plus-maze. Acute ALCAR (100 mg/kg), on the other hand (tested 6 hours after administration), demonstrated anxiogenic effects. Our data suggest that chronic ALCAR administration may produce an inverted U-shape curve of dose dependent changes in anxiety-like behavior. The precise mechanism by which Acetyl-L-carnitine decreases anxiety-like behavior after peripheral administration remains to be determined.

Correlation between blood-free testosterone concentration and sleep duration in healthy young men

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Background: Healthy young men who underwent varicocelle chemical embolisation, required reduced sleep duration. Testosterone, an androgenic anabolic steroid, affects the central nervous system. We measured serum free testosterone in a group of these patients, to determine whether there is a correlation with decrease sleep duration. Methods: Thirty young men in general good health, underwent varicocelle chemical embolisation for infertility treatment. They were requested to complete a questionnaire regarding their sleep habits. They were asked to fill in the questionnaire before treatment and again 3 months after start of treatment. Serum free testosterone was measured at the same times. Results: In 40 young men (mean age 31 ± 7) serum free testosterone increased 3 months after the varicocelle procedure (6.5 ± 3.5 vs. 11 ± 3.1; P < 0.05). Sleep duration significantly decreased during the same period (7.9 ± 1.1 vs 7.1 ± 1.3; P < 0.05). Conclusions: An increase in free serum testosterone concentration, following varicocelle chemical embolisation, was associated with a decreased Sleep duration..

Coupling TMS with EEG to "close the loop" between measurement and perturbation - first steps towards a "brain pacemaker"

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We are using a novel, integrative approach that uses EEG and TMS (transcranial Magnetic Stimulation) to "close the loop" between measurement and intervention. EEG is constantly being measured from the subject's scalp, and the signal analyzed online. The results of this analysis are used to trigger the stimulation and control the stimulation parameters. Triggering the TMS stimulation with the ongoing EEG activity enables, for the first time, a controlled stimulation based on the brain activity itself. The response of the brain to the magnetic stimulation is immediately recorded by the EEG system, in this way "closing the loop". In one experimental paradigm, we measured the effect of TMS on alpha wave oscillations, as TMS was applied at different phases and different locations relative to a reference EEG electrode. The ability to intervene, enhance and synchronize alpha oscillations will be discussed. In the second paradigm we applied the "closed loop" system to a case where the breakdown of brain activity results in the emergence of schizophrenic symptoms. We intervene in a subject suffering from drug resistant delusions and exhibiting 1 Hz spikes.

Probing synchronous internal processes by precisely controlled Transcranial Magnetic Stimulation

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A task such as synchronization of finger tapping by a metronome couples the auditory input to the motor output via an application of higher brain functions such as intention and sensory feedback. Perturbing this connection via precisely administered and well controlled auxiliary excitations yields a picture of the internal processes and an understanding of how this coupling is obtained. In the present experiment we interfere with finger tapping at the level of the motor cortex by using TMS (non invasive Transcranial Magnetic Stimulation) over the M1 cortical hand area. During the tapping task trains of TMS were applied in the rate of the metronome, either in or out of phase. The effect of the magnet on the motion of the finger is measured with high precision for both in phase and out of phase relations between the metronome and TMS excitation, and at different tapping frequencies. The results are modeled in terms of a forced oscillator to enable quantification of the spectrum of behaviors at the different frequencies and phase relations. Results are compared between the group of normal subjects and a group of schizophrenia subjects, where differences in psychomotor performance have previously been shown. Implications of this study to affecting other forms of oscillations, e.g. EEG activity, via TMS perturbations will be discussed.

A central role for JNK pathway in antidepressant-induced weight gain and metabolic changes.

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Several antidepressants, mainly selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs), were shown to induce severe weight gain and metabolic changes, but the mechanism and major early key players underlying it remain unclear. In previous study we demonstrate marked dose-dependent activation of the c-Jun amino-terminal kinases (JNK) patheway, following exposure to selective antidepressants. Also, JNK activation and phosphorylation has been shown to play a central role in obesity and insulin resistance. Because selective antidepressant both induce severe weight gain and are potent JNK activation, the present study asked to characterize the molecular pathway underlying antidepressant-induced metabolic changes. First, we demonstrate that applying the antidepressant Paroxetin , two hours prior to insulin induce insulin receptor activation, significantly block insulin receptor phosporylation in rat hepatoma cell (FAO). This effect was dose-dependent starting at dose of 1-10 *f*YM Paroxetin. Paroxetin blockade of insulin receptor phosporylation did not accompaniment with changes in the level of insulin receptor protein. These changes in insulin receptor activation were correlated with rapid increases in p-c-Jun levels and the upstream target, p-JNK. To check for non-specific activation of other MAPK pathways, e.g. the MEK/ERK pathway, we determined p-Erk activation under the same conditions and found that p-c-Jun, but not p-Erk, was activated by paroxetine. To test if paroxetin induced insulin receptor phosporylation depend on c-Jun activation, we used the specific c-Jun activity blocker, SP 600126. We found that paroxetin effect on insulin receptor activation abolish if we block c-Jun activation. In this study we suggest a central role for JNK in antidepressant-induced obesity and metabolic changes.

Electrical Brain Stimulation of the Medial Forebrain Bundle Reduces the Effect of Cocaine Related-Cues on Locomotion and Craving

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The development of drug addiction is associated with synaptic plasticity and neuronal adaptations including alterations in glutamate receptors such as GluR1 and NMDAR1 in reward-related brain regions, mainly in the mesoaccumbens pathway. Intra-cranial self-stimulation of the medial forebrain bundle (MFB) was reported to affect glutamatergic transmission and receptor levels in these regions. We investigated the influence of repeated electrical stimulation of the MFB on the sensitized response and the seeking behavior for cocaine in rats previously exposed to daily cocaine. In addition, we examined the level of glutamate receptor subtypes (NMDAR1 and GluR1) in the mesoaccumbens pathway of these rats, using immunonhistochemistry. Chronic cocaine injections (15mg/Kg/day for 7 days) induced a gradual increase in the psychomotor response, as previously reported. Chronic treatment with electrical stimulation of the MFB (ten days, 30 min/day) did not affect the sensitized psychomotor response to a cocaine challenge. However, in a following saline challenge, which typically induces conditioned psychomotor activation, the chronically stimulated rats did not show psychomotor activation. Furthermore, the electrical stimulation treatment induced some alterations in NMDAR1 levels in the mesoaccumbens pathway. Other groups of rats were trained to self-administer cocaine in an operant chamber. We found that the electrical stimulation treatment caused a decrease in cocaine seeking behavior in a drug-free trial. These results indicate that repeated electrical stimulation of the MFB fails to attenuate the psychomotor and perhaps the rewarding effects of cocaine per se but it does attenuate the incentive effects of the drug-related cues. The attenuation induced by the electrical stimulation may result from changing synaptic strength that is related to the incentive salience of drug-associated cues. Hence, we suggest a potential treatment for addiction using electrical stimulation.

Supralinear summation of inhibition underlies sublinear spatial integration in the barrel cortex

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Little is known about the mechanisms of spatial integration in the cortex. In the barrel cortex the response to simultaneous activation of multiple whiskers is sublinear and even suppressive (Higley and Contreras 2003, Mirabella et al. 2001, Simons and Carvell 1998, Goldreich et al 1998). The important role of inhibition in suppressing

responses when neighboring whiskers are coactivated was reveled by blockade of inhibition using bicucullin (Kyriazi et al. 1996). However, the exact mechanism that leads to sublinear spatial integration remains unclear. Here we explored the mechanism of spatial integration by recording the membrane potential of neurons in the barrel cortex of the rat. We studied the integration of excitatory and inhibitory components arriving to the cell from two sensory pathways by stimulating two neighboring whiskers. Conductance measurements and intracellular blockade of inhibition demonstrated directly that excitatory components arriving from the pathways are summed almost linearly, suggesting that excitatory inputs do not share significant amount of common inputs and are independent from one another. On the other hand, inhibitory components are summed supralinearly: inhibition was on average ~50% larger than predicted. These findings strongly suggest that sub linear spatial integration arises from nonlinear properties of the cortical network leading to activation of inhibitory inputs that are not activated by either stimulus alone.

Strain-related differences in response to neuroprotective therapy based on mucosal administration

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Ability to cope with ongoing neurodegeneration after optic nerve injury differs among animal strains and depends on the ability to manifest a T cell-mediated protective response. In strains that show a higher neuronal survival following injury this ability also correlates with well-controlled, moderate, transient activation of local microglia to express MHC-II. We show that CD4+ T cells that infiltrated mechanically injured nerves in mice that vary in their ability to cope with the injury exhibited similar memory phenotypes, after 3 days the percentage of activated CD4+ T cells was significantly higher in mice with the higher neuronal survival. Both strains benefited from active immunization with myelin-related antigens. However, immune-based manipulations (via mucosal administration) evoking regulatory-cell generation and a shift in cytokine balance were neuroprotective only in mice with poor ability to cope with the insult and only when directed against certain epitopes. The results support a link between poor ability to cope with injury and susceptibility to development of experimental autoimmune encephalomyelitis, and suggest that immune regulation as neuroprotective therapy should be considered with caution.

Ubiquitylation of synphilin-1 and its role in Parkinson"s disease

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Parkinson's disease (PD) is one of the most common neurodegenerative diseases and it is due to a progressive degeneration of dopaminergic neurons in substantia nigra. Mutations in the alpha-synuclein gene and its presence in Lewy bodies of PD patients indicate that alpha-synuclein plays an important role in the disease. We have found that alpha-synuclein interacts with a protein we have called synphilin-1. Synphilin-1 is enriched in brain, interacts with alpha-synuclein in vivo and is present in Lewy bodies of PD patients. Co-transfection of synphilin-1 with alpha-synuclein into mammalian cells leads to the formation of eosinophilic inclusions that resemble Lewy bodies, suggesting that synphilin-1 could modulate alpha-synuclein aggregation. We also found that synphilin-1 is a neuronal protein, widely expressed in brain and localized to presynaptic nerve terminals. Co-immunoprecipitation experiments show that synphilin-1 specifically associates with synaptic vesicles. More recently we found that synphilin-1 interacts with the ubiquitin-ligase called SIAH. SIAH promotes the ubiquitylation and degradation of synphilin-1 through the ubiquitin-proteasome system, and the formation of robust amount of inclusion bodies in the presence of proteasome inhibitors. Ubiquitylation is required for inclusion formation, since a catalytically inactive mutant of SIAH, which still binds to synphilin-1, fails to promote inclusions. SIAH is present in Lewy bodies of patients with PD, raising the possibility that synphilin-1/SIAH inclusions may be relevant for Lewy body formation. We hypothesize that dysfunction of ubiquitin-proteasome pathway and accumulation of ubiquitylated synphilin-1 could be an early event in the pathogenesis of PD. We are currently extending our studies on synphilin-1-SIAH interaction and the role of ubiquitylated-synphilin-1 in cell death.

Hypoxia-sensitive, nonselective cation channels in layer 5 pyramidal neurons are activated by decreases in evtracellular calcium

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We previously showed in neocortical neurons that when all voltage-dependent channels are blocked, a large, non-specific, outwardly rectifying, cationic current is revealed (Icat). The characteristics of Icat are rapidly altered during an hypoxic episode, which elicits a significant increase in the inward Icat at negative voltages and a parallel decrease in the outward current at depolarized voltages. We now show that Icat is also activated by a drop in extracellular Ca2+ to nanomolar concentrations, such as may occur during hypersynchronous neural activity and seizure. Reduction of [Ca2+]o resulted in complete loss of Icat rectification, massive influx of cations at negative potentials and consequent membrane depolarization. Using cell-attached recordings from Ca2+-activated K+ channels, we monitored membrane potential and changes in [Ca2+]i. Hypoxia elicited a large, reversible depolarization which was accompanied by up to 1000-fold increase in [Ca2+]i. These changes in Icat properties during hypoxia or during activity associated with seizures may contribute to neuronal vulnerability by providing a route for cation entrance and thereby depolarizing the neurons and increasing [Ca2+]i. It is noteworthy that many of the properties of Icat, including its partial blockade by La3+, are similar to those previously reported for TRP channel-mediated currents, which are also very sensitive to metabolic stress. It thus seems likely that in neocortex, as elsewhere, changes in the properties of TRP channels directly contribute to the neuronal pathogenic responses.

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Animal models for investigating the basis of the Thyroid hormon T3"s activity in the treatment of depression

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T3 is long being used in the clinical setting for treating depressed patients, in two major paradigms: 1) monotherapy- in which T3 is given as a sole agent. 2) augmentation and acceleration- in which T3 is given as a supplementation to an antidepressant in order to induce a response to the drug or to accelerate an existent response to it, respectively. In order to investigate the basis to this clinical activity of T3, we first employed the in vivo microdialysis technique in order to measure the activity of presynaptic inhibitory serotonergic receptors and serotonin levels in selected brain areas. We hypothesized that significant changes in these parameters values may account for the clinical effects of T3. These changes (namely: the desensitization of the receptors, and the elevation of the serotonin levels) were found, in male rats, in a way that more indicates T3's value as a sole pharmacotherapeutical agent and less as an effective supplement to increase or to accelerate the activity of another antidepressant. In contrast, the measured parameters didn't change appreciably in female rats, either in the model mimicking T3 monotherapy or in the augmentation model. In order to create a link between the pharmacodynamical changes we've measured and the known activity of T3 in the clinical setting, and in

order to further elucidate the gender differences found in the microdialysis experiments, we've employed the behavioral paradigm of the modified forced swim test to rats of both genders. No consistent effect was found in this test to T3 and fluoxetine given in low doses for 2 weeks, but high T3 doses given for a week did generate an antidepressant effect, but only in female rats, and only in a delayed fashion (72 hours after the last injection), again constituting a marked gender difference.

Distribution of the pro-apoptotic protein ARTS in rat brain

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The distribution of the pro-apoptotic protein ARTS (Apoptosis Related protein in the TGF-beta Signalling pathway) has been examined by immuno-histochemical technique in normal rat (Sprague-Dawley) formalin-fixed brain. The antibody employed (K21) was directed against the unique C-terminal 27 amino acids of the human ARTS molecule. This antibody gave a single dominant band in rat brain tissue (cortex, striatum and cerebellum) by Western blot at apparent molecular weight of about 27 Kd, similar to that of human ARTS. ARTS was constitutively expressed in a proportion of neurons in most parts of the brain. In cortex many ARTS-positive cells were seen in the external and internal pyramidal cell layers. The piriform cortex showed a high density of stained cells. In hippocampus, most neurons in the pyramidal cell layer were ARTS-positive. In striatum, medium spiny neurons were generally not ARTS-positive, but a small number of interneurons showed dense ARTS staining. In the substantia nigra, neurons of both pars compacta and pars reticulata showed ARTS-positive staining in cytoplasmic and nuclear components. Double fluorescent staining was performed to detect co-localisation of ARTS and tyrosine hydroxylase in the pars compacta. Most ARTS-positive neurons were not tyrosine hydroxylase-positive, but a small percentage of neurons were positive for both ARTS and tyrosine hydroxylase. In many, but not all neurons, ARTS occurs in nuclei as well as in the cytoplasmatic compartment. This contrasts with the picture seen following ARTS over-expression in peripheral cell lines such as Cos, Hela, in which ARTS has a predominantly mitochondrial occurrence, and enters nuclei at the onset of apoptosis. The significance of this finding is not currently clear.

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Expression of the pro-apoptotic protein ARTS in normal human brain and in Alzheimer"s and Parkinson"s diseases.

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The pro-apoptotic protein ARTS (Apoptosis Related protein in the TGF-beta Signalling pathway) is a broadly expressed 32 Kd septin-like protein found in a variety of tissues including CNS (Larisch et al, 2000). Following transfection of ARTS in COS, HeLa and A549 cell lines, apoptosis induction by several different pro-apoptotic stimuli is enhanced. The occurrence of ARTS in normal and Parkinsonian (PD) brain has been studied by immunohistochemistry, and in PD and Alzheimer's disease (AD) brain by Western blotting using antibodies specific for the unique C-terminal 27 amino acids of the ARTS molecule. Expression of ARTS in individual neuronal cells was studied in paraffin blocks of tissue from cortex (cx), hippocampus (hp), cerebellum (cb), striatum (st) and mesencephalon (ms). In cx and hp, light ARTS-immunopositive staining was seen in a small proportion of neurons, mainly the large pyramidal cells. Cb and st were largely ARTS-immunonegative. In ms, ARTS-positive cells were seen in periaqueductal gray, pontine nucleus, red nucleus and substantia nigra. In the latter areas, the intensity of staining was markedly increased in PD brains. ARTS expression level was quantitated by Western blotting from deep-frozen tissue. Similar levels were seen in cx (inferior temporal gyrus) of normal, PD and AD brain, and in st of normal and AD brain. Brain ARTS has a lower apparent molecular weight (about 28 Kd) than peripheral ARTS. Although ARTS levels do not markedly change in PD or AD brain, individual neurons may express high levels during the brief period of time that the apoptotic process is active.

Supported by a grant from the Chuttick Foundation, Technion Larisch S et al (2000) ARTS, a novel mitochondrial septin-like protein, mediates apoptosis dependent on its P-loop motif. Nature Cell Biol., 2:915-21.

The Role of a Reference Tone in Auditory Discrimination Tasks

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Auditory discrimination tasks are often used in testing verbal working memory. Tasks are defined as easy or hard based on the memory resources necessary to achieve success. Previous research found that the presence of a reference tone aids in the performance of difficult discrimination taks. A simple discrimination task asks the subject to make a simple judgement about a tone pair, e.g. if two tones are the same or different. A difficult task requires a more detailed judgement, like identifying which tone in a pair is the higher tone. It has been found (K. Banai '04) that if one tone is a fixed reference, i.e. it is always the lower tone, then the difficult task becomes easy. To further investigate the efficacy of the reference tone we divised a new task where the reference tone was always 1000 Hz, but sometimes it was higher and sometimes it was lower than the other tone in the pair. 23 teenage girls were tested in the six conditions - fixed reference, variable reference and no reference in the simple and difficult paradigms. In the simple paradigm the just noticible differences (JND) for the variable reference condition were the same as in the fixed reference condition (~7% vs. ~10%). In the difficult paradigm, on the other hand, JNDs in the variable reference condition were like those when no reference was present (~20%). These results indicate that a reference is only useful when it can be given a label – in this case "low". Possibly, this ability to categorize is what changes a difficult task, using more memory resources, into a simpler, less demanding task.

DHEA and cocaine seeking behavior

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The aim of this study was to determine weather neurosteroids are involved in cocaine addiction and abuse. The effect of chronic DHEA injection on cocaine–seeking behavior was tested using the self-administration model. In addition rats were tested for brain neurosteroids levels following chronic exposure to cocaine. We also tested brain levels of different neurotransmitters (NT) known to be involved in the brain reward system, following chronic DHEA injection. Behavioral tests showed that DHEA attenuates cocaine-seeking behavior in rats. Biochemical tests revealed that DHEA elevates levels of relevant NT's (DA, 5-HT) in brain regions involved in the reward system. We also found that chronic exposure to cocaine increases the levels of neurosteroids in different brain regions. Conclusions: neurosteroids are involved in mood, motivation and reward. DHEA modulates the response to cocaine reward, acting as an anti-craving agent. Increased DHEA brain levels following cocaine self-administration support a protective role for this neurosteroid by helping to maintain homeostasis of the involved neuronal systems and possibly protecting them from extreme conditions.

SR141716A improves cognitive and neurological function in a model of secondary biliary cirrhosis in the rat

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Background/Aims: Hepatic encephalopathy (HE) is a major neuropsychiatric complication of both acute and chronic liver failure. However, the pathogenesis of this disease is still unknown. It has been suggested that the cognitive deficits characterizing this state result from changes in some neurotransmitter systems in the brain, including the glutamatergic, cholinergic and monoaminergic systems. These changes may result from an ammonia accumulation in the circulation and in the brain due to an impaired metabolism of this substance by the liver. Endocannabinoids function as neurotransmitters and immunomodulators in the CNS via specific receptors. Recently the endocannabinoid system was found to be involved in the vasodilated state associated with liver cirrhosis. Aims: We hypothesize that the endocannabinoid system might be involved also in Hepatic encephalopathy. Methods: Male, Sprague-Dawley rats were subjected to a ligation of the bile duct (BDL), under ketamine hydrochloride anesthesia. Sham operated animals were used as controls. 2 and 4 weeks post-surgery, animals receiving either vehicle or SR141716A, a CB1 receptor antagonist, were evaluated for cognitive and neurological function in the Morris Water Maze and in the Neurological Severity Score (NSS) tests, respectively . Results: Cognitive function in the Morris Water Maze was significantly impaired in the BDL rats 2 and 4 weeks post surgery. SR141716A improved these deficits in the BDL animals compared to controls. NSS was significantly higher in the BDL group compared to the sham group and SR141716A returned this score to normal values in BDL animals. Conclusion: These results indicate an involvement of the endocannabinoid system in the pathogenesis of HE. Modulation of this system by CB1 cannabinoid receptor might have therapeutic potential.

Studying the representation of the human body schema using fMRI

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In primates, multimodal neurons representing peripersonal space, respond to tactile stimuli applied to the hand, and to a visual stimulus when present in proximity to the monkey's hand. This indicates the existence of a mechanism for integrating visual-tactile information, which is centered on body parts. Analogously, recent neuropsychological studies with extinction patients, suggest a multisensory representation of nearby space in humans. Such a representation should lead to different patterns of activity when a visual stimulus is approaching a body part, than when it is far from the body (although both stimuli are present in the same position on the retina). Using fMRI, we tested this hypothesis: we presented visual stimuli moving towards a target on the subject's hand ("near"), and compared it with the case in which the same stimuli are moving towards a further target ("far"). The contrast between the "near" and "far" conditions showed substantial activation in frontal and parietal areas (BA 6 and 40), which correspond to regions representing peripersonal space in monkeys. To account for possible differences stemming merely due to the different locations of the visual stimuli in the two conditions, we repeated the same procedure, only this time the subject's hand was positioned far away from both stimulus trajectories. However, under these conditions, no differential activation was seen in the referred areas. These results suggest that visual information in these areas is encoded in the hand's coordinate frame. Future experiments will examine whether the hand position is visually determined, or rather based on proprioception. Our results may shed more light about the way information from different modalities (i.e. vision, touch and proprioception) are integrated to form the human body schema.

A dual role for cAMP in regulating myelin phagocytosis by microglia/macrophages

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Microglia/macrophages play critical roles in CNS and PNS injury and disease. One is the removal of degenerating myelin by phagocytosis. Myelin degeneration occurs after injury to axons and in autoimmune demyelinating diseases such as multiple sclerosis and EAE. Degenerated myelin inhibits axonal regeneration and further activates the complement system to form membrane attack complexes that disintegrate intact myelin and axons. The rapid removal of degenerating myelin is vital, therefore, for repair and for minimizing damage to intact myelin and axons. In injury, myelin phagocytosis is mediated by complement-receptor-3 (CR3/MAC-1) and scavenger-receptor-AI/II (SRAI/II). We examined the role of cAMP in CR3/MAC-1 and SRAI/II mediated myelin phagocytosis. Elevation of cAMP levels by 8-bromo-cAMP (mimics cAMP), forskolin (activates adenylyl cyclase to produce cAMP) and IBMX (inhibits phosphodiesterases that hydrolyze cAMP) inhibited myelin phagocytosis. Pertussis toxin, which elevates cAMP levels by inhibiting Gi protein mediated inhibition of adenylyl cyclase, further inhibited myelin phagocytosis. Gi protein coupled receptors may thus up-regulate myelin phagocytosis by inhibiting adenylyl cyclase and consequently reducing cAMP levels. cAMP-dependent protein kinase A (PKA) mediates most of the effects of cAMP. We thus expected PKA inhibition to augment phagocytosis. Surprisingly, PKA inhibition by H89 and PKA-inhibitor peptide, inhibited myelin phagocytosis. cAMP activated PKA thus augmented myelin phagocytosis. A dual role – augmentation and inhibition of CR3/MAC-1 and SRAI/II mediated myelin phagocytosis – is thus suggested for cAMP. Such dual effect could take place by cAMP acting in distinct cellular compartments; via PKA and as yet unidentified another target molecule(s).

In-context training prior to stress exposure reduces the after-effects of the stressor: The role of brain derived neurotrophic factor (BDNF)

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Posttraumatic Stress Disorder (PTSD) does not develop in everyone exposed to a traumatic event. It is quite clear today that exposure to the stressor alone is not sufficient to trigger the disorders, and in fact a minority of those exposed will go on to develop the full-blown clinical conditions. Premorbid vulnerability and risk factors, are under extensive study, both at the behavioral and molecular levels. The aim of this study was threefold: to study the effect of in-context training prior to stress exposure on vulnerability and resilience in the development of acute and long-term behavioral changes in an animal model of post-traumatic stress disorder; to seek evidence for the involvement of these molecules; and to address the question whether circulating levels of corticosterone influence the expression of the neurotrophic factors. Rats were randomly divided into 4 groups: 1) Trained rats in the Morris water-maze for 2 days (8 inputs /day) to locate the hidden platform (trained only). 2) Same as the first group plus an under-water trauma (30 seconds) the next day (trained + stress). 3). Naïve rats (Naïve). 4). Naïve animals that exposed to under water trauma (Naïve + stress). One day after the trauma the rats were tested for behaviors associated with PTSD, including anxiety-like behavior as measured by the elevated plus-maze, hyperarousal as measured in the acoustic startle response, and spatial learning in the Morris water-maze. 24 hours later, the rats were sacrificed and blood (for corticosterone) and brains area (for neurotrophic factors) were collected. Our preliminary results have clearly shown that in-context spatial learning prior to underwater stress reduced the after-effects of the stressor and reduced the posttraumatic stress response in rats. Moreover, trained animals were less affected by the stressor than naïve (but handled) animals. The role of brain derived neurotrophic factor will be discussed.

Hypothalamic beta-endorphin and the HPA axis in two different genetic animal models of childhood depression

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A consistent finding in biological psychiatry is that hypothalamic-pituitary-adrenal (HPA) axis function is altered in adults and children with major depression. Recently, we found that juvenile rats from two different depressed lines- the Flinders Sensitive Line (FSL) and their controls, Sprague–Dawley (SD) rats, and the Wistar Kyoto (WKY) line and their controls, Wistar rats, show abnormality of the HPA axis. FSL juveniles demonstrated significantly lower plasma levels of corticosterone and ACTH, compared to their controls, while WKY juveniles demonstrated significantly higher plasma levels of corticosterone and ACTH compared to their controls. Experiment 1 asked if these two different depressed lines have different basal levels in the hypothalamus of a neuropeptide which has behavioral effects diametrically opposite to those of ACTH – beta-endorphin. Experiment 2 examined HPA axis function of these two lines after chronic stress (-two weeks of social isolation). FSL juvenile rats demonstrated significantly higher basal levels of beta-endorphin and lower plasma levels of corticosterone and ACTH after chronic stress, compared to their controls, while WKY juveniles demonstrated similar basal levels of beta-endorphin, and similar plasma levels of corticosterone but lower plasma levels of ACTH after chronic stress, compared to their controls. Both depressed lines showed significantly lower levels of HPA hormones after chronic stress compared to basal levels, while the control lines showed stable unaltered levels of these hormones compared to basal levels. These results suggest that both FSL and WKY are genetic animal models of depression in adolescent rats, exhibiting distinct abnormal patterns of the HPA axis function at basal and reactive states.

Gene expression profiling of Parkinsonian substantia nigra pars compacta; Alterations in ubiquitin-proteasome, cell adhesion/cellular matrix and related genes

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Gene expression profiling of human substantia nigra pars compacta (SNpc) from Parkinson's disease (PD) patients, was examined employing high density microarrays. We identified alterations in the expression of 137 genes, with 68 down regulated and 69 up regulated. The down regulated genes belong to signal transduction, protein degradation (e.g. ubiquitin-proteasome subunits), dopaminergic transmission/metabolism, ion transport, protein modification/phosphorylation and energy pathways/glycolysis functional classes. Up-regulated genes, clustered mainly in biological processes involving cell adhesion/cytoskeleton, extracellular matrix components, cell cycle, protein modification/phosphorylation, protein metabolism, transcription and inflammation/stress (e.g. key iron and oxygen sensor EGLN1). One major finding in the present study is the particular decreased expression of SKP1A, a member of the SCF (E3) ligase complex specifically in the substantia nigra (SN) of sporadic parkinsonian patients, which may lead to a wide impairment in the function of an entire repertoire of proteins subjected to regulatory ubiquitination. These findings reveal novel players in the neurodegenerative scenario and provide potential targets for the development of novel drug compounds.

Activity-dependent neuroprotective protein regulates neurogenin1: A novel gene important for neurogenesis

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Activity-dependent neuroprotective protein (ADNP) was recently cloned in our laboratory (J Neurochem 1999, 72, 1283; J Biol Chem 2001 276, 708). ADNP is a novel zinc fingers and homeodomain - like profile containing protein. In a previous study, mouse ADNP was shown to be expressed at E7.5 with gradual increases during embryogenesis (Brain Res Dev Brain Res 2003 144, 3). To assess the function of ADNP, knockout mice (KO) were established. Embryos lacking the ADNP protein were shown to die at E9-E9.5, an embryonic stage at which a series of major developmental events takes place. ADNP KO embryos were impaired at the stage of neural tube closure and brain formation. The current study was set out to reinforce these previous findings while revealing the specific pathways through which ADNP operates. A 14000-Affymetrix gene array was used in order to compare gene expression patterns of ADNP KO embryos to normal and heterozygous littermates. Data was analyzed using the Affymetrix web tools and the novel expender and prima software (Elkon et al. Genome Res. 2003, 13, 773). The data analysis enabled the partial deduction of a presumed mechanism by which ADNP deficiency may cause lethality as follows. The lack of ADNP expression resulted in a dramatic down-regulation of a number of essential genes such as neurogenin1 and neuroD1 as well as genes that are associated with neuronal development and activity, such as galanin. Using non denaturing protein gel electrophoresis we have now shown that ADNP may interact directly with the neurogenin1 promoter. As neurogenin1 has been intimately associated in neurogenesis pathways (Geling et al., Development. 2004 131, 1993) the current study places ADNP as a key player in neurogenesis.

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Modulation of the GABAeric system following prenatal hypoxia in mice; partial protection by magnesium sulfate

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Fetal low brain oxygenation is associated with increased risk of fetal brain damage. Loss of GABAergic neurons was demonstrated, in particular following perinatal asphyxia and anoxia in rats. A prophylactic treatment is maternal loading with MgSO4 (Mg). We have previously shown that Mg partially prevented the fetal damage induced by hypoxia. Here we examined components of the GABAergic system in brains of adult mice, after prenatal hypoxia (PH-2h of 9%O2, 3% CO2 on E17) and the interaction of Mg pretreatment (4h Mg 75mg/kg) with the hypoxic effect. Using IHC we show that PH did not modify the immuno-reactivity to glutamate-decarboxylase 65/67 (GAD, expressed in inhibitory cell soma and synapses) in the primary motor cortex (M1) region. However, when combined with Mg an increase in GAD was observed in layers 2-3 of M1. In contrast, the number of Parvalbumin (PV) cells in layers 2-3 of M1 was decreased by PH (73% of control, $P<0.01$), this effect was prevented by treatment with Mg. In layers 5-6 of M1, PH had a stronger effect: reduced number of PV cells to 45% ($P<0.01$). In these layers Mg did not protect against cell loss but enhanced the effect of PH as indicated by reduction in PV cell number to 20% ($P<0.01$). In the hippocampus PH did not affect the expression of GAD in the CA1 and in the hilus, though the number of PV cells in the hippocampus was reduced to 45% ($P<0.01$) of the control mice. This was not prevented by Mg (44%, $P<0.01$). When the effect of Mg alone was

tested we found an elevation of GAD in M1 layers 4-6 ($P<0.05$) and the hippocampus ($P<0.01$, compared to control. In contrary, PV cell loss was observed in M1 layers 4-6 ($P<0.01$) and the hippocampus ($P<0.01$). Our data indicate that hypoxia induced loss of PV cells without affecting GAD. Lack of effect on GAD could suggest that hypoxia induced an increase in inhibitory synapses to compensate for the PV cell loss. Alternatively, differentiation of other types of inhibitory neurons may be facilitated.

Neuroprotective influence of plasminogen activator during CNS inflammation.

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Multiple sclerosis (MS), a demyelinating disease of the central nervous system (CNS), is characterized by perivascular infiltrates containing auto reactive T cells and macrophages. Extracellular proteases such as plasminogen activators (PA) and matrix metalloproteinase (MMP) play a role in tissue remodeling and response to injury. In the present study we tested the role of PA in axonal and myelin damage during CNS inflammation in experimental autoimmune encephalomyelitis (EAE), the latter being the animal model used for MS studies. EAE was induced in mice lacking tissue PA (tPA -/-), urokinase PA (uPA -/-) and uPA receptor (uPAR -/-). In comparison to the wild type group, all knockout (ko) mice exhibited more severe neurological dysfunction, tPA -/- mice displaying most severe clinical symptoms. The extent of demyelination and axonal loss correlated with aggravated clinical outcome. T-cell reactivity towards the encephalitogenic peptide MOG 35-55, was reduced in ko animals while macrophage responses were enhanced. The urokinase derived peptide, A6, that blocks the interaction between uPA and its receptor, markedly inhibited encephalitogenic T-cell reactivity. Our results indicate that the PAs system is involved in axonal and myelin damage occurring during EAE in CNS tissue. Accordingly, we suggest that the PAs system may be a potential target for treatment of CNS inflammatory and demyelinating disease.

The Posner Spatial Orientation Paradigm as an Examination of Lateralized Striatal Dysfunction in OCD

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The frontal cortex and striatum have consistently been proposed as possible sites of dysfunction in OCD, based on converging evidence including neuroimaging studies emphasizing abnormalities in neural loops connecting these areas. There is increasing evidence attributing OCD to lateralized CNS pathology, but research is inconsistent with respect to which hemisphere is preferentially involved, and in what manner. The present study employed the Posner spatial orientation paradigm, which has been used to study lateralization in psychiatric and neurological cases, in an attempt to examine patterns of lateralized dysfunction in OCD. Seventeen OCD patients were compared with ten healthy controls on reaction time and asymmetry measures derived from the paradigm. Comparisons were also carried out after subdividing the patient group based on demographic and clinical data, to examine relationships between task performance and specific characteristics of OCD. Control subjects responded significantly faster to targets in the left visual field than to those in the right, while in OCD patients this asymmetric pattern was absent or reversed, in line with earlier suggestions regarding lateralized pathology in OCD. The lack of asymmetry was positively correlated with obsession severity, particularly for aggressive and sexual obsessional content, supporting recent findings relating different symptom dimensions to distinct components of fronto-striato-thalamic circuits involved in OCD. The altered pattern of asymmetry was not related to medications influencing the serotonergic system, suggesting that one or more chemical systems additionally implicated in OCD are more directly related to the lateralized deficits. The relevance of the dopaminergic system is discussed, based on the nature of its involvement in the modulation of attention.

The infralimbic prefrontal cortex is required for consolidation and reconsolidation of object recognition memory

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Consolidated memory could regain susceptibility to consolidation blockers upon its reactivation. This process of destabilization and the ensuing restabilization of reactivated long-term memory is termed reconsolidation. It has been shown that both consolidation and reconsolidation require protein synthesis, but it is not yet known how similar these processes are, in terms of molecular, cellular, and circuit mechanisms. Here we aimed to examine the role of infralimbic cortex (IL) in consolidation and reconsolidation of object recognition memory involving spontaneous exploratory behavior of the rat. We found that the protein synthesis inhibitor anisomycin and the N-methyl-D-aspartate (NMDA) receptor antagonist D,L-2-amino-5-phosphonovaleric acid (APV), infused in the IL immediately following the recognition training phase, resulted in failure to discriminate between the old and new object 24 hrs later. This indicates that the drug treatments have disrupted consolidation of the recognition task. In contrast anisomycin and APV to the IL had no effect on short-term memory. We also found that anisomycin and APV infused in the IL immediately following reactivation of the memory trace by brief reexposure to the learned objects, resulted in failure to discriminate between the old and new object 48 hrs later. Thus, the drug treatments have disrupted reconsolidation of long-term recognition memory. The present findings show for the first time that the IL is necessary for long-term consolidation and reconsolidation of recognition memory, and that both processes are dependent on protein synthesis and NMDA receptor function.

PRS-211,375, a novel CB2 selective cannabinoid agonist, with neuroprotective effect in thre animal model of MS

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Numerous studies report that cannabinoids have beneficial effect in the treatment of neurodegenerative diseases. Cannabinoids have two identified receptors, the CB1 receptor located in the central nervous system, and the CB2 receptor, expressed by immune cells. PRS-211,375, a synthetic CB2 selective cannabinoid receptor agonist developed by Pharmos, was tested for its effect in 3 EAE animal models for MS. The models were: (i) MBP induced acute EAE in rats; (ii) PLP induced remitting relapsing EAE in mice; (iii) MOG induced progressive EAE in mice. PRS-211,375 60 mg/kg administered PO after the clinical signs occurred (i.e. as treatment), reduced the clinical score induced by MBP by 1 point as compared to vehicle control (2.5 ± 0.3 vs. 1.5 ± 0.2, $p<0.05$). PLP resulted in 3 relapse - remitting episodes. Treatment with 60 mg/kg of PRS-211,375 after the first relapsing event postponed the initiation of the second relapsing event by 5 days and reduced the severity of this event (0.8 ± 0.1 vs. 0.5 ± 0.1). Finally, PRS-211,375 treatment resulted in inhibition of MOG induced EAE progression in a dose dependent manner. Daily administration of 40 mg/kg and 60 mg/kg completely stopped the disease progression. Taken together, these data show that PRS-211,375 administered PO, as treatment was highly beneficial in controlling EAE progression in three animal models. This suggests highly therapeutic potential of PRS-211,375 in the treatment of MS patients.

Subthreshold cross-correlations between cortical neurons: A reference model with static synapses

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The structure of cross-correlations between subthreshold potentials of neocortical neurons was recently examined. Characteristic features included broad widths and significant peak advances. It was suggested that dynamic synapses shape these cross-correlations. Here a reference model is developed comprising leaky integrators with static synapses. Subthreshold correlations are derived analytically for two different forms of synaptic input: steady drive and populations bursts. For the latter case the model captures the widths seen in experiment. However, the model could not account for the peak advance. It is concluded that models with static synapses lack the necessary biological details for describing cortical dynamics.

Slow and sustained oscillations emerge in a network with dynamic synapses

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Emergent neocortical oscillations have been broadly studied, both experimentally and theoretically, for their ability to convey information. However, the mechanisms that induce sustained oscillations in neural microcircuits are still largely unknown. Using a firing rate model to represent interconnected excitatory and inhibitory populations with constant external inputs, we showed that activity dependent synapses give rise to slow and sustained oscillations in the network. We found that the dynamic mechanisms of the synapses determine the frequency and shape of the oscillations. Networks with slow (timescale of seconds) facilitating synapses generate population burst activity. When fast (hundreds of milliseconds) facilitating synapses are incorporated, the networks generate sinusoidal synchronized activity at higher frequency. These results suggest a novel role for facilitating synapses in shaping the oscillations in neocortical neural circuits.

Regional disturbances in axonal integrity are involved in first episode schizophrenia: Evidence based on high b-value diffusion weighted imaging

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Accumulating evidence is pointing to disturbed neural connectivity as source of brain abnormality in schizophrenia. Diffusion tensor imaging showed decreased anisotropy in various white matter regions, suggesting reduced organization along some white matter tracts. However the physiological significance of these findings is not clear. Recent works using high b-value diffusion imaging have shown that this method might be more reflective of white matter pathophysiology as it relates to intra-axonal water. Six first episode symptomatic paranoid schizophrenia patients and five healthy subjects underwent MRI scan with a high b value diffusion imaging protocol. Image histogram of the high b value images from the acquired brain volume revealed a decrease in the values corresponding to white matter, indicating loss of white matter volume and integrity in the schizophrenic group. The three peaks, corresponding to white matter, gray matter and CSF, were extracted via spectral analysis, exhibiting a lower WM peak in the schizophrenic group ($t=-3.5$, $p<0.01$). Region of interest blind analysis of both groups found that these white matter changes originated mainly from superior and middle frontal gyri, revealing a nearly significant difference in left frontal regions ($t=-2.12$, $p=0.06$), while no such effects were seen in fibers of the superior temporal gyrus and occipital areas. These results suggest that white matter damage measured by high b value DWI is a pathological brain marker in schizophrenia that can be detected in the individual patient level. Brain atrophy has been shown in previous studies in frontal and temporal regions. We show, however, that white matter damage is more evident in frontal areas. This finding suggests disturbed connectivity of fiber bundles reaching the PFC, presumably involved in early stage brain abnormalities in schizophrenia.

What does it take to make a stable taste memory?

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We are interested in understanding the process of memory consolidation. For this purpose we use a taste learning model. Using the Condition Taste Aversion (CTA) paradigm and latent inhibition of CTA (LI), we learn about the properties of this labile phase. Using Latent Inhibition paradigm we find that an input of 10 or 15 ml of saccharin 0.1% creates LTM and reduces significantly the aversion level to saccharin. (A volume of 15 ml causes a bigger reduction than a volume of 10 ml does). However, smaller volume of 5 ml of saccharin 0.1% does not create LTM. Following the definition of sub-threshold taste input we tested the hypothesis that strong input will facilitate memory consolidation of a weak input. Indeed, an input of 5 ml of saccharin 0.1% (weak input), which normally does not create LTM, did create LTM (reduced the aversion level to saccharin) when an input of 10 ml NaCl 0.3% (strong input), was given 30 min before it. Additionally, when we increase the time interval between the two inputs up to 5 h, there is no reduction in the aversion level to saccharin. Our results are in accordance with the electrophysiological results known as the tagging hypothesis. Key words: Consolidation, CTA, Latent Inhibition, Tagging hypothesis.

A new platform to study the molecular mechanisms of exocytosis

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The exocytotic process in neurons and neuroendocrine cells consists of a sequence of reactions between well-defined proteins. In the present study, we have, for the first time created, a comprehensive kinetic model that reconstructs the physiological process using a standard chemical kinetic formalism. The interactions between the synaptic proteins were transformed into differential rate equations that, upon their integration over time, reconstructed the experimental signal. The model can perfectly reconstruct the kinetics of exocytosis, the calcium-dependent priming and fusion processes and the effects of genetic manipulation of synaptic proteins. The model suggests that fusion occurs from two parallel pathways and assigns precise, non-identical synaptic protein complexes to the two pathways. In addition, it provides a unique opportunity to study the dynamics of intermediate protein complexes during the fusion process, a possibility that is hidden in most experimental systems. We have used the Genetic Algorithm analysis to achieve high level of accuracy and to find a single global minimum, over a multi dimensional parameter space. Our study demonstrates that complex biological processes can be mathematically modeled and gain high predictive power, up to the level of serving as research tools. It is our intention to expand the model from the level of a comprehensive description of the whole exocytotic process, to the level of cell physiology.

In vivo two-photon imaging of newborn neurons in the adult mouse olfactory bulb

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As a consequence of adult neurogenesis the olfactory bulb (OB) receives a continuous influx of newborn neurons well into adulthood. Although general features of neurogenesis have been described, how newborn neurons intercalate into adult circuits, their rates of generation and elimination, and the factors controlling their survival remain enigmatic. To visualize the dynamics of adult neurogenesis, we developed a strategy combining genetic manipulations and in vivo imaging that enabled us to image the development of newborn neurons into the adult OB. We produced a line of

transgenic mice expressing green fluorescent proteins (GFP) driven by the Thy-1 promoter. This new line expressed GFP in a subset (77%) of periglomerular neurons (PGNs). These GFP-labeled PGNs comprise a range of phenotypes including GABA, dopamine, calbindin and calretinin. GFP expression levels are relatively weak but individual cell bodies can be readily imaged using in vivo two-photon microscopy. Time-lapse analysis of PGN cell bodies (n=150, 3 mice) over several weeks reveals a detectable, but low, neuronal turnover rate of ~2% per/month. While new neurons appeared and older ones disappeared, the number of PGNs remained constant. This approach provides the first dynamic view of the actual appearance and disappearance of neurons in the mammalian central nervous system.

On The Significance of In Vivo Observed Patterns in Membrane Potential Dynamics During Spontaneous Activity of Cortical Neurons.

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Several studies report existence of recurrent patterns in cortical activity.It has been suggested, that information is propagated by precisely timed sequences of synchronous activity (Abeles et al. 1993), but there is a controversy regarding the stochastic nature of theses events (Oram et al. 1999). A recent in vivo study reports existence of repeating motifs during long(10 – 20 min) cortical intra-cellular, recorded spontaneous activity (Ikegaya et al. 2003). Following up Ikegaya et al., and using the same similarity index (SI), we further analyze the nature of observed repeating motifs during spontaneous activity of single neurons in rat barrel cortex. These preliminary results are based on several patch-clamp intracellular, high resolution recordings of neurons in a lightly anesthetized rat. All recorded traces showed to have repeating patterns to different extents. Using a Bayesian formulation, we quantified the degree to which patterns are found in a recorded data. Our analysis shows that the probability of finding a pattern is much affected by slow changes in membrane potential dynamics. To test this further, we produced a surrogate data, with the same power spectrum as recorded data but phases of frequency components being random. This procedure has its own limitiation since original data contained spikes which introduced high frequency components,. As we expected, surrogate data contained a significant portion of repeating motifs, but less than observed in original data. These findings indicate that power spectrum of neuron's electrical activity, and especially slow components of the power spectrum, can account for a significant portion of the above chance level SI scores observed in spontaneous activity. However, further investigation is required for better understanding the nature of recurrent patterns during spontaneous activity of cortical neurons, and their relation to power spectrum and spiking behaviour.

In-vivo study of coupled neural/synaptic dynamics in an autonomously learning neural network

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We study the behavior of a spike-driven long-term plastic synapse model embedded into a recurrent network of spiking neurons. The resulting coupled neural/synaptic dynamics enables the network to dynamically store and recall a set of randomly coded stimuli, following training, in which the set of stimuli is repeatedly presented in random order (stimulus-delay) (Mongillo, Curti, Romani, Amit 2004). The patterns of neural activity exhibited by the network before, during and after training reproduce most of the details physiologically observed in-vivo (Shadlen & Newsome 1998, Erickson & Desimone 1999). The synapse is characterized by an internal, bounded analog variable with time constant ~ 10ms. The dynamics of this variable is driven by presynaptic spikes and coincident postsynaptic depolarization levels. Long-term stability is ensured by a refresh mechanism. The resulting plasticity mechanism is biologically realistic, producing behaviors similar to most experimental in-vitro protocols of long-term plasticity. A network of spiking neurons with these synapses displays in vivo-like patterns of neural activity. The plastic synapse behaves so that: 1. In absence of external, relevant stimulation, the acquired synaptic structure persists over very long time scales; 2. Upon stimulation, it produces long-term plasticity, on short time scales (~ 100ms), within the activated synaptic populations: High pre- and postsynaptic emission rates produce LTP, high pre- and low postsynaptic rates produce LTD. It endows the network with a stable, Hebbian learning process. We study the dependence of the long-term plasticity dynamics on the characteristics of the stimulus response (average emission rates, time course, synchronization), and on the statistics of firing times (CV).

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Precise fidelity of human auditory cortex neurons during cinematic stimulation

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Cortical neuronal activity is highly variable even under tightly controlled stimulation paradigms. Previous studies in the monkey have found the level of this variability to be on the same order of magnitude as the response itself. Therefore in order to reach sufficient signal-to -noise ratio numerous repetitions of the same stimulus are needed. Hence, it may be inferred, that during complex and continuous natural stimulation this variability may even be accentuated. Here we report that surprisingly, single neuron responses recorded in the human temporal lobe during exposure to a popular movie, manifested a highly reproducible stimulus-locked modulation, with average correlations above 0.5. This reproducibility was apparent even when only two repetition of the movie were compared. This high fidelity was particularly striking in human auditory cortex where the correlation between first and second movie presentation reached as high as 0.8. Although it may appear that such high fidelity implies highly linear relationship to the acoustic stimuli, in fact the neuronal responses appeared highly non-linear showing particular selectivity for spoken words and musical phrases. Interestingly, the high fidelity of the neuronal responses was expressed only at temporal windows of 300 msec and higher. These results reveal precise reproducibility of single neuron responses across repeated presentations of natural stimuli, but also suggest a limit of "temporal graininess" of the neural code expressed by human temporal lobe neurons.

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Development of dendritic spines in the rodent anterior cingulate cortex is modulated by prenatal stress

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Studies in rodents and non-human primates demonstrate that maternal stress during pregnancy dramatically influences fetal brain development, resulting in behavioral and endocrine abnormalities. In humans, prenatal stress is believed to be a risk factor for developmental psychopathologies, such as schizophrenia and depression. Studies in prenatally stressed animals revealed altered emotional reactivity, anxiety, depressive-like behavior and deficits in cognition, learning and memory, however, very little is known about the effect of gestational stress on synaptic development in the limbic system. Based on previous behavioral studies (Weinstock, Stress 5: 167-176, 2002), our objective was to investigate the effects of

gestational stress on the development of synaptic networks in the prefrontal cortex of rats and to clarify if the presumed synaptic changes can be prevented or reversed by postnatal treatments such as daily handling of the offspring during the first 10 postnatal days. By using the Golgi-Cox staining technique we quantified the density of spine synapses and dendritic length of pyramidal neurons in the anterior cingulate cortex (ACd) in male pups of the following experimental groups: i) prenatally-stressed (PS), ii) PS + postnatal handling, iii) naïve controls, iv) naïve controls + postnatal handling. Our data indicates changes in the density of dendritic spines on basal dendrites and alterations in the length of apical dendrites between PS pups and PS pups, which were handled. Alterations in the length of basal dendrites were found in PS rats, compared to naïve controls. The results of this study provide the first evidence that prenatal stress and handling interferes with the development of cortical dendritic spines and dendritic growth. These synaptic changes might be causally linked to the behavioral abnormalities, which have been described after prenatal stress and handling.

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Are protein alterations in schizophrenia due to early environmental insult?

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Both genetic inheritance and perinatal environmental insult contribute to schizophrenia manifestation. Recent studies of the etiology of schizophrenia concentrate on the genetics of aberrant brain proteins or on epidemiological retrospective studies of environmental insults. Little is known concerning the biological and physiological processes, such as morphological changes, neural transmission and signal transduction, that mediate the environmental contribution. The neurodevelopmental hypothesis of schizophrenia suggests that an early life brain maldevelopment, predisposed and/or acquired, manifests the pathophysiology of schizophrenia later in life. Possible non-genetic risk factors for aberrant neurodevelopment are viral infection, starvation/malnutrition, stress, premature birth and perinatal hypoxia. A strategy to study the contribution of perinatal insults to schizophrenia is by induction of a risk factor in an animal model. We chose to address the search for etiological factors of schizophrenia by combining the two distinct approaches that dominate the literature, namely, the role of genetically aberrant brain proteins and perinatal insult. We are focusing on four distinct rat models for schizophrenia and assessing brain levels of six proteins that were found to be altered in empiric studies of postmortem brain from schizophrenic patients. We hypothesize that the alterations in the levels of some of these proteins may reflect the contribution of environmental insults to schizophtrenia rather than genetic factors of the disorder.

Speech Intelligibility & Binaural Interactions: Effects of Stimulus Familiarity, Stimulus Similarity & Set Size

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The magnitude of the contribution of binaural interactions to speech intelligibility, as measured by the Binaural Intelligibility Level Difference (BILD), is not well understood, and, in contrast to speech detection, has even been estimated as marginal. We reasoned that the magnitude of BILD may depend on stimulus characteristics and asked whether factors such as stimulus familiarity, inter-stimulus similarity and set size affect identification thresholds of speech in noise, under diotic vs. dichotic conditions. We tested 25 subjects under 8 different identification conditions that manipulated familiarity of the stimulus set (digits versus pseudo-words), similarity (changes in a single phoneme or in all phonemes) and set size (2 or 10 words). We applied an adaptive procedure to measure thresholds for 80% correct identification when noise was in-phase in the two ears, and stimulus was either in-phase or anti-phase. BILD is the difference between these thresholds. Identification thresholds depended significantly on all tested factors. Thus, highest thresholds were found for largest set, minimal familiarity, and maximal similarity (10 pseudo-words). The dominant factor for lowering of the threshold was similarity, while set size (2 vs. 10) was the weakest factor. On the other hand, the magnitude of BILD depended only on inter-set stimulus similarity, with no effect of set size or familiarity. Very small BILDs were found when stimuli were perceptually similar (~3dB), whereas up to 9dB were found when word pairs were very different. Taken together, our results show that all 3 factors examined affect absolute identification thresholds of speech in noise. On the other hand, the benefit of binaural cues may be rather small, as previously documented in the literature, depending on the structure of stimulus set. Surprisingly, however, quite large binaural effects were found when stimulus set consisted of words that differed along multiple perceptual dimensions.

Cholinergic modulation of inflammatory and autoimmune responses

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Various immune cells possess muscarinic and nicotinic cholinergic receptors as well as acetylcholinesterase (AChE). Down-regulation of pro-inflammatory cytokine production by activation of α7 nicotinic receptors was recently noted in macrophages. These observations prompted us to examine the effect of cholinergic up-regulation (CURE) on CNS inflammation using various AChE inhibitors. CURE induced by EN101 (anti-sense of AChE mRNA) ameliorated clinical and pathological symptoms of experimental autoimmune encephalomyelitis (EAE) in mice. Clinical improvement was accompanied by decreased ex-vivo reactivity of encephalitogenic T cells. Similarly, EN101 decreased human T-cell reactivity toward mitogens and TNF-α production, whereas, IL-10 production was unaffected. We have examined the efficacy of bifunctional compounds containing nonsteroidal anti-inflammatory drug (NSAID) and CURE moiety (pyridostigmine, AChE inhibitor), in EAE model in mice and obtained a significant reduction in clinical symptoms and T-lymphocytes reactivity. The bifunctioonal compounds IBU-PO and IBU-PD (Ibuprofen Octyl (or Decyl) Pyridostigmine) were tested in vitro in lymphocytes and astrocytes and inhibited dose-dependently at micromolar levels production of inflammatory mediators (nitric oxide and prostaglandin E2). The contribution of each component of the bifunctional compound to the attenuation of inflammation was evaluated. It was noted that both moieties could suppress lymphocyte reactivity to a lesser extent than the bifunctional compound. Thus, bifunctionals act synergistically compared to their components. Inflammatory mediators production was not affected by AChE inhibitors alone yet bifunctional compounds augmented the anti-inflammatory effect of the NSAID moiety. Our data are consistent with anti-inflammatory activity elicited by the ChEI moiety only when it resides in the bifunctional molecule.

Features of Human Movement Imitation

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Human movement imitation is a complicated phenomena, involving a transformation from perceived to executed movements. What are the features of movement that are being extracted and used in this transformation? We developed a novel experimental scheme to tackle this question using virtual movements. Two setups were developed along this scheme for arm and finger movement imitation. Using these setups, we investigated the hypothesis that observed movements are automatically mapped to the corresponding motor representation (the 'direct matching' hypothesis). We tested the 'direct matching' hypothesis by manipulating the orientation of observed movements, using several forced-choice tasks. In these tasks subjects had to perform one of two movements (for example lifting the index or the middle finger), as

quickly as possible, in response to the same movement of a virtual hand. We found an orientation effect (longer reaction-times for stimuli that are further rotated from the executing hand) in some tasks (e.g. lifting one of two fingers) but not in others (e.g. opening or closing of the hand). Based on these results, we claimed that in forced-choice imitation tasks subjects do not map observed movement into their own movement repertoire. We hypothesized that subjects extract simple, task-related features of the movement, for example, the appearance of the movement on the left or the right sides, in order to choose the appropriate response. By introducing another task, where subjects had to lift either their left or right arms in response to movements of a rotated human figure, we managed to directly contrast the two accounts for the transformation from perceived to executed movements in forced-choice imitation tasks, and to provide support for our task-related features account. Our results question the validity of using forced-choice tasks in behavioral (Brass et al., 2000) and fMRI (Iacoboni et al., 1999; Koski et al., 2003) studies of imitation.

Are voltage-gated calcium channels volume-regulated ion channels?

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Ion channels were originally defined according to their main mode of gating as; voltage-gated, ligand-gated, mechano-gated and volume-regulated ion channels. However, studies in recent years have demonstrated that ion channels may be gated, or regulated, by more than one modality. For example, it is well established that the activity of calcium channels can be regulated by a variety of ligands (neurotransmitters, G-proteins, protein kinases etc). In addition, recent studies have pointed to the possibility that voltage-gated calcium channels are osmosensitive or mechanosensitive. We examined the possibility that voltage-gated calcium influx may be regulated by alterations in cell volume. Our studies have shown that voltage-gated calcium influx in pituitary cells is suppressed by osmotic induced cell shrinkage, and augmented by osmotic induced cell swelling. In a series of control experiments we ruled out the possibility that this regulation of calcium influx, by cell-volume, can be attributed to alterations in cell membrane surface area (during cell shrinkage and swelling), to activation or inactivation of other ionic conductances or to changes in access resistance. Additional experiments have shown that this volume dependent regulation of voltage-gated calcium channels stems from alterations in the activity (NPo) of calcium channels but not from changes in single channel conductance. However, whether these changes in activity stem from changes in open probability (Po), or from changes in the number of channels activated (N), is still unknown. Hence, our results suggest that voltage-gated calcium channels in pituitary cells may also be considered as volume-regulated ion channels. The cellular mechanisms underlying this regulation are unknown yet. However, it is possible that alterations in mechanical membrane tension, or alterations in intracellular ionic strength, are involved in this regulation.

Tracing the affective modulation of cognitive brain activity with electrophysiological functional brain imaging

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Rationale: An experimental paradigm was designed to study the exact time course of the emotional modulation of cognitive brain activity. Brain activity related to emotional and cognitive processing has been typically traced with fMRI's temporal resolution of seconds. In this study, the time course of activation in the brain areas involved was traced with millisecond temporal resolution. Methods: EEG was recorded while 12 normal subjects performed an auditory cued attention task, in which cues, in most cases accurate, provided information on the appropriate response to a subsequent target tone. Verbal distracters, administered at different times between the cue and the target in one third of the trials, were first names. Distracters' subjective affective valence was assessed after the experiment using a validated questionnaire designed for that purpose. Evoked potentials to the targets were averaged according to the preceding cue's validity and the affective valence of the distracter. Potentials were averaged across different onset times of distracters, so that brain activity was locked in time to the targets but not to the distracters. Brain sources of scalp electrical activity were estimated time frame by time frame, for the 800 ms after target onset, using LORETA. Statistical comparisons were conducted in order to assess the effect of the distracters' affective valence on brain activity to the following target tones. Results: Brain response to targets was enhanced following distracters with subjective affective valence, compared to neutral distracters. The distinct activity pattern involved prefrontal cortex, secondary auditory cortex and limbic system association areas, depending on the subjective emotional significance of the preceding distracters. Summary: Processing of neutral tones was modulated by the subjective emotional significance of preceding distracters. Exact time course of the associated unique brain activity was characterized.

Endocannabinoid Signaling Regulates Bone Mass.

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Endocannabinoids signal via G-protein coupled central CB1 and peripheral CB2 cannabinoid receptors. Although both receptors were discovered more than a decade ago, the physiologic function of the CB2 receptor remains obscure. Here we report the presence of CB2 receptors in trabecular, diaphyseal and MC3T3 E1 osteoblasts as well as osteoclasts. Reminiscent of post-menopausal osteoporosis in humans, the skeletal phenotype of CB2 deficient mice, which are otherwise normal, is characterized by a low trabecular bone mass, cortical expansion and increases in bone formation rate and osteoclast number. To extrapolate these findings to the human scenario, we performed genetic association studies in a case-control approach typing single nucleotide polymorphisms covering a region of about 100 kb. We found a highly significant difference of allelic and genotypic distributions, strongly arguing for a causative involvement of this locus with human osteoporosis. In line with the low trabecular bone mass phenotype of CB2 knockout mice we found that HU-308, a specific CB2 agonist, stimulated dose dependently the number and activity of primary and MC3T3 E1 osteoblastic cells. Using the same dose range, HU-308 also restrained osteoclast differentiation of bone marrow derived monocytes. Most importantly, HU-308 attenuated ovariectomy-induced bone loss mainly by inhibiting osteoclast number. Collectively these results assign a skeletal regulatory role for the endocannabinoid system and offer a new molecular target for the diagnosis and treatment of osteoporosis.

The metabotropic glutamate G-protein-coupled receptor mGluR3 is voltage sensitive.

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G-Protein Coupled Receptors (GPCRs) comprise the largest superfamily of proteins in mammalians and play a key role in signal transduction processes. In spite of GPCRs being transmembrane proteins they are not considered to be voltage sensitive. Recently it was shown that the muscarinic M2 receptor is voltage sensitive. Here we examine whether a metabotropic glutamate receptor, a GPCR, exhibits voltage sensitivity. Using fresh rat brain synaptosomes we show that presynaptic glutamate receptors bind glutamate in a voltage dependent manner. Namely, Depolarization reduces the maximal binding of

[3H]Glu. Pretreatment of the synaptosomes with Pertussis Toxin (PTX) reduced the [3H]Glu binding altogether and greatly diminished its voltage dependency, indicating that the voltage dependent binding could be attributed to PTX sensitive metabotropic glutamate receptors. We used the heterologeous expression system of Xenopus oocytes to directly study the properties of mGluR3, a presynaptic receptor, and a member of the mGluRs of group II. mGluR3-mediated potassium channel currents were used to assay the activity of the receptor. We found that the apparent affinity of mGluR3 toward glutamate was reduced upon depolarization. We ruled out the possibility that the voltage sensitivity resides in steps that are downstream to the activation of the mGluR3 by glutamate. Our cumulative results are compatible with the notion that the mGluR3 exhibits, by itself, voltage sensitivity. In addition, the fraction of the high affinity receptors was significantly reduced in oocytes that did not overexpress Galpha. This, together with the abolishment of the voltage dependent binding in syneptosomes, in the presence of PTX indicates that the voltage sensitivity may reside in the region that couples to the G-protein. Furthermore, analysis of the time course of mGluR3-mediated K+ currents reveals that depolarization affects the Koff of the receptor.

Representation of magnitude in parietal cortex from quantity to number and back

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Numbers are represented in symbolic (Arabic & verbal) and analog magnitude format. Reflecting these formats, different, partially overlapping, representations are found in parietal cortex (PC; Dehaene et al., 2003). How are continuous quantities, such as size and luminance, encoded in the brain? It has been hypothesized that a single system in PC represents both the above-mentioned non-symbolic analog numbers and an abstract code of continuous quantities. This system is seen as a high-level magnitude estimator that produces the abstract value of a scaled magnitude and makes this value available for the cognitive or executive system. We tested a first prediction of this hypothesis: that this region should respond to a quantity value (e.g. object size) irrespective of the modality that senses it (visual or somatosensory), when the value is readout by the hand movement system and re-represented in terms of a corresponding amplitude of grasping-like finger movement. We applied a block-designed fMRI test (1.5 T; EPI). Three subjects evaluated the size (main condition) or surface texture (control) of different objects presented visually or explored haptically with the left hand. Then, by uniformly moving their right thumb and index finger on the surface of a textured sheet, they either indicated the size of the object (main condition) or compared the sheet texture with that of the object (control). We obtained differential fMRI signals (main condition minus control) in left intraparietal cortex and the superior parietal gyrus, areas overlapping the analog number representation. These preliminary data support the above hypothesis, that a single system represents both analog numbers and continuous quantities.

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3D-reconstruction and quantitative ultrastructural characterization of novel spines in hippocampus cultures

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Light-, confocal laserscan (CLSM- and electron microscopic studies in intact animals and cell cultures (Helmeke, Ovtscharoff jr et al., 2001, Cereb. Cortex, 11:717; Braun, Segal, 2000, Cereb. Cortex, 10:1045; Poeggel et al PNAS 2003, 100:16137) revealed that early stress can alter the densitiy of dendritic spines in prefrontal cortical and hippocampal areas. In order to identify the cellular mechanisms for this synaptic plasticity a spine-producing protocol in cultured hippocampal neurons (Goldin et al 2001 J Neurosci. 21:186) was used to measure changes of size and shape of new and old spines. Furthermore, presynaptic structures on novel and "old" spines were characterized. Single neurons, transfected with GFP were immunostained and embedded for electron microscopy. CLSM analysis revealed that a total of 1.52±0.10 spines per 10µm dendritic segment (n=18 cells), 0.94±0.08 (62%) were 'old' spines, i.e. spines which were found both at the beginning and at the end of the experiment, 0.58±0.05 were novel spines, and 0.19±0.03 spines/10µm were lost during the experiment. After identification of the spine-producing neurons in the ultrathin sections the images of serial sections were taken with a CCD camera attached to the electron microscope LEO 912. After alignment of serial sections using SEM software, some neurons and segments were 3D reconstructed using IGL software and "3D Studio Max". As result we found that the ratio of novel spines with/without presynaptic structure was 60%/36 %, i.e. the majority of novel spines was contacted by at least one presynaptic structure. The ratio of "old" spines with/without presynaptic structures was 55%/45 %), indicating that a little more than half of the pre-existing spines resemble functional synaptic structures after the spine-creating protocol.

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Brain activation of dominat vs non dominat hand areas during linguistic activity - an fMRI study

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In this study we wish to investigate the connection between language functions and the motor system by comparing the dominant and non-dominant hand areas during linguistic activity. We present here preliminary results from seven right-handed native Hebrew speakers that were scanned in a 1.5 T GE scanner during two experimental sessions. The first experiment was comprised of motor and linguistic tasks within a block designed experiment. Motor tasks included simple movements of right and left hands for all subjects and simple movements of right and left feet for three of the subjects. The linguistic task comprised of a covert association generation to a given noun. We used the neuronal activity during movement periods in order to delineate the primary motor areas of the hands and feet and then examined the relative neuronal activity (BOLD signal change) in these regions during the free association task. Across subjects, the right hand area showed a significantly increased signal than the left hand, and this difference was not significant for the right and left feet. In the second experiment the same subjects were asked to listen to a story for 6 minutes. Based on the regional definitions from the first experiment we correlated between the time courses in the motor areas and the time course in broca's area throughout the story. The results showed that the right hand area was significantly more correlated with broca's activity than the left hand area, but no such difference was observed for the feet areas. These results suggest that the neuronal mechanisms related with language functions and hand manipulation may share a common neuronal system.

Endocannabinoid 2-AG Exerts Neuroprotection Through NF-kB Inhibition and Downregulation of Proinflammatory Cytokines

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We reported that closed head injury (CHI) in mice causes a sharp elevation of brain 2-arachidonoylglycerol (2-AG) levels, and that exogenous 2-AG reduces brain edema, infarct volume and hippocampal death and improved clinical recovery after CHI. 2-AG robustly reduced CHI-induced disruption of the blood brain barrier (BBB) at 4h, and abolished the 3-4 fold increase of NF-kB transactivation, at 24h after CHI. Proinflammatory cytokines such as TNF-a, IL-1b and IL-6 are known as NF-kB inducers. TNF-a is also one of the major promoters of BBB disruption after CHI. CHI was caused to Sabra mice and mice were sacrificed at 2 timepoints after injury: 2 and 4 hours. Total RNA was extracted and RT-PCR was

performed. We checked proinflammatory cytokines profile at 2 and 4h after CHI using RT-PCR. b-actin served as house-keeping gene and cytokines expression was evaluated against b-actin. TNF-a was undetected in untreated animals and CHI caused to massive release which was partly inhibited by 2-AG treratment at 2h but not at 4h timepoint: 113.43 vs. 84.15. IL-1b level at 2 and 4h was the same and 2-AG caused to decrease of IL-1b level at 4h: 124.22 vs. 103.52. IL-6 level at 4h was higher than at 2h and 2-AG treatment led to decrease in IL-6 level at 4h: 94.01 vs. 67.06. Conclusions: TNF-a, IL-1b and IL-6 levels increase short time after brain injury in mice and this subsequently lead to BBB disruption and NF-kB transactivation. All these detrimental effects inhibited by endogenous cannabinoid 2-AG.

Is visual extinction a natural consequence of spatial neglect? Evidence from contrast detection experiments

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Cases in which a unilateral spatial neglect (USN) patient is able to detect the stimulus on the neglected side when presented unilaterally, but fails in the case of bilateral stimulation, are termed "extinction". This extinction effect is very common in USN patients, and has a large impact on their everyday life, but its relation to the main neglect syndrome is poorly understood. Here we asked whether the extinction effect is a specific property of the USN syndrome, or alternatively it is due to the low saliency of the stimulus presented on the left, making the extinction effect a natural consequence of neglect. Three brain-damaged patients with USN and 4 normal controls were given a detection task using Gabor patches presented on a computer display with different eccentricities. Following a contrast calibration stage where we measured the detection threshold at each side, we set the stimulus on one side at its contrast detection threshold, and used multiples of that threshold on the other side. We then tested performance on a stimulus detection task with interleaved trials of unilateral and bilateral simultaneous stimulation (BSS). Both USN patients and controls showed extinction during BSS, i.e. made more errors in detecting the weak stimulus when one side was set at contrast threshold level, thus compensating for possible attenuation due to USN. However the patients and controls differed in their sensitivity to the contrast level of the extinguished stimulus. While a 1.5-fold increment eliminated extinction for the controls, a 2.5-fold increment was needed to release a stimulus from extinction in the USN patients. We conclude that the extinction effect in contrast detection is, in part, a natural consequence of the low saliency of the stimulus on the neglected side, but is more severe for the patients, suggesting an additional extinction-specific deficit. This extinction-specific effect could be a robust measure and used for clinical diagnosis.

Binding of the Drosophila Gliotactin Intracellular Part

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The Drosophila protein gliotactactin (Gli) is a single-pass transmembrane cholinesterase-like adhesion molecule (CLAM), which is necessary for glial ensheathment of axons in the peripheral nervous system and for the formation of the glial-based blood?nerve barrier. In glial cells Gli co-localizes with the proteins Coracle and Discs-large (Dlg) at the septate junction. The extracellular amino-terminal part of the protein is 24% identical to Drosophila acetylcholinesterase, but lacks the serine residue of the catalytic triad (like other CLAMs). The intracellular domain of Gli (Gli-cyt) bears no sequence homology to any known protein. Physicochemical studies show that Gli-cyt is natively unfolded when expressed in E. coli. The four C-terminal amino acids of Gli constitute a type-I PDZ domain-binding motif. Dlg belongs to the membrane-associated guanylate-kinase (MAGUK) protein family and contains three type-I PDZ domains, which are protein-protein interaction modules. We postulate that Gli-cyt binds to Dlg, through one of the latter?s PDZ domains and that this interaction may result in induced folding of Gli-cyt. Chromatographic and spectroscopic methods are being used to study the Gli-cyt Dlg interaction.

Plasticity and complexity: A neuroscience model for psychiatry

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Achievements in biological psychiatry reflect the consensus that psychiatric mental disorders are brain disorders. However, we do not have brain-related psychiatric diagnosis. Without understanding the specific causes for mental disorders, their diagnosis is descriptive and subjective, thus unreliable and deceptive. A model is proposed for a neuroscientific-oriented definition of mental disorders. Plasticity refers to all brain processes involved in dynamic alterations within communicating neuronal ensembles or networks, in the brain. Complexity refers to certain formulations from system theories relevant to brain dynamics. Plasticity processes are divided into three types based on time domains, 1) "developmental plasticity," 2) "tuning plasticity" and 3) "fast stabilizing plasticity." Each type of plasticity is related to different complexity models achieved by the brain. Mental disorders can be reconceptualized as disorders of plasticity resulting in disturbances of state-space brain configurations, matching and neural complexities. The new neuroscience-oriented diagnostic system generates testable predictions regarding diagnosis and treatments of mental disorders, which may be the future science for psychiatry.

Synthesis and opener properties of novel derivatives of N-phenylanthranilic acid on recombinant KCNQ2/Q3 potassium channels and activity on cortical neurons

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The voltage-dependent M-type potassium current (M-current) plays a major role in controlling brain excitability by stabilizing the membrane potential and acting as a brake for neuronal firing. The KCNQ2/Q3 heteromeric channel complex was identified as the molecular correlate of the M-current. Furthermore, the KCNQ2 and KCNQ3 channel subunits are mutated in families with benign familial neonatal convulsions, a neonatal form of epilepsy. Enhancement of KCNQ2/Q3 potassium currents may provide an important target for anti-epileptic drug development. In this study, we synthesized novel KCNQ2/Q3 channel openers, derivatives of N-phenylanthranilic acid, using meclofenamic acid and diclofenac as primary templates. External application of these molecules in the micromolar range results in activation of KCNQ2/Q3 K+ currents, heterologously expressed in Chinese hamster ovary (CHO) cells. These openers activate KCNQ2/Q3 channels by causing a leftward shift of the voltage activation curve and by markedly slowing the deactivation kinetics. SAR studies revealed that the pharmacophore of the newly synthesized N-phenylanthranilic acid series includes esters or secondary amides derivatives with a terminal hydroxy group. Thus, the novel molecules increase KCNQ2/Q3 current amplitude at physiologically relevant potentials and lead to a hyperpolarization of the resting membrane potential. In rat cortical neurons, they inhibit both evoked and spontaneous spiking activity. These derivatives of N-phenylanthranilic acid constitute novel drug templates for the treatment of neuronal hyperexcitability, including epilepsy, ischemic stroke, migraine, and neuropathic pain.

The role of LPA1 in formation of synapses among cultured hippocampal neurons

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We studied the lysophosphatidic acid receptor-1 (LPA1R) gene which we found to be expressed endogenously in cultured hippocampal neurons. Overexpressed GFP-tagged, membrane-associated LPA1R accumulated in a punctate manner over the entire dendritic tree and caused an increase in dendritic spine density. About half of the spines in the transfected neurons displayed distinct LPA1R puncta, and this subset of spines was also substantially larger than puncta-free, LPA1R transfected or control GFP spines. Exposure of LPA1R transfected cells to LPA caused a rapid (<15 min) aggregation of receptors into endocytotic puncta, which were then rapidly transported along the dendritic cytoplasm. Finally, while spontaneous miniature synaptic currents were of the same amplitudes, they decayed slower in LPA1 transfected neurons compared to GFP controls. We propose that LPA1R can regulate local morphological plasticity of dendritic spines in cultured hippocampal neurons.

Toward the isolation and characterization of the VIP receptor that mediates neuronal survival

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Vasoactive intestinal neuropeptide (VIP) provides neuroprotection through binding to high affinity receptors on glial cells that activate increases in the production and release of survival promoting proteins. Three VIP binding sites that belong to a subfamily of 7 trans-membrane-spanning G protein coupled receptors have been cloned: VPAC1, VPAC2 and PAC1. PAC1, while recognizing VIP at a very low affinity, recognizes the VIP-related peptide, pituitary adenylate cyclase activating polypeptide (PACAP), at a very high affinity. Six different splice variants in the third cytoplasmatic loop of the PAC1 mRNA were isolated. An antisense oligodeoxynucleotide specific for HOP2 (a splice variant of PAC1) kills neurons in cell culture, and reduces VIP binding to glial cells. Thus, HOP2 is implicated in VIP-mediated neuroprotection (J Mol Neurosci. 1997;9:211). The aim of the present work was to examine the affinity of the cloned HOP2 receptor to VIP and its analogues. The PAC1 cDNA was PCR-cloned from rat cerebral astrocytes and genetically manipulated to obtain the HOP2 splice variant. It was then inserted into an expression vector and transfected into COS-7 cells that were used for 125I-VIP and 125I-PACAP binding assays. Results showed that VIP and its agonist, Stearyl Nle17 VIP (SNV), bound the cloned HOP2 PAC1 splice variant. Stearyl-Neurotensin6-11 VIP7-28(SNH), that potently kills neurons, was found to bind HOP2 as well. These results support the hypothesis that HOP2 may be involved in the neuroprotective effects attributed to VIP.

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Temporal properties of collinear facilitation

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Visual masking refers to impaired performance on a target stimulus when a mask stimulus is presented for a brief presentation time before, during or after the target presentation. However, the threshold for contrast detection improves when a target is presented with two collinear flankers (Polat & Sagi 1993). Facilitation is found when the target is presented simultaneously with the flankers or with a delay (Tanaka & Sagi 1998). Here we test the temporal properties of lateral facilitation by manipulating asynchrony of both onsets and offsets of the target and flankers. In the experiments, the contrast threshold for a Gabor target was measured in isolation or in the presence of two collinear Gabor masks using a 2AFC staircase method. Experiments were carried out where the mask (60 ms) was presented before (Forward Masking: FM, isi=60 ms), simultaneously (SM) or after the target (Backward Masking: BM, isi=60 ms). The results showed target facilitation, 0.15-0.30 log units, (1) for simultaneous target and mask presentations (SM) with all durations tested, 60-320 ms, (2) when the mask preceded the target (FM), but (3) not when the target preceded the masks (BM), where some suppression at 3 lambda was observed instead. Additional experiments showed that a second pair of masks presented after SM (isi=60) cancels the SM facilitation. This pattern of results implicates a long integration time for lateral excitatory effects. The results point to the existence of a neuronal network with slow excitatory processes that are activated by low contrast inputs (target) and fast inhibitory processes that are activated by high contrast inputs (flankers). Presentation of the maskers after the offset of the target reinforces the inhibitory effects.

Generation of peripheral sensory-like neurons generated from human embryonic stem cells

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Human embryonic stem cells (hESC) are pluripotent cell lines that hold out great promise for drug development, study of early human developmental processes and transplantation therapy. A number of recent studies have shown that like mouse ES, human ES can be coaxed to produce cultures enriched in neurons/neural precursors. Multiple culture techniques have been used for eliciting neurogenesis from hESCs and several CNS cell types with potential clinical importance have been produced including dopaminergic and cortical pyramidal-like neurons, spinal motoneurons and oligodendrocytes. However, for study and treatement of peripheral neuropathies such as Familial Dysautonomia (FD), it will be necessary to produce peripheral neurons from HESC. hESC-derived human sensory neurons could be useful for developing in-vitro models of and screening for drugs for treating FD and other peripheral neuropathies. It is possible that eventually such neurons could be used for cell replacement therapy in patients who have significant sensory neuron loss. The group of Sasai has shown that neurons are efficiently induced from ES of mice and primates when co-cultured with the mouse stromal line PA6 (SDIA). They found that SDIA, with addition of BMPs after a few days of culture, induced a population of neurons from mouse ES expressing both peripherin (a molecule characteristic of neurons with peripheral axons, autonomic, sensory and motor) and Brn3a, (a transcription factor characteristic of peripheral sensory neurons and small population of CNS neurons) (Mizuseki et al Proc Natl Acad Sci USA. (2003) 100:5828-33). Expression of this combination of markers is characteristic almost exclusively of peripheral sensory neurons. Rhesus monkey ES cells generated peripherin+/Brn3a+ sensory neurons spontaneously when cultured with PA6, with BMP4 enriching for this phenotype We here use a modification of the SDIA technique to elicit sensory neuron-like differentiation from hESC.

The "what" and "where" subsystems in human olfaction: A full-brain study.

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Although considerable evidence suggests distinct dorsal and ventral neural pathways for processing object identification and localization respectively (the so called 'what' and 'where' pathways) in visual and auditory modalities, no test has been made of this bifurcation in olfaction. We conducted an event-related functional magnetic resonance imaging (fMRI) study to dissociate these functions in olfaction. The study consisted of two major event types, 'what' events in which subjects were asked to identify an odor as one of four alternatives, and 'where' events in which subjects were asked to determine

whether the odor was presented from the left or right side. Four odorants were used: rose (PEA), cloves (eugenol), banana (amyl acetate) and vinegar (proprionic acid). Odors were generated by an air-dilution olfactometer and delivered via a divided nasal mask with separate left and right entry ports. In addition to functional imaging data, behavioral responses were collected as was 100Hz continuous sampling of the air-flow rate in each nostril. As a group, the 16 subjects were able to perform the identification task for all four odors used. (proprionic acid accuracy = 91.3 +/- 3.6%, p-value <.0001, t-value =18.47, eugenol, accuracy = 64.6 +/-4.7%, p-value<.0001, t-value = 8.413, amyl acetate accuracy = 82.3 +/- 3.8%, p-value < .0001, t-value=14.92, and PEA accuracy = 59.9 +/- 5.9%, p-value < .0001, t-value=5.94). As a group the subjects were also able to perform the localization task for three of the four odors used. (proprionic acid accuracy = 86.4 +/- 3.7%, p-value<.0001, t-value=9.864, amyl acetate accuracy = 63.6 +/- 5.7%, p-value <.05, t-value=2.38, PEA accuracy = 63.5 +/- 4.0%, p-value <.005, t-value=3.41, and eugenol accuracy = 57.3 +/- 5.2%, p-value =.18, t-value=1.40). Contrast maps computed for the two comparisons show task-specific activations within previously identified 'what' and 'where' processing streams, namely in frontal and parietal structures.

Morphing Memories through Continuous Associations

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Storage of concurrent information into human memory captures the context in which it is acquired and the associations it has with stored memories. However, it is not clear how the existing memories are affected, if at all, due to exposure to contextually related stimuli. To study this, we designed a psychophysical training procedure on humans that captures these association effects on memory of faces. Subjects were trained to recognize a set of faces. After the memories of the faces were confirmed by an identification task, subjects repeated the identification task on various faces, including a sequence of stimuli gradually transforming between a pair of faces - from one memorized face to another initially distinguishable face (morph sequence). For each subject, this task was repeated in multiple daily sessions on the same pair of faces. This protocol led to a gradual change in identification of the morph sequence by more than half of the subjects, eventually resulting in wrongly remembering the two pair faces as the same one and to an increase in their perceived similarity. A critical parameter for this effect to take place was the extent to which the subject initially distinguished between the pair faces (faces that seemed very different initially, stayed distinguishable; faces that were perceived as different but more similar, eventually were remembered as one). A similar procedure, with the exception that at every session the morph sequence was presented in a random order did not yield any significant change in identification, recognition or similarity of the two pair faces. These results show that long-term memory of perceptual objects can be dramatically modified, up to the point where two different objects are remembered as one. We show an attractor-based neural network model of associative memory that supports this experimental result.

Neurofilament-light increases cell surface expression of the N-methyl-D-aspartate receptor and prevents its ubiquitination

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The N-methyl-D-aspartate subtype of glutamate receptors (NMDARs) are among the selectively enriched, core components of the dendritic spine post synaptic densities (PSDs). The mechanisms of NMDAR targeting, clustering and anchoring in neuronal synapses are poorly understood but presumably involve their linkage to the postsynaptic cytoskeleton. The neuronal intermediate filament protein, neurofilament-light (NF-L), also a component of the PSD, is among the cytoskeletal elements known to bind to the cytosolic carboxyl-terminal tail of the NMDAR subunit, NR1. In this study, we examined the role of NF-L in the regulation of NMDAR expression and function in a heterologous system. NMDAR subunits did not reach the cell surface when expressed singly in HEK293 cells, but were readily detected when co-expressed, as measured by surface biotinylation, cell ELISAs and confocal microscopy. Co-transfection of NF-L with NMDARs however, resulted in a 20% increase in the surface abundance of NR1 when compared to control transfections of NMDARs alone, along with a concomitant increase in NMDAR-mediated cytotoxicity. Investigating the origin of this increase, we found that NR1 subunits are ubiquitinated in HEK293 cells and can be co-immunoprecipitated with transfected ubiquitin. Ubiquitination of NR1 was significantly reduced by the co-expression of NF-L. These results suggest a possible means of stabilization of membrane-bound NMDARs via the interaction of the NR1 subunit with NF-L.

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Visual cortex activation in the blind is associated with episodic retrieval success

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There is accumulating evidence that the visual cortex is adaptable when deprived of its original input. We recently showed that the occipital cortex of congenitally blind subjects is activated during tasks requiring verbal-memory processes. Activation was found in regions corresponding to retinotopic visual areas of sighted, including the calcarine sulcus (V1). No such occipital activation was found in the sighted. One year later the same blind subjects participated in a second fMRI scan, to study the contribution of semantic elements and episodic memory in the occipital activation. During the current scan, subjects performed an episodic memory task, requiring them to identify words that were originally presented in the first scan. We demonstrate here that the magnitude of V1 activation during this task is correlated with online memory performance. During the current scan, recognition-memory performance differed significantly between two sets of words due to extensive practice on one of the sets prior to the previous scan. Across the blind, the better-remembered set of words elicited greater V1 activation than words from the poorly-remembered set, although the semantic components and the behavioral task were similar in the two sets. This indicates that activation in V1 of the blind is associated with long-term episodic memory, on top of semantic processing as suggested previously. Furthermore, within the blind subjects, those who showed better recognition-memory performance demonstrated greater V1 activation compared with the poorer performers. These results suggest that in the congenitally blind; the posterior occipital cortex (including V1) may be involved in episodic retrieval.

Spatio-Temporal Aspects of Perceptual Visual Grouping under Inattention

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Behavioral findings suggest that the attentional demands of grouping by color similarity depend on the complexity of the formed configurations. This study compared event-related potentials (ERPs), recorded from 22 scalp electrodes, in response to displays with grouping into a simple pattern (columns) and a more complex shape (triangle) under conditions of inattention. Fourteen subjects performed a similarity judgment task concerning two successive briefly presented central target displays. Subjects were told nothing about the display backgrounds that included the grouping patterns. Measuring the influence of background organization on target judgments replicated previous behavioral findings. Difference waveforms associated with columns or triangle grouping were obtained by subtracting ERPs to central targets only from ERPs to the entire first display (targets with background). The early Nd1 and Pd1 ERP components and the Nd2 component revealed larger amplitudes to columns than to triangles at occipital, frontal and parieto-temporal sites, respectively. Source current density estimations were conducted by low-resolution electromagnetic tomography (LORETA). Columns and triangles evoked similar

activation in some regions (BA 17, 19), and a column advantage was found relatively late in others (BA 20, 21, 38). Several regions (BA 18, 31, 4, 6, 10 and Hippocampus) were more strongly activated for columns than for triangles throughout the time course. However, processing triangles preceded processing of columns in most regions of interest (BA 17, 18, 19, 21, 31 and Hippocampus). Thus, compared to grouping into shape, grouping into an orientation is associated with higher activation in different brain areas albeit with an initially longer latency. Interestingly, this activation did not induce awareness of the grouped pattern.

Mapping descending pathways related to atonia and antinociception during anesthesia

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Microinjection of minute quantities of pentobarbital into a restricted region of rat brainstem, the MPTA (mesopontine tegmental anesthesia area) induces a general anesthesia-like state, characterized by atonia, antinociception and loss of consciousness (Devor and Zalkind, Pain 2001). The use of neuroanatomical tracers revealed that the MPTA has direct projections to the spinal cord as well as projections to the rostro-ventromedial medulla (RVM), an important relay station for spinal pain modulation. Since these two pathways may mediate the motor and sensory effects of anesthetic agents, it is important to characterize them in greater detail. We microinjected the tracer CTB (cholera toxin b-chain) into the RVM or the spinal cord at several rostrocaudal levels in order to retrogradely label MPTA neurons that project to these targets. The size and shape of CTB-labeled neurons was evaluated quantitatively using the Neurolucida system. MPTA neurons that project to the spinal cord are significantly larger than neurons that project to the RVM, suggesting that they represent distinct cell populations. It is unclear whether MPTA neurons that project to different levels of the spinal cord are also distinct, or whether individual neurons collateralize and terminate throughout the length of the cord. With the aid of a double retrograde tracing technique using CTB microinjected into one site, and fluorogold microinjected into a second, we established whether MPTA-RVM and MPTA-spinal neurons constitute distinct populations, and whether MPTA-spinal neurons have specific, localized terminations or collateralize broadly.

Exposure to stress impairs extinction of fear conditioning

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Experimental extinction is the decline in frequency or intensity of the conditioned response following the withdrawal of reinforcement. Converging evidence indicates that extinction of fear memory requires plasticity in both the medial prefrontal cortex (mPFC) and the basolateral amygdala (BLA). Recent data show that the mPFC is critical for the inhibition of the responses mediated by the amygdala and thus for its role in reducing exaggerated fear responses. In the present study we aimed to examine the kinetics of fear extinction following different number of pairings of the conditioned and unconditioned stimuli during conditioning. To that end, rats were exposed to 1, 3, or 7 pairings of tone and shock. We found that higher number of tone and shock pairings resulted in more resistance to extinction of fear. Next we aimed to examine whether exposing the rat to out-of context stress prior to extinction training would also affect the kinetics of extinction of fear. We found that animals exposed to the elevated platform stress prior to extinction training showed more resistance to extinction compared with non stressed rats. We suggest that exposure to behavioral stress may impair extinction by reducing mPFC input to the amygdala and concurrently increasing the relative contribution of the amygdala. Our findings could bear relevance to the potential involvement of extinction abnormalities in anxiety disorders such as post traumatic stress disorder, in which individuals show more resistance to extinction.

Novel derivatives of GABA and typical anti-psychotic agents induce efficacy and diminish extrapyramidal (ESP) effects in animal models

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The inhibitory neurotransmitter g-aminobutyric acid (GABA) plays a key role in various psychiatric diseases. Pathogenesis of schizophrenia has been recently shown to be associated with GABA deficiency in the brain. However, treatment with GABA is hampered by poor BBB penetrability. To overcome this constraint, the novel compounds AN-168, AN-218 and AN-187, that display neuroleptic activity, were evaluated po on rats at equimolar doses of typical neuroleptics for: a) catalepsy; b) blood prolactin levels; and c) efficacy in a model of D-amphetamine (AMP) induced hyperactivity. Acute catalepsy was determined by the wall and bar tests for 8 h and sub-chronic catalepsy was measured 2 h after drug administration daily/3 weeks. AN-168, AN-218 and AN-187 at doses of 0.5-9.5 mg/kg, induced no or mild levels of catalepsy, significantly lower than those elicited by similar doses of typical neuroleptics ($p<<0.05$). Animal weights receiving a daily sub-chronic, high dose of perphenazine (PER), were considerably lower than those of rats treated with an equimolar dose of AN-168 or vehicle only, suggesting that the GABA-PER derivative possesses lower toxicity. Blood prolactin levels increased 2 h after administration of either PER or its derivatives and decreased thereafter. AMP (2.5 mg/kg) induced hyperactivity manifested by increased climbing attempts and head movements in the rats, while PER administered po 1.2-2.5 mg/kg, 1.5 h prior to AMP, abolished these activities, leading to sedation and catalepsy, while AN-168 and AN-218, at equimolar doses, reduced them to control level. In conclusion, AN-168 and AN-218 that were efficacious in the AMP-induced hyperactivity model and caused significantly lower ESP side-effects constitute a new type of neuroleptics that may play an important role in therapy of schizophrenia and related diseases.

Green tea polyphenol (-)-epigallocatechin-3-gallate (EGCG) induces neurorescue via activation of PKC pathway and promotes neurite outgrowth in PC12 cells

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The neuropathology of neurodegenerative diseases is associated with a gradual loss of neurons in the respective affected brain areas. Our previous studies have shown that the green tea polyphenol (-)-epigallocatechin-3-gallate (EGCG) prevents neuronal cell death, caused by several neurotoxins, both in vivo and in vitro. The present study seeks to determine the neuroprotective effect of EGCG when it is administered after the induction of cell damage ("neurorescue"). In an attempt to imitate a progressive mode of death, PC12 cells were initially subjected to serum-starvation conditions for a period of 1 or 3 days, before administration of EGCG (0.1-10 mM) for up to 3 days,. Serum-starved PC12 cells exhibited retracted cell bodies and processes in parallel to increased biochemical apoptotic markers, with a mortality index ranging between 1.5-17 folds over full-serum (FS) conditions. In spite of the high percentage of cell death, particularly after long-term serum withdrawal, single or repetitive administration of EGCG (1 mM) significantly attenuated cell death. The neurorescue effect of EGCG was abolished by pretreatment with protein kinase c (PKC) inhibitor GF109203X (2.5 mM), suggesting the involvement of PKC pathway in neurorescue by the drug. This is consistent with the rapid (15 min) translocation of PKCα isoform to the cell membrane in response to EGCG. The correlative neurite outgrowth activity of EGCG on PC12 cells, as evidenced by the expression of the typical differentiation marker growth associated protein, GAP-43 may contribute, as well, to its neurorescue effect. The present findings suggest that EGCG may have a positive impact on aging and neurodegenerative diseases to retard or perhaps even reverse the accelerated rate of neuronal degeneration.

Interactions Between Sensory and Cognitive Abilities in Early-Blind Individuals

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Several studies reported superior auditory perception and superior memory in blind individuals. Yet findings are mixed, particularly regarding cognitive abilities. In this study, we show that the cognitive advantages may rely on the sensory advantage. We examined the perceptual-cognitive profile of early blind individuals and compared it to that of sighted controls. We replicated findings that blind individuals show advantage in auditory tasks of frequency discrimination and in verbal short-term memory spans. To assess whether their memory has a greater capacity in terms of element number, or their superior spans stem from superior perception, we tested their threshold intensity (80% correct repetition) for speech perception (pseudo-words) in quiet and in noise, and assessed their span under "perceptual clamp" conditions (speech intensity presented for each participant at his/her threshold level). Blind individuals had significantly lower threshold levels in quiet, but no difference was found under noisy conditions. This suggests that their general speech perception system is less noisy, but in a manner which does not stem from better-tuned speech detectors. When memory spans are measured under "perceptual clamp" no significant advantage was found for blind individuals, indicating that they have no superior memory per se. Taken together, these results suggest that blind individuals' advantage in cognitive tasks stems from superior sensory abilities. These, in turn, stem from a quieter auditory system for speech perception, and not from finer tuned speech detectors.

The spatio-temporal organization of the climbing fiber input to the cerebellar cortex

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Optical imaging of voltage sensitive dyes combined with standard electrophysiological techniques was used to characterize spatio-temporally the response of the cerebellar cortex to the climbing fiber input. Fluorescence was measured by a 128 photodiode array from the in vitro whole cerebellum preparation. The white matter was stimulated with a concentric electrode and both optical and electrical responses were measured simultaneously. This stimulation occasionally evoked a typical climbing fiber field response and a parasagitally oriented optical response. In these cases the width of the parasagital band of activity was 300 im and its length was stimulus intensity dependant ranging from 400 im to more than 1200 im. Activity was always synchronous throughout the parasagital band with an average delay of 1.5 ms. The average rise time was 8 ms and the average response duration (at half amplitude) was 26 ms. These findings are in agreement with previous morphological and electrophysiological analyses. The characterization of the climbing fiber response enabled us to study the spatial distribution of the long term interaction between the climbing fiber and parallel fiber inputs, known as cerebellar LTD. We found that conjunctive stimulation of climbing fibers and parallel fibers at a rate of 2 Hz for 50 s reduced significantly the responses to parallel fiber stimulation. This reduction was confined to the area where the two responses overlapped.

Chondroitin Sulfate Proteoglycan – a "SOS" Molecule in CNS Repair

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Chondroitin sulfate proteoglycans (CSPG) inhibit central nervous system (CNS) axonal regeneration, and their local degradation promotes recovery. The assumptions underlying our present study were that the increased expression of CSPG, observed after injury and neurodegenerative disorders (e.g. Alzheimer's disease), is part of the self-repair mechanism. Accordingly, we proposed that CSPG is needed for transient demarcation of the lesion site as well as the induction and regulation of the local immune response and its degradation products (generated following its degradation with chondroitinase ABC), participate in subsequent events leading to neuronal repair. In the present study, we show that CSPG as an intact molecule can affect both microglia and T cell. CSPG induces microglia activation to a phenotype that supports neuronal survival, and in synergy with IFN-γ, it allows microglia to acquire a phenotype of an antigen-presenting cell needed for the dialog with T cells. The degradation products of CSPG are highly potent compounds that can further contribute to the local immune response, promote neuronal survival and growth, and serve a neuroprotective function in several in vivo models of neurotoxicity and spinal cord injury. Our results suggest that CSPG, both in its intact form and via its degradation products, plays a vital role in modulation of the local immune response as well as in CNS regeneration, and serves as an integral part of the mechanism regulating CNS repair.

Learning in realistic networks of spiking neurons and spike-driven plastic synapses

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We study by simulations a recurrent network of spiking neurons connected by plastic synapses. Synaptic efficacies display spike-driven plasticity on both short and long time scales. Short-term dynamics is driven by presynaptic spikes and the fraction of available synaptic resources (Tsodyks, Markram 1997). Presynaptic emission reduces the fraction of available resources, hence the synaptic efficacy. Resources recover in ~100ms. Long-term dynamics is driven by presynaptic spikes and postsynaptic depolarization (Fusi et al. 2000). The synapse is Hebbian: high pre- and postsynaptic emission rates cause LTP; high pre- and low post-synaptic emission rates cause LTD. Long-time stability is ensured by a refresh mechanism. During training, the network is subjected to a stream of stimulus-delay trials, in which one of a set of external stimuli is presented. To each stimulus corresponds a randomly selected subset of neurons, whose emission rates are enhanced upon presentation of the corresponding stimulus. Neurons can be selective to more than one stimulus. The repeated presentation of the stimuli belonging to the training set (in random order) structures the network to the point of sustaining active memory for every one of them: enhanced delay activity in the corresponding selective neural population. The underlying synaptic structuring is the result of the long-term plasticity produced by the stimulus dependent patterns of neural activity experienced along training. No external intervention is involved at any stage. The patterns of neural activity exhibited by the network before, during and after training reproduce most of the details of the corresponding observed physiological phenomena. The robustness of the structuring and performance is exhibited.

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Intelligence, EEG alpha activity and contrast sensitivity - The magical number 10

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The magnitude of EEG waves at the alpha (~10 Hz) range during rest and the Event Related Desynchronization (ERD) during visual and mental activity are both known to be correlated with verbal intelligence. Previously in our lab, a positive correlation was found between subjects' intelligence score and their contrast sensitivity (CS) to 10Hz flickers. Combining these two lines of research, we now asked whether the magnitude of alpha waves at rest is correlated with behavioral CS to10 Hz flicker. Our initial findings (n=9 students) show a significant correlation ($r=0.76$, $p<0.05$) between the relative proportion of alpha power and contrast sensitivity. Finding that alpha magnitude is correlated with behavioral sensitivity, we now asked whether we can further increase alpha magnitude at rest by exposure to 10Hz flicker. Subjects passively watched interleaved series of 2-sec flickers of 5 and 10Hz,

at both low and high contrasts, for 30 minutes, during which their EEG activity was recorded. Their behavioral CS to 10 Hz flicker and their alpha magnitude at rest were both measured before and after this passive viewing. Preliminary results show larger ERD in the alpha band for high compared with low contrast flickers during exposure, and a tendency for an increase in relative alpha magnitude at rest. These findings suggest that we can behaviorally increase a person's alpha power, and yield the challenging question whether such an increase would impact the person's cognitive skills.

A Molecular Switch for Translational Control in Taste Memory Consolidation

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In a variety of species memory consolidation following different learning paradigms has been shown to be dependent on protein synthesis. However, it is not known whether modulation of protein synthesis is a critical component of the consolidation process, not is the identity of any protein(s) subject to translational regulation, known. We report here that phosphorylation of eukaryotic elongation factor-2 (eEF2), an indicator for translational elongation attenuation, is correlated with input that produces taste memory consolidation in the relevant cortex. The temporal pattern of eEF2 phosphorylation is similar to ERKII activation and p70 S6 kinase phosphorylation, known to stimulate translation initiation. In addition, eEF2 increased phosphorylation and *f*NCaMKII increased expression during memory consolidation are detected in a synaptoneurosomal fraction made from taste cortex. The results suggest that increased initiation rate together with decreased elongation rate, during memory consolidation, shift the rate limiting step of protein synthesis from initiation to elongation, to produce a local switch-like effect in the expression of neuronal proteins.

Neurofibrillary tangles and a memory deficit in transgenic mice expressing tau protein with two mutations associated with severe dementia in humans

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Objective: To generate an authentic transgenic(tg) animal model for tauopathy and Alzheimer's disease(AD). Background: While the amyloid plaques pathology has been intensively investigated in the last decade, the neurofibrillary tangles(NT), the AD component which correlates better with dementia, has only recently been investigated in animal models. A few mutant tau tg animals have been created recently, presenting NT with a clinical phenotype varying from no neurological deficits at all, to some late-onset behavioral deficits, and to non-AD characteristic motor deficits, including paraparesis. Design&Methods: 1. We introduced, into the tg tau gene, two pathogenic mutations[P301S;K257T] associated with severe phenotypes of tauopathy in humans. 2. We used the original tau promoter, in order to express authentically the tau protein and avoid neurological deficits not characteristic to tauopathy or AD. Results: The tg-mice generated by us - express the human double mutant tau in the hippocampus and cortex. At 6 months we detected argyrophilic intracellular inclusions in neurons in the cortex and hippocampus by Gallyas-staining. Presence of NT was confirmed by immunohistochemical- analysis. As early as 5-6 months the mice showed a cognitive deficit in the eight-arm maze and morris water maze; with no irrelevant motor deficits at-least till 18-months. Conclusion: We generated mutant tau tg mice presenting NT in the cortex and hippocampus, with an early-onset cognitive deficit and without any motor impairment. These mice provide an authentic animal model for tauopathy and AD, within short time-frames.

Learning-induced reduction in predisposition for LTP: a possible mechanism for protection against runaway synaptic strengthening

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We studied the relations between learning-induced modifications in the strength of synaptic connectivity and in the threshold for LTP and LTD induction. Rats were trained in an olfactory discrimination task to distinguish between positive and negative odor cues until they demonstrated rule learning. Learning-induced cellular and molecular modifications were subsequently studied in the piriform cortex. Two types of cellular modifications appear one day after learning: enhanced neuronal excitability, which is the result of reduction in an intrinsic potassium current (Saar and Barkai, 2003) and reduced predisposition for LTP induction (and increased predisposition for LTD induction). This shift in the threshold for LTP and LTD is a consequence of a change in the subunit composition of the NMDA receptor, resulting in receptors with a higher complement of the NR2a subunit protein relative to NR2b (Quinlan et al., 2004). Learning-induced synaptic strengthening becomes apparent on the third day after training, and is maintained by different mechanisms than these affecting LTP and LTD induction. Enhanced synaptic release is indicated by reduced paired pulse facilitation (Saar et al., 1999), post synaptic modifications in the neuronal cable properties are indicated by enhanced rise time of the post-synaptic potentials (Saar et al., 2002), and enhanced synaptic connectivity is indicated by increased spine density along dendrites of pyramidal neurons (Knafo et al., 2001). One possible function that learning-induced molecular and physiological modifications in the NMDA receptors may serve is protecting the neuronal circuit against runaway synaptic strengthening. Such protection is achieved by razing the threshold for activity-dependent synaptic enhancement. However, once an external stimulus reaches this threshold, the information it carries would be stored quickly and efficiently.

Hyperanxiety and memory deficits induced in rats by prenatal stress are associated with a reduction in synaptic connectivity in hippocampal and cortical regions

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Prenatal stress in rats has been shown to reduce neurogenesis in the hippocampus and increase the size of the lateral amygdaloid nucleus. These structural alterations are associated with deficits in spatial memory, hyperanxiety and depressive behaviour. The present study examined the effect of gestational stress during the last week of gestation in Sprague-Dawley rats on the length and density of dendritic spines, and on genes related to synapse formation and activity in the hippocampus and cortical areas in 21 day old male offspring. Spatial and episodic memory was assessed in adult littermates (3-4 months) by the Morris water maze and object recognition tests, respectively. Dendritic morphology was assessed by means of Golgi-cox staining, and gene changes, by the Affimetrix microarray (8 samples x 19,000 genes each), followed by RT-PCR. Prenatal stress caused a significant decrease in spine length and density in the orbitofrontal and anterior cingulate cortex. In the hippocampus, 2.4% of the genes were markedly reduced, the largest group of which included components of neurogenesis and synapse formation, activity and trafficking, such as complexin 1 and 2, endophilin-1 and PSD-95/SAP90-associated protein-3. The study shows for the first time that prenatal stress can interfere with synapse formation in the hippocampus and reduce synaptic connectivity in the cortex. These changes are present at the time of weaning and probably result from altered neuronal programming of the foetal nervous system by maternal stress hormones like corticosterone. The structural changes in the hippocampus and cortex contribute to the deficits in behaviour and memory seen in adulthood.

The Significance of Impedance Profiles of Pacemaker Neurons in Frequency Regulation of the Pyloric Rhythm

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Autorhythmic neurons show impedance profiles that peak at a frequency called the resonance frequency, often close to their intrinsic oscillatory frequency. When such a neuron is embedded within a network it is subject to electrical and chemical synaptic inputs which can affect the cycle frequency. According to the impedance profile of the neuron, inputs coming at certain frequencies will be more important than others. Hence the impedance of a neuron that participates in the production of a rhythm may be a critical component of the mechanism by which cycle frequency is stabilized in the whole network. We examined this question in the pyloric circuit of Homarus americanus, which produces a robust oscillation (cycle frequency fpyloric ~ 1Hz). We focused on neurons of the pacemaker group, the pyloric dilator (PD) and the anterior burster (AB) neurons. In the isolated neurons, we recorded the voltage responses to intracellularly injected sine waves of different frequencies. Since the responses to negative and positive currents were not symmetrical, we measured two different curves for the impedance profile: Z-(f) and Z+(f), respectively. We found that the PD and AB neurons have characteristic impedance profiles not shown by any other pyloric neuron: in the physiological range (f<3 Hz) Z-(f) was almost flat; at low frequencies, Z+(f) increased with f and peaked at fpeak=0.27+-0.12 Hz. At higher frequencies Z+(f) strongly decreased with f, decaying below Z-(f) at f>0.7+-0.2 Hz. Hence, at low frequencies, Z+(f)>Z-(f) and therefore depolarizatory inputs are favored over hyperpolarizatory inputs; these relationships are reversed for f>0.7 Hz (N=22). Thus, we hypothesize that when cycle frequency transiently decreases below, or increases above, fpyloric depolarizatory (e.g., electrical coupling) or hyperpolarizatory (e.g., chemical inhibitory) inputs are differentially weighed such that the cycle frequency is brought back to fpyloric.

Development and distribution of voltage-gated potassium conductances in neocortical pyramidal neurons

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The seminal investigations of Hodgkin and Huxley (1952) paved the road for exploration of neuronal excitability. Understanding the physiology of any electrically excitable cell requires describing the kinetics and membrane density of the voltage-gated ion channels it expressed. The calculated conductance densities obtained by us (Korngreen and Sakmann, 2000) and by others (Bekkers, 2000) to construct a compartmental simulation describing the firing of neocortical pyramidal neurons we discovered that the estimates we obtained from nucleated patches and from cell-attached and outside-out patches were smaller than those required to reproduce the physiological firing pattern of the neurons. In order to produce a realistic simulation the somatic conductance density of voltage-gated potassium channels had to be several fold higher than that we have measured. To address this conundrum we developed a new technique that correct space-clamp distorted voltage-clamp recordings performed in the whole-cell configuration in non-spherical structures (Schaefer et al. 2003). The rational was that the whole-cell configuration is less damaging to the plasma membrane than the extraction of a nucleated patch and will allow a more accurate estimation of the conductance density once space-clamp distortions were corrected for. Using this technique we re-examined the conductance density of voltage-gated potassium channels in layer 5 pyramidal neurons. We show that the conductance density is higher than the one reported previously from nucleated patches. We use the new recording mode to investigate the postnatal development voltage-gated potassium channels at the soma. We also show that as previously reported the density of voltage-gated potassium channels decreases along the apical dendrite of L5 pyramidal neurons.

FMRI driven seed ROI choosing Procedure for DTI based fiber tractography in the presence of space occupying lesion

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Diffusion tensor imaging (DTI) can be used for 3D visualization of specific fiber bundles, and to indicate the involvement of white matter in vicinity of brain lesions. Diffusion tensor imaging based fiber tractography necessitates definition of a seed region of interest (ROI) that is located at the path of the investigated fiber network system. Based on known anatomical location a large number of fiber bundles systems could be identified on healthy subjects with high accuracy. Mapping of well-defined functional systems (motor, visual, language) using fMRI is routinely done today for pre-surgical mapping. Nevertheless, brain lesions, especially space occupying lesions (SOL) often involve the white matter and alter the known anatomical path on which the fibers pass. Indeed, white matter deviation is a common consequence of SOL. Nonetheless in many of these cases only partial or no functional deficit is observed leading to the assumption that the fibers are still partially intact and therefore take a different route. In such cases, white matter mapping using seed ROI based on known, normal, anatomical location might be misleading. In this work we used fMRI driven seed ROI choosing procedure in patients with space occupying lesions where probable deviation of white matter tracts have been observed. The fMRI data was co-registered with the DTI to provide a 3D data set of both white matter connectivity and task related functional activity superimposed on high-resolution anatomical data set. From the fMRI activated areas we followed on white matter tracts using DTI to map the task related white matter tract. We used mainly the motor and language related fMRI tasks and concentrated in tracking the pyramidal track (to connect the motor related network) and the superior longitudinal fascicules (to connect the language related network). This methodology opens a window for assessment of brain connectivity in diseased patients.

Local Blood-Brain Barrier Disruption and Cortical Albumin Exposure Induce Epileptic Focus

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Perturbations in the integrity of the blood-brain barrier have been reported in both humans and animals under numerous pathological conditions. The blood-brain barrier prevents the penetration of many blood constituents into the brain extracellular space, but it is not known whether perturbations of the barrier can affect brain function and consequently have a role in the pathogenesis of cortical diseases. In this study we established a model for focal disruption of the blood-brain barrier in the rat cortex by direct application of bile salts. Importantly, direct neurotoxic effects of the bile salts were excluded by unaltered intra- and extracellular recordings in vitro. However, exposure of the cerebral cortex in vivo to bile salts resulted in a prolonged opening of the blood-brain barrier with subsequent long-lasting extravasation of serum albumin to the brain extracellular space. This was associated with a prominent activation of astrocytes with no inflammatory response or marked cell loss. Using electrophysiological recordings in brain slices we found that a focus of epileptiform discharges developed within 4-7 d after treatment and could be recorded up to 49 d postoperatively in >60% of slices from treated animals but only rarely (10%) in sham-operated controls. Epileptiform activity involved both glutamatergic and GABAergic neurotransmission. It was also induced by direct cortical

application of native serum, denatured serum, or an albumin-containing solution. In contrast, perfusion with serum-adapted electrolyte solution did not induce abnormal activity, thereby suggesting that the exposure of the serum-devoid brain environment to serum proteins underlies epileptogenesis in the blood-brain barrier-disrupted cortex. Although many neuropathologies entail a compromised blood-brain barrier, this is the first direct evidence that it may have a role in the pathogenesis of focal cortical epilepsy, a common neurological disease.

The role of non-NMDA glutamate receptors in the Ventral Tegmental Area in opioid reward and sensitization

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The role of the mesocorticolimbic dopamine system in mediating the rewarding properties of drugs of abuse is well known, the cross talk with other neurotransmitter systems, however, is less established. The mesocorticolimbic dopamine system originates from the mesencephalic Ventral Tegmental Area (VTA) and projects to several forebrain regions, including the nucleus accumbens (NAcc) both of which have been implicated in opiate-induced reward. The present study seek to estimate whether blockade of non-NMDA glutamate receptors in two different sub regions of the VTA would modulate the rewarding properties of morphine and the development of sensitization to the drug. Methods: Rats were implanted with bi-lateral cannula (24 GA) 1.5 mm above the anterior or posterior VTA to allow intracranial administration of the non-NMDA antagonist, CNQX (1 nmol, 0.5 *f*Yl per side), in order to find its impact on the rewarding effect of morphine in the Conditioning Place Preference (CPP) paradigm (unbiased procedure), and the induction of morphine sensitization in the same apparatus. Result: Regional administration of CNQX into the anterior VTA blocked the rewarding but not the development of sensitization to the locomotor stimulating effect of morphine. However the effect of morphine on locomotion was attenuated by CNQX injected into the anterior VTA. Regional administration of CNQX into the posterior VTA had different impact on the rewarding and stimulating effects of morphine which has still to be analyzed. Conclusion: Our data suggests a critical role for non-NMDA receptors in the VTA in opioid reward and dissociation between the rewarding and psychomotor sensitization effects of morphine.

Out of water reaching movements of the octopus

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Given their flexibility and kinematic redundancy, the control of the octopus arm movements is computationally quite complex. In previous studies a stereotypic reaching movement was discovered which reduces the complexity of motor control. Study of out of water (OOW) reaching movements showed that during these movements the bend point does not travel within a single plane, probably due to the lack of enough muscle forces. Almost all OOW reaching movements were directed in a perpendicular direction to the water surface, and indicated constant attempts by the octopus of keeping the proximal part in that arm orientation. Although no evidence was found that octopuses use correction strategies in the course of reaching movements in the water, such corrections were observed during the OOW reaching movements. Loss of steadiness was characterized by the fall of the proximal part of the arm towards the water and this was corrected towards having a perpendicular orientation during the movement. The kinematic analysis of these movements suggests that two distinct, independent mechanisms are operating during these reaching movements. The first one takes part in propagating the bend along the arm towards the distal part, and is probably carried out by the PNS (peripheral nerve system) of the arm, as was found previously for reaching movements in the water. The second mechanism controls the orientation of the proximal part of the arm, and is probably carried out by the CNS. The second mechanism is active during the whole reaching movement and is probably based on proprioceptive information.

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Chronic dietary lithium supplementation attenuates markers of aging in the hippocampus of C57BL mice

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Lithium (Li) attenuates apoptosis and glutamate-induced calcium influx and increases brain derived neurotrophic factor level. Since these actions oppose mechanisms of aging in the hippocampus, the present study examined the effect of chronic dietary lithium supplementation on markers of aging in the hippocampus of adult C57BL mice. Clusters of grains were detected by antibodies to inducible heat shock protein 70 and to glucose-regulated protein 78, and astrocytic activation (increased astrocyte size) was detected by anti-glial fibrillary acidic protein. Chronic dietary Li supplementation reduced the number of clusters of grains by 70% and reduced astrocyte size in hippocampal CA1-2 field by 25-30% without affecting the dentate gyrus. The reduction in markers of aging was not secondary to caloric restriction since Li supplementation did not change body weight. Since Li inhibits glycogen synthase kinase (GSK)-3beta*fz* and since GSK-3beta promotes apoptosis, the present study also examines the effect of knockout reduction in GSK-3beta level on the markers of aging. Surprisingly, knockout reduction of GSK-3beta increased the number of clusters of grains by 2-4 folds and increased astrocyte size in hippocampal CA1-2 field by 25-30% without affecting the dentate gyrus. Thus, life long reduction in GSK-3beta level may result in acceleration of some aging processes. This study warrants further examination of the conditions under which dietary Li supplementation to adults can prevent aging-associated cognitive decline.

Strain related gender differences in cortical 5-HT autoreceptors response to sub-chronic fluoxetin

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Selective serotonin reuptake inhibitors are the most prescribed antidepressants for treating depression. One problem of SSRIs is a 2-3 weeks delay of response after onset of administration. Previous studies showed that acute administration of the SSRI fluoxetine to rats increases synaptic 5-HT levels, and long-term administration of fluoxetine desensitizes 5-HT1A and 5-HT1B autoreceptors. This effect may play a role in the delayed response to treatment in humans. Mood disorders are more frequent in women. It was also suggested that there are gender differences in the response to antidepressants. Yet, most of the animal researches are done with male rats. In this work we asked whether 5-HT autoreceptor response to fluoxetine administration is differ between male and female rats. We treated Sabra male and female rats, and Sprague-Dawley female rats, with fluoxetine (10 mg/kg, 7 or 12 days). 5-HT levels, 5-HT1A and 5-HT1B autoreceptor activity were measured by in vivo microdialysis and analyzed by HPLC. We found that both 5-HT1A and 5-HT1B autoreceptor activity, as measured in the cortex, were reduced in Sabra male rats after 7-day administration of fluoxetine (10 mg/kg). However, the same treatment, as well as a 14-day treatment with fluoxetine (10 mg/kg), had no effect on 5-HT autoreceptors activity in the Sabra female rat. Early research found that 7 and 14 days administration of fluoxetine (10 mg/kg) desensitized 5-HT1A autoreceptor in the cortex of Sprague-Dawley male rat. In this study we found the same effect in Sprague-Dawley female rats, as well as desensitization of cortical 5-HT1B autoreceptor. We

conclude that the gender differences in 5-HT1A and 5-HT1B autoreceptor response to sub-chronic fluoxetine administration are strain related. Whereas sub-chronic fluoxetine has the same effect on 5-HT aoutoreceptors in males and females in the Sprague-Dawley strain, 5-HT autoreceptors response to fluoxetine differs between male and female in the Sabra strain.

The effect of mood stabilizers on nerve growth cones is additive and specific

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Lithium salts (lithium), valproic acid (VPA) and carbamazepine (CBZ) are the commonly used mood-stabilizers. Yet, despite years of treatment, their mechanism of action is still unknown. A heuristic hypothesis for mood stabilization by lithium is the inositol depletion hypothesis proposed by Berridge. It suggests that inhibition of inositol monophosphatase by lithium results in depletion of brain inositol leading to subsequent dampening of overactive neurotransmission. It has recently been found that lithium, VPA and CBZ share the same effect of spreading of primary cultured rat neuronal dorsal root ganglia (DRG) growth cones. Interestingly, myo-inositol reverses the effect of all three drugs, implicating inositol depletion in their action. In the present study DRGs were dissected from rats spinal cord, cultured individually and then incubated with psychotropic drugs, inositol or drugs plus inositol. Intriguingly, lithium and VPA show an additive effect of growth cones spreading, as occurs in the clinical use of these two drugs. Among eight psychotropic drugs other than the three mood stabilizers only imipramine and chlorpromazine had a similar spreading effect on rat neuronal DRGs growth cones, albeit their effect was not reversed by myo-inositol, implicating a different mechanism of their action. At 3 mM, unlike myo-inositol, scyllo- and epi-inositol did not reverse the effect of lithium on the growth cones spreading, reflecting specificity of the active stereoisomer and supporting the notion of intracellular myo-inositol depletion as the mechanism of action of the three antibipolar drugs.

The frontal lobes are involved in affective mentalistic significance of eye direction

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Individuals with prefrontal cortex (PFC) damage suffer from behavioral difficulties in social interaction despite relativly preserved intellectual abilites. A failure to understand other people's mental states (an ability that has been termed "theory of mind" [ToM]), has been proposed to account for the social impairment in these patients. However, this hypothesis has been challenged by findings that some patients with PFC damage can pass ToM tasks. Based on our previous findings, it is suggested that the behavioral deficit of individuals with PFC damage may be due to an impaired 'affective ToM' and difficulty at the level of integration between the cognitive and the affective facets of ToM, rather than to a general impairment in ToM. To test this hypothesis we designed a novel computerized task that assesses the ability to judge first and second order affective vs. cognitive mental state attribution, based on eye gaze. The performance of patients with localized lesions in the PFC (n=23) was compared to responses of patients with posterior lesions (n=12) and healthy control subjects (n=46). Whereas, healthy controls and patients with posterior lesions made less errors on affective as compared to cognitive onditions, the frontal patients showed the opposite trend. In addition, patients with PFC lesions made significantly more errors and were significantly slower to respond in the affective conditions, as compared to controls. Furthermore, both right and left PFC lesions were associated with a selective impairment in both first and second order affective ToM whereas they were not impaired in cognitive ToM tasks.

The neural correlates of understanding the other: a positron emission tomography investigation of accurate empathy

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The purpose of the present study was to assess the relationship between brain metabolism and the empathic response. Six right-handed healthy volunteers were scanned with positron emission tomography (PET) and [F-18] fluorodeoxygloucose twice; during an interactive interview about neutral story themes and during an interactive interview about an empathic response-eliciting story. Participants were rated for the level of their empathic response using the Truax rating scale (1961). Metabolic values in the medial and superior frontal gyrus, occipitotemporal cortices, thalamus and the cerebellum were higher during the empathic response than during the neutral theme interview. Furthermore, the subject's empathy scores were positively correlated with metabolism in the medial aspects of the superior frontal gyrus. Our results suggests that empathy consists of both affective and cognitive components, and therefore, may involve cortices that mediate simulation of emotional processing and mental state attribution.

Impaired empathy and affective theory of mind in patients with schizophrenia

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Patients suffering from schizophrenia show impaired emotional and social behavior, such as misinterpretation of social situations and luck of meta-representations (also known as Theory of Mind [ToM]). However, the empathic abilities of these patients has never been examined before and there are conflicting evidences regarding their ability to to pass basic ToM tasks. Based on previous findings, it was suggested that the behavioral deficit of individuals with schizophrenia may be due to an impaired empathy and 'affective ToM' abilities, rather than to a general impairment in ToM. To test this hypothesis a computerized task was used to assess the ability to judge first and second order affective vs. cognitive mental state attribution, based on eye gaze. Empathic ability was further assessed using self-rating questionnaires(QMEE, IRI). The performance of patients with schizophrenia (n=15) was compared to that of healthy control subjects (n=46). Results indicated that patients with schizophrenia showed impaired empathy in both cognitive and affective measurements of empathy. Moreover, these patients impaired empathy was significantly correlated with their level of negative symptoms and to their performance in the affective ToM conditions. Whereas healthy controls made less errors on affective as compared to cognitive conditions, schizophrenic patients showed the opposite trend. Although the pattern of reaction time did not differ significantly between groups, the patients made significantly more errors in the affective conditions, as compared to controls. Our results indicate that Individuals with high level of negative symptoms of schizophrenia demonstrate selective impairment in their ability to attribute affective mental states.

Postmortem Parietal Cortex TPH2 Expression is Not Altered in Schizophrenia, Unipolar Depressed and Bipolar Patients vs. Control Subjects

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Objectives: Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter synthesized in the raphe nuclei of the brain stem in the CNS and also in the periphery. Dysfunction of the serotonergic system has been implicated in the pathogenesis of psychiatric disorders. Tryptophan hydroxylase (TPH) is the rate limiting enzyme in 5-HT biosynthesis. For more than a decade only one gene encoding TPH was identified in vertebrates. Recently, a

second TPH gene, designated TPH2, was detected and located on human chromosome 12, a susceptibility region for affective disorders. TPH2 is predominantly expressed in the brain, while the classical TPH gene, TPH1, is expressed in peripheral tissues. The discovery of the brain-abundant TPH2 gene justifies a new concept of the CNS serotonergic system. TPH2, rather than TPH1, has now become a candidate gene for 5-HT-related affective disorders. Methods: We compared TPH2 mRNA levels in postmortem parietal cortex of unipolar-depression, bipolar and schizophrenia patients vs. control subjects and using real-time RT-PCR. Results: No significant difference in TPH2 mRNA levels was found among the four diagnostic groups. Conclusions: The lack of difference may suggest that this gene is not involved in the etiology of either of these psychiatric disorders. Alternatively, it may be that the parietal cortex is not the relevant brain area involved in the pathophysiology of these disorders, or that posttranscriptional modifications of TPH2 mRNA occur in these patients, causing changes in protein levels and/or enzymatic activity.

Interaction of calbindin D28k and inositol monophosphatase in human postmortem cortex; possible implications for bipolar disorder

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Objectives: Therapeutically-relevant concentrations of lithium (Li) exert an uncompetitive inhibition on inositol monophosphatase (IMPase). It has recently been shown that calbindin D28k (calbindin) activates IMPase. Purified calbindin attaches to a specific amino acid sequence on purified IMPase enhancing its activity by several hundred fold. We studied whether calbindin activates IMPase in postmortem human brain crude homogenate, whether differences in calbindin levels between lymphocytes and brain may be responsible for our previous finding of reduced IMPase activity in lymphocytes but not brain of bipolar patients, and whether calbindin protein levels are altered in postmortem brain from bipolar patients vs. control subjects and schizophrenic and major depressive patients. Methods: IMPase activity in human postmortem brain specimens with or without 10 μM human recombinant calbindin was quantified spectrophotometrically in an ELISA reader. Calbindin protein levels in postmortem brain were determined using Western blot analysis. Results: Supplementation of human recombinant calbindin to postmortem human brain crude homogenate enhanced IMPase activity by 3.5 fold. No difference in postmortem temporal cortex calbindin protein levels was found between bipolar patients vs. comparison groups. Two-fold higher calbindin protein levels were found in Li-treated bipolar patients compared with other bipolar patients. Sub-chronic Li treatment in mice did not affect brain calbindin protein levels significantly. Chronic Li treatment reduced calbindin protein levels in the frontal cortex but not in the hippocampus. Conclusions: Calbindin is a physiological activator of IMPase in human brain. Protein levels of calbindin are not altered in postmortem temporal cortex of bipolar patients.

The relation between understanding of deception and knowledge of social display rules among children with brain damage

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Children with brain damage, particularly influencing the frontal lobes, often show deficits in social behavior with less evidence of recovery in this domain than in others. Among the impaired social functions is the ability to understand deception of emotions through facial displays. This has been shown using short narratives in which a character feels a certain emotion but must modulate or inhibit its display. Previous studies suggest that perception of emotional deception is related to both Theory of Mind (ToM) and knowledge of social display rules. The objective of the current research was to examine the relationships between these functions, and extend the knowledge about their developmental interactions among children with brain damage. The performance of twelve 8 to14-year-old children with documented brain damage was compared to that of eleven age matched healthy controls, on tasks that measure emotional and cognitive deception, social display rules and second-order false belief. Results indicated that children suffering from brain-damage were significantly less accurate in their understanding of social display rules and emotional deception, but did not differ from controls in their understanding of second-order false belief and cognitive deception. In addition, significant correlation between social display rules and emotional deception was evident. The pattern of results suggests that knowledge of social display rules is linked to, and may depend on the ability to understand emotional deception in social situations. It appears to be less related to more cognitive ToM tasks, but these may still be prerequisites for this ability. Results may suggest areas on which to focus when treating such children with social problems.

Spatial response properties of neurons in the Anterior Ectosylvian Sulcal Auditory Field (FAES)

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Both the primary auditory cortex (AI) and Anterior Ectosylvian Sulcal Auditory Field (FAES) are believed to be involved in localization of sound. In both fields, neurons have been found to be sensitive to the direction of sound sources, although spatial tuning curves tend to be rather wide. Furthermore, FAES is known to project heavily to the deep layers of the superior colliculus. We examined the single unit selectivity to azimuth and elevation in the FAES and compared it to neural responses in A1. We used virtual space stimuli consisting of short noise bursts (100 ms) filtered through head-related transfer functions covering the frontal region (from -75 to 75 degrees in azimuth, -60 to 30 degrees in elevation). In order to find the physical cues to which the neurons were sensitive, we tested the same neurons with modified stimuli in which some of the physical cues were changed. In particular, we eliminated the spectral notches that are a prominent cue for both elevation and azimuth; we generated stimuli without interaural time differences, keeping all the other cues present; and we generated stimuli that had the same interaural level differences as the original stimuli, superimposed on white noise. Both in A1 and in FAES, a substantial number of neurons had significant sensitivity to azimuth and elevation. This sensitivity was due to binaural interactions, and was not purely the result of spectral processing in one ear. Modifying any of the physical parameters resulted in significant reduction in the sensitivity of the population response in FAES but not in A1, although single neurons in A1 showed changes in spatial sensitivity too. In Particular, removing the spectral notches reduced sensitivity not only to elevation (as expected), but to azimuth as well. The major determinant of azimuth selectivity in FAES seemed to be the coarse spectral structure of the stimuli in both ears, whereas elevation sensitivity depended on the spectral notches as well.

Inflammatory cytokines and cholinergic signaling modulate surgery stress-induced alterations in mood and cognition

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To examine the role of inflammatory cytokines and cholinergic signaling in mediating the effects of stress on mood and memory, 33 generally healthy volunteers were administered a comprehensive neuropsychological test battery before and after a moderate surgical procedure. Each subject was tested on three occasions: Several days before surgery (baseline), on the morning of the surgery day (i.e., psychological stress), and one day after surgery. Acetylcholinesterase (AChE) activity, and the levels of interleukin (IL)-1, IL-1ra, IL-6 and cortisol in the serum were measured in each session. 18 control subjects went through the same procedure. At baseline, lower levels of AChE activity were significantly associated with elevated

anxiety levels. Anxiety and depressed mood were significantly increased before and after surgery. Surgery-induced mood alterations were associated with changes in AChE activity: Patients who demonstrated stress-induced reduction in AChE activity showed a marked elevation in anxiety and depressed mood, whereas patients who demonstrated elevation in AChE activity displayed almost no mood alterations. Both on the surgery day, and on the day after surgery, there was a marked decline in memory. Following surgery, the levels of IL-6 were significantly increased, and were significantly correlated with smaller impairments in word list and complex figure delayed recall. Polymorphism in IL-1beta was significantly associated with IL-6 elevation following surgery (i.e., the surgery-induced increase in IL-6 levels was twice as high in allele 1 homozygous patients compared to patients with allele 2). In addition, memory impairment in the allele 1 homozygous patients was smaller compared to the other group. Thus, while cholinergic signaling is associated with surgery-induced mood modifications, IL-6 is associated with protection from surgery-induced cognitive disturbances, which vary according to genetic predisposition in stress-induced IL-6 production.

Rat brain synaptosomes contain a functional thrombin receptor PAR-1.

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Background: Thrombin is a key factor in coagulation and is considered to have a role in seizure production. Thrombin mediates many of its effects through specific protease activated receptors (PARs). The discovery of PARs in the nervous system has led to new insight regarding the potential physiological functions of thrombin. Objectives: To examine PAR-1 agonist peptides pharmacological effects on synaptosomes which may contribute to seizures. Methods: Crude synaptosomes were prepared from rat brains by centrifugation. The levels of phosphorylated ERK-1/2 induced by thrombin and PAR-1 agonist peptides were measured using western blot. Results: We observed a 2-3 fold increase in the level of ERK-1/2 phosphorylation in response to thrombin and PAR-1 agonist peptides relative to control non stimulated synaptosomes. A 2 peaked dose response curve was obtained with maximal responses at 30 microM and 10 nanoM. Conclusions: The results indicate that rat brain synaptosomes contain functional PAR-1. The physiological effects of the signal transduction pathways activated by this receptor remain to be evaluated.

Heat Acclimation Induced Neuroprotection: Possible Involvement of Hypoxia Inducible Factor 1á Upregulation and Increased Erythropoietin Signaling

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Background: Long-term exposure to heat (heat acclimation, ACC) was shown to protect against brain damage after closed head injury (CHI) in rats (Restor Neurol & Neurosci 6:107, 1994). Similarly, we have previously shown that this neuroprotective effect is sustained in mice as well. Hypoxia inducible factor 1 (HIF1), a transcriptional activator, regulates the expression of various genes including erythropoietin (Epo), several glycolytic enzymes, some glucose transporters and transferrin, all of which can potentially play a role in promoting cell survival. Epo, known as the key promoter of erythrocyte production, has been shown to be protective in a variety of brain injury models including our model of CHI (Yatsiv et al. Presented at the 11th annual ISFN meeting). This study examined the effect of ACC and CHI on the expression of HIF1á, Epo and its specific receptor, the erythropoietin receptor (EpoR). Methods: Mice were held at ambient temperature of 24°C (controls) or 34°C (ACC) for 30 days (Basic Res Cardiol 98/3, 185) and then subjected to left cerebral hemisphere CHI, by a weight drop device (under ether anesthesia), or sham surgery. 4 and 24h after surgery or CHI, mice were sacrificed and their brains removed for Western blot analysis of HIF1á, Epo and EpoR. EpoR/Epo ratio was calculated as a measure of Epo signaling. Results: HIF1á and EpoR levels were found to be higher in ACC mice as compared to controls ($p<0.05$ and $p<0.01$ respectively). EpoR/Epo ratio was also higher ($p<0.01$) indicating increased Epo signaling in these mice. Preliminary data indicates that both HIF1á and EpoR levels continue to be higher in ACC mice following CHI as well. Discussion: Our findings indicate that ACC induces higher basal and possibly post injury expression levels of HIF1á and EpoR, leading to increased Epo signaling in ACC mice. This increase taken together with the protective effect of Epo in our model, suggests the involvement of this pathway in ACC induced neuroprotection.

Endogenous D-Serine is Essential for NMDA-Elicited Neurotoxicity in Organotypic Hippocampal Slices Cultures.

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Overactivation of NMDA receptors is involved in neuronal cell death that occurs following brain ischemia. Calcium influx through NMDA receptors requires the binding of both glutamate and a coagonist, glycine or D-serine. Since both glycine and D-serine occur in the brain, the relative roles of each NMDA receptor coagonist is not known. To examine whether endogenous D-serine plays a role in neuronal death resulting from excitotoxic insults in the hippocampus, we used rat brain organotypic slice culture as a model. HPLC analysis revealed significant synthesis of D-serine by cultured hippocampal slices, ranging from 6 to 12 micromolar in the culture medium. Robust cell death was observed by addition of either NMDA (0.5 mM) or kainate (0.1 mM) as determined by propidium iodide uptake. Application of recombinant D-serine dehydratase (DSDA), an enzyme that specifically degrades D-serine, depleted D-serine levels in the culture medium and slices. This was associated to a drastic inhibition of neuronal death elicited by NMDA, but not by kainate. The neuroprotective effect of DSDA was fully reversed by addition of excess glycine or D-serine, indicating that the effect of DSDA was not due to a nonspecific inhibition of NMDA receptor activity. The present results indicate that endogenous D-serine is essential for neuronal injury involving NMDA receptor overactivation.

Ras dependent ErbB4 signaling , possible mechanism of regulation.

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The ErbB subfamily of receptor tyrosine kinases consists of four receptors. ErbB4 receptor is highly expressed in the nerve system and its high affinity ligand is neuregulin (NRG). NRG recognition event activates the receptor's intrinsic tyrosine kinase activity and initiates a network of signaling pathways regulating cellular proliferation, survival, chemotaxis, or differentiation. Among the cascades activated by ErbB4 is the prominent Ras-dependent signaling pathway. Our previous studies have shown that NRG induces neurite outgrowth and protects the PC12-ErbB4 cells from death caused by various apoptotic stimuli. Furthermore it was shown that activated Ras can activate ErbB4 receptor in a ligand independent manner. This activation depends on multiple Ras effector pathways in an autocrine independent manner. In the present study we demonstrate that the Ras inhibitor FTS, inhibits the NRG-mediated PC12-ErbB4 rescue from serum deprivation treatment. In addition the expression of dominant-negative Ras in these cells prevents cell differentiation. In order to examine whether the phosphorylation of ErbB4 by activated Ras is due to the tyrosine kinase activity of the receptor itself or due to the activity of an unknown cytoplasmtic factor, we have constructed an ErbB4 receptor with a point mutation in the ATP binding site. Preliminary results have shown that this receptor, transiently expressed in BOSC cells, does not bind gamaATP and therefore abolishes the intrinsic tyrosine kinase activity. Based on these results we suggest that Ras signaling pathways on one

hand, lead to cell differentiation and viability, and on the other hand involved in a positive feedback signal to activate the ErbB4 receptor. Our future plans are to stably express this mutant receptor in PC12 cells in order to better understand the mechanism of Ras mediated ErbB4 activation.

Double dissociation between the ventral and dorsal streams during object and action recognition

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Neuropsychological case studies indicate the existence of two functionally separate visual streams, but due to the few cases, this distinction remains controversial. Using fMRI in humans, we provide here evidence for the dissociation between observed action and object recognition. In experiment 1, subjects viewed movie clips of the right hand, on the right visual field, reaching and grasping objects placed on the left side of the screen. A mirror image of those movies (left hand grasping objects on the right side of the screen) was also shown. Contrasting the fMRI activation in the two conditions, we find that in dorsal areas (i.e. anterior intra-parietal sulcus: aIPS) the dominantly contralateral hemispheric activation is determined by the hand location while in ventral areas, (i.e. fusiform gyrus) the activation is in the hemisphere contraletral to the object's position. Next, subjects watched clips showing ten different (or identical) hand manipulations of various (or the same) objects. Using a two-factor ANOVA, we measured the adaptation effects of repeated viewing of object manipulation and/or object identity. Voxels showing significant fMRI adaptation during the observation of same grasping compared with different grasping movements of different objects, were mainly found in the parietal cortex, (i.e. aIPS and postcentral sulcus). On the other hand, voxels showing significant adaptation during the repeated observation of the same object, compared to different objects were found in the occipito-temporal cortex. Thus, we show a double dissociation of function between the two pathways. These results are congruent with the "direct matching hypothesis", that suggests that action recognition is based on mapping external actions to our own motor system and extend the classic division of labor between the vental and dorsal visual streams, suggesting that the dorsal stream may also be involved in the recognition of actions made by others.

Dominant eye priority in visual search

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While it is clear that one eye is visually dominant, the function of dominance is not fully understood. For example, Mapp et al. (2003) argue that eye dominance does not play any role in vision, and recent research found that dominance may be defined differently using different tests (e.g. Pointer 2001, Walls 1951). We were interested in the effects of dominance without competition; for example, fMRI reveals stronger activation for visual stimulation of the dominant eye (Rombouts et al. 1996). Detection of an element that differs significantly in a single dimension is an easy task, with performance that is independent of the number of distractors (Treisman & Gelade, 1980). We looked for effects of eye dominance on visual search. 13 subjects participated in the experiment; each had similar visual acuities in their two eyes, and normal or corrected-to-normal vision. Dominant eye was determined using the Hole-in-the-Card test (Durand & Gould, 1910). Using red-green glasses, subjects viewed a briefly presented 8x8 array of green and red lines oriented at 60 degrees, followed by a masking stimulus after a variable stimulus-to-mask onset asynchrony. On half of the trials, one element was replaced by a red or green line oriented at 40 degrees, with the 8 lines surrounding this target having the same color as the target, the opposite color, or a mixture of the two colors. We tested for differences in performance when subjects used the dominant vs. the non-dominant eye, and checked if any difference depends on the eye viewing surrounding elements. We found significantly better performance when the target was seen by the dominant eye, especially when surrounding elements were seen by the opposite eye. We conclude that the dominant eye has visual processing priority, perhaps arising from inhibition of non-dominant eye information.

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Oxidative stress induced by intraventricular streptozotocin (icv-STZ) suppresses protein kinase C beta 2 activity in rat brain and induces memory deficits: Prevention by rasagiline

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Intracerebroventricular (icv) injection of streptozotocin (STZ) in rats decreases glucose utilization in the cortex and hippocampus. We have found evidence of oxidative/nitrative stress, detected by antibodies to nitrotyrosine in the septo-hippocampal system as an early event after icv STZ injection. This was associated with damage to myelin and disruption of spatial learning. Activity of protein kinase C (PKC) isoforms has been implicated in development and maintenance of myelin and in learning. The present study explored the effect of STZ on PKC beta 2 (PKCb-2). STZ 0.5 mg was injected bilaterally to male rats weighing 300-320g. Immunohistochemical staining of brains 7 days later revealed a 10-30% reduction of PKCb-2 levels in cortex, hippocampus, striatum, corpus callosum, and internal capsule. Deficits in episodic and spatial memory were seen 15-60 days after icv STZ injection. In order to verify a contribution of oxidative stress to the memory deficits and enzyme changes, rats were given daily sc. injections for 2 weeks of 0.2 mg/kg of rasagiline. Rasagiline has shown efficacy in patients with Parkinson's disease and to prevent cell death induced by oxidative nitrative stress in SH-SY5Y neuroblastoma cells. We found that rasagiline increased PKCb-2 immunoreactivity in all brain regions in which this was decreased by STZ, and completely restored it to control levels in the hippocampal CA1 pyramidal layer. Rasagiline significantly reduced the spatial memory deficits seen 60 days after two STZ injections. Our findings support the hypothesis that the damage to myelin and memory deficits induced by icv-STZ involves a cascade initiated by oxidative stress and reduction in PKCb-2. Icv-STZ can serve as an in vivo model with which to screen potential neuroprotective agents for their ability to prevent myelin damage and memory impairment.

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The involvement of 5-HT and octopamine in short-term plasticity in the octopus vertical lobe

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Octopuses are unique invertebrate mollusks with a highly developed centralized brain and learning abilities comparable to those of vertebrates. In a previous study we discovered a hippocampal-like LTP in the octopus vertical lobe (VL), an area of the octopus brain involved in learning and memory. To find out whether the well known mechanisms of molluscan synaptic plasticity are conserved in the octopus VL, we first looked for the presence of 5HT in the VL complex. Fibers immunopositive for 5HT were found in the VL complex and stained terminals were found mostly in the VL neuropil. This finding led us to reinvestigate the involvement of 5HT in VL synaptic plasticity. In contrast to our previous work, where we tested only 5HT concentrations effective in Aplysia (10-50μM), a 2-6 fold facilitation of the synaptic field potential was induced when higher concentrations (100-200μM) of 5HT were used. In contrast to the activity-dependent potentiation, the effect of 5HT was readily reversible upon washout and was not occluded by induction of LTP. Octopamine had a similar and synergistic effect. The phosphodiesterase inhibitor IBMX facilitated the effect of 5HT suggesting the involvement of cyclic nucleotides. Paired-pulse facilitation was altered by 5HT and by

octopamine, suggesting that these substances act presynaptically. The effects of 5HT on the biophysical properties of identified presynaptic and postsynaptic cells of the VL were studied in whole-cell current clamp in enzymatically dissociated neurons. Preliminary experiments showed an increase in membrane excitability which resembles, at least in part, the 5HT-induced modification of these properties in Aplysia sensory neurons. Taken together, these results suggest that 5HT-dependent short-term neuronal plasticity, which is associated with simple forms of learning in mollusks, is conserved in brain areas of the octopus that mediate complex forms of learning and memory.

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Isolating the role of visual perception in dyslexia

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Despite the current prevalence of phonological theory of dyslexia, there are several theories (e.g. the magnocellular hypothesis) that attribute a key role to visual deficits as a basis for dyslexia. They stem from dyslexics' introspective reports of visual discomfort while reading and are supported by findings of various visual deficits in dyslexic subjects. However, these findings were argued against and largely explained as resulting from impaired perceptual memory rather than poor immediate perception. To assess the role of (possibly impaired) visual perception in dyslexics' reading, we composed a task that was similar to normal reading in its visual features, but lacked other aspects of reading (phonological, morphological, semantic etc.), and compared performance of dyslexics and controls on it under several paradigms. The task was to identify a letter of an alphabet unknown to subjects, but similar to Hebrew and English in all graphical details (11 similar Georgian letters). Eight different conditions were assessed, measuring threshold duration of presentation (SOA) and threshold contrast levels for identification of small and large letters, with and without flanker letters, with and without white noise. Twenty adult native-Hebrew speaking dyslexics, mainly students, and 20 controls, matched for gender, age, and general cognitive abilities, participated in this study. We found all the predicted effects in both groups. Namely, adding flankers and decreasing letter size increased threshold SOAs, and adding white noise increased contrast thresholds. However, there was no difference between the experiment group and the controls, neither in single-set comparison, nor in effect magnitude, nor in an all-inclusive analysis of variance (MANOVA $d=0$; $p>0.9$). We conclude that the visual processing deficits found among dyslexic individuals by other researchers do not affect reading performance, and that therefore, the cause of their reading deficit resides elsewhere.

Mechanism and circuitry for coarse and fine discrimination in the insect olfactory system

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We propose a solution to a major challenge in the study of olfaction, differences in coding between fine and coarse discrimination of odors. We hypothesize the existence of a hard-wired circuitry in the insect brain connecting the antenna lobe (AL), the mushroom body (MB), and the lateral horn (LH), constructed of repetitive and non-overlapping substructures that govern the connections between these regions. Using the above circuitry, we propose two parallel mechanisms, one for odor clustering and one for fine discrimination. In line with results suggesting that the KCs are coincident detectors, fine discrimination is encoded by the activity of the Kenyon cells (KCs) in the MB. Our mechanism for coarse discrimination is new, and uses a population code of groups of inhibitory neurons in the LH. We show that these mechanisms can explain the experimental results that AL oscillations are required for fine but not for coarse discrimination. Our theory also fits the data showing that non-associative discrimination can still be performed when the MB is completely removed. In addition, it sheds light on physiological results recording the activity of the various neurons when an odor is presented; for example, it predicts that odors that strongly activate the AL will also strongly activate the LH neurons, while the KCs fire sparsely. Our hypothesized circuitry also sheds light on the results of many experiments that map the connectivity between these regions.

Cortical plasticity in the visual cortex of the bilingual blind: an fMRI Study

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Recent studies, using imaging (fMRI) or transcarnial magnetic stimulation (TMS) techniques in humans, indicate that the visual cortex of the blind is recruited for other sensory functions as well as language processing. Is this plasticity restricted by a critical period? While so far this question has been tackled using a comparison between early blind vs. late blind, we took advantage of the fact that our polyglot subjects acquired their two languages at different ages. Using fMRI, we examined 9 bilingual congenitally blind subjects whose mother tongue is Hebrew and learned English later in life (~age 10). The subjects listened to "chimera" nouns (a superposition of a Hebrew noun and an English noun, recorded one on top of the other). During one condition subjects were instructed to repeat the noun heard (i.e. "repeat"), while during the other, they were asked to generate a verb to the heard noun (i.e. "verb generation, VG"). This procedure was carried out in each language, (i.e. Hebrew & English), in a block design fashion, according to heard instructions. When contrasting activation elicited during VG and repeat conditions, similar left lateralized activation was found for both languages throughout the whole brain including the visual cortex. Left lateralization was also observed in classical language areas (IFS, precentral sulcus) in congruence with findings from sighted subjects performing the same task. However, there was no significant difference in the fMRI activation generated by the two languages, in any cortical region, including the visual cortex. This suggests that either the second language was acquired within the critical period for plasticity, (which is thus longer than 10 yrs), or alternatively, regions in the visual cortex of the blind might be engaged in semantic processing, at an abstract level (regardless of the language of the heard words).

Effects of bilateral electric stimulation of the insular cortex on conditioned taste aversion in rats

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Newly acquired memories can be disrupted by agents such as protein synthesis inhibitors, during a maturation period called consolidation. Ample evidence now indicates that mature memories can also be disrupted by the same agents immediately after memory reactivation, in a process dubbed reconsolidation. We set out to find parameters for transient targeted brain stimulation that could lead to temporal dysfunction of brain substrates during acquisition, consolidation and reconsolidation of memory. Toward that end, we used conditioned taste aversion (CTA), a taste-malaise association, which is known to be subserved by the insular cortex, which contains the taste cortex in the rat. Our preliminary results show that acquisition of conditioned taste aversion (CTA) can be disrupted by bilateral electrical stimulation (30 min. high frequency) of the insular cortex, but not when stimulation is performed dorsal or lateral to the insular cortex. The stimulation was preformed from the presentation of the conditioned stimulus (taste) until 10 min prior to the presentation of the unconditioned stimulus (malaise inducing agent, LiCl). These results suggest that electrical stimulation of a localized brain region could be used as a tool to disrupt memory processes such as encoding, consolidation, and possibly post reactivation reconsolidation. In the latter case, it could pave the way to the development of a new treatment for non responsive post traumatic stress disorder (PTSD) patients.

The Recombinant Fusion Protein VP-22-Activity-Dependent Neuroprotective Protein Protects Pheochromocytoma Cells against Oxidative Stress

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Activity-dependent neuroprotective protein (ADNP) is a recently discovered homeobox profile containing gene that is essential for brain formation (Dev Brain Res. 2003, 144:83-90). Previous studies demonstrated an active site of the protein that included an eight amino acid peptide NAPSVIPQ (NAP) that showed a wide range of neuroprotective activity in vivo and in vitro (J Neurochem. 1999, 72:1283-93). In the present study, we examined the neuroprotective properties of ADNP. The Human ADNP cDNA (J Biol Chem. 2001, 276:708-14) was sub-cloned into a vector that contains VP22, a Herpes virus protein that allows penetration of fused proteins through cellular membranes. The recombinant fusion protein VP22-ADNP, was expressed in E. Coli, purified and assayed in differentiated pheochromocytoma (PC12) cells. VP22-ADNP was detected within the cells after 25-min incubation by western blot hybridization. However, using immunocytochemistry only minute amounts of ANDP were detected intra-cellularly after a 25 min. incubation period. Pre-incubation with VP22-ADNP protected PC12 cells against beta amyloid peptide toxicity as well as from oxidative stress. VP22 by itself was devoid of protective activity. To examine if VP22-ADNP protects against an apoptotic-like mechanism, alterations in the amount of the pro-apoptotic protein P53 were measured in PC12 cells. Results showed that p53 increased by 3.5 fold from control levels in the presence of H2O2, while treatment with VP22-ADNP prior to H2O2 exposure significantly reduced the p53 protein level. Thus, ADNP inhibited stress-induced p53 expression indicating protection against apoptosis. Taken together, these studies suggest that recombinant ADNP provides cellular protection against various toxic insults. *Supported by ISF, BSF, the Lily and Avraham Gildor Chair for Investigation of Growth Factors, Allon Therapeutics and the Institute for the Study of Aging.*

PKC isoforms play selective roles in the migration, differentiation and proliferation of multipotential precursor cells

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Multipotential neural precursor cells (MNPC) exhibit self-renewal potential and are capable of differentiating along different lineages of the CNS. The fate of the MNPC requires molecular cues mediated by extracellular factors and intrinsic signaling molecules. In this study we explored the role of protein kinase C (PKC) in the proliferation, migration and differentiation of MNPC. PKC, a family of phospholipid-dependent kinases is highly expressed in the CNS and plays important roles in the proliferation and differentiation of glial and neuronal cells. We found that the neurospheres expressed PKCalpha, beta2, delta, epsilon, zeta and mu and their differentiation was accompanied by increased expression of PKCbeta2 and PKCzeta*f*n *f*nand by a restricted expression of PKCgamma *f*nin the neuronal cells. We observed a slower electrophoretic mobility of PKCalpha and PKCepsilon and an increased phosphorylation of PKCepsilon on serine 729.The PKC activator PMA specifically increased the generation of astrocytes. To further explore the role of specific PKC isoforms in the differentiation of the MNPC, we employed adenovirus vectors expressing PKC*f*nisoforms and their respective kinase dead-mutants. We found that overexpression of PKCgamma selectively increased the generation and migration of neurons. In contrast, overexpression of PKCepsilon selectively increased the proliferation of GFAP+ cells, whereas the KD mutant increased the generation of oligodendrocytes. Mutation of serine 729 on PKCepsilon to alanine abolished the its proliferative effect. PKCalpha and PKCdelta did not play a significant role in the proliferation or differentiation of MNPC, however, the PKCalpha KD mutant abolished the effect of PMA on migration of GFAP+ cells. Our results implicate PKC as a major signaling pathway in the function of MNPC and suggest that different PKC isoforms can selectively direct the fate of MNPC and affect the generation of neurons astrocytes and oligodendrocytes from these cells.

Music, Memory and Hemispheric Asymmetry in the Visual Cortex of the Congenitally Blind

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While the occipital cortex of the congenitally blind can be activated by tactile stimuli (as well as auditory ones), most of the evidence indicates that this activation is associated with verbal tasks, such as verb generation and Braille reading. Furthermore, tactile related activation in the occipital cortex can be found in blindfolded sighted subjects, after 5 days. This suggests that Braille, connecting phonics with tactile sensations, may be the critical link for the recruitment of the visual cortex, to take part in language processes. This study re-examines the emphasis on language, while demonstrating a larger effect of mnemonic properties of the task, especially in the primary visual cortex. We compared verbal and musical mnemonic tasks, as well as verbal and musical perceptual tasks. The mnemonic tasks included the recognition of previously learned words and tunes, and the perceptual tasks were the detection of a repeated tone or letter. We found that the mnemonic tasks generate robust activation in the visual cortex of blind compared with the perceptual tasks. Higher activation in V1 of the blind, in both hemispheres, was found during the musical mnemonic condition than during the verbal task. This preference may be partially attributed to the depth and length of the encoding process of the lists, to-be-remembered, into long-term memory, which was greater during the musical condition. Hemispheric differences in activation pattern were found in the lateral ventral occipital regions. Thus, the left lateral occipital cortex was significantly more activated than the right one, during the verbal perceptual (phonological) task. This hemispheric difference is compatible with the asymmetry observed in the conventional language regions, grossly maintaining a lingual dominance in the left hemisphere and a musical dominance in the right hemisphere.

EM evidence for a mechanism of analgesia during general anesthesia

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Microinjection of minute quantities of pentobarbital into a restricted region of the rat brainstem, the MPTA (mesopontine tegmental anesthesia area), can induce a general anesthesia-like state characterized by atonia and failure to respond to strong noxious stimuli (Devor and Zalkind, Pain 2001). To understand the neural circuitry associated with the different components of the anesthetic state we investigated the afferent and efferent connections of MPTA using retrograde and anterograde neuroanatomical tracers (cholera toxin beta subunit, CTB and biotinylated dextran amine, BDA respectively). MPTA has a major descending projection to the rostral ventromedial medulla (RVM), a key relay component of the descending bulbospinal pain inhibitory system. To clarify if MPTA neurons that project to RVM indeed terminate on cells that project to the spinal cord we performed a double-labeling experiment. Bulbospinal RVM neurons were retrogradely labeled by CTB microinjected into the lumbar spinal cord and MPTA efferent projections were labeled using BDA microinjected into the MPTA. At the light microscopic level we found numerous labeled MPTA axons in close apposition to retrogradely labeled spinally projecting RVM neurons. These connections were confirmed to be synaptic contacts at the electron microscopic (EM) level. Specifically, anterogradely labeled terminals were found to synapse on retrogradely labeled neuronal somata and dendrites. The projection of MPTA neurons onto bulbospinal RVM neurons could be a route whereby barbiturates, and perhaps other general anesthetics, suppress responsiveness to noxious stimuli during general anesthesia.

Temporally Coherent On-going Activity in Auditory Cortex is Demonstrated through LFP Recordings from Anesthetized Cats

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Electrical activity in the brain shows organization at multiple time and spatial scales. Here we studied the correlation between well-separated units, clusters of units, and local field potentials (LFP) recorded from 2-4 electrodes simultaneously during on-going activity in auditory cortex of halothane-anesthetized cats. We show that the local neural tissue has a significant degree of burst activity and temporal correlation. The number of spikes fired by single units during 200 ms periods with no stimulation was found to be correlated with the responses of other units recorded from the same and from nearby electrodes. Moreover, LFP recorded from those electrodes was significantly correlated with the number of spikes recorded at the same time period. These results support the hypothesis that the recorded spikes are only a few representatives of a temporally coherent on-going activity in the neural tissue. These findings imply that LFP, which is much easier to record than well-separated spikes, can have substantial amount of information about sensory stimuli and is therefore a good candidate for decoding the neural activity, as it can replace spike sorting in some cases. For example, stimulus-specific adaptation, which was previously demonstrated in A1 at the single neuron level by analysis of the spike counts in response to standards and deviants in an oddball paradigm, is shown here to be present in the LFP recorded by the same electrodes as well.

Traumatic Brain Injury-Induced Stimulation of Systemic Bone Formation

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Recent reports on communication pathways between the central nervous system and bone has attracted particular attention to the central control of bone mass. Perhaps the most direct clinical evidence for such a control system is the highly consistent observation of heterotopic ossification and enhanced fracture healing in patients with traumatic brain injury (TBI). To study the mechanisms involved in this phenomenon we have developed a mouse model whereby closed head injury (CHI) induces systemic increase in bone formation measurable in the femoral trabecular and cortical bone. Stimulation of trabecular bone formation, unaccompanied by changes in bone resorption, was observed in the distal femoral metaphysis 1- 8 days post CHI. Periosteal bone formation in the mid-diaphysis was initially enhanced and then declined with time after CHI. The CHI-induced increase in bone formation was independent of the mouse strain and gender. We then used mice deficient of the neuronal, predominantly central cannabinoid receptor (CB1) to explore the bone-to-brain pathways involved in the CHI-induced increase in bone formation. These mice have a basal low bone mass phenotype secondary to low bone formation and high bone resorption. The bone formation rate of the CB1 knockout mice was unaffected by CHI. Together with the previously demonstrated CHI-induced stimulation of endocannabinoid production, these findings imply stimulation of the neuronal CB1 receptor signaling as a key component mediating the TBI stimulation of systemic bone formation. These data portray an important role for the endocannabinoid system in brain-to-bone communication.

The Role of Bad in the Neuroprotective Action of the Major Green Tea Polyphenol, (-)-Epigallocatechin 3-Gallate (EGCG)

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Green tea cathechins and their derivatives have potent pharmacological activities. They act as radical scavengers and exert indirect antioxidant effect through activation of transcription factors and antioxidant enzymes. Its major polyphenol, (-)-epigallocatechin-3-gallate (EGCG) has been reported to exert potent neuroprotection in vitro and in vivo models of neurodegeneration. We have demonstrated that the neuroprotective action of EGCG is mediated by activation of protein kinase C (PKC). The aim of this study was to further determine the potential cell signaling pathways, downstream from PKC, involved in EGCG neuroprotective activity. EGCG (1microM) promoted a biphasic effect on the pro-apoptotic Bad protein: an immediate (30 min) down- regulation (~35%) of its protein levels, returning to control values 2h later and a more pronounced long-term (24h) reduction (~55%). The expression of Bax was not affected during the first 24h exposure to EGCG. The acute Bad reduction was accompanied by a 1.65 fold increase in phosphorylated PKC alpha isoform. By contrast, pretreatment with a general PKC inhibitor GF 109203X (2.5microM), abolished EGCG-induced Bad decline. This result indicates that PKC is a tight regulator of Bad protein expression levels, being essential for its degradation or synthesis. In view of this finding, the potential involvement of the Ubiquitin Proteasome System (UPS) in EGCG-induced Bad degradation was examined. Pre-incubation with MG-132 (25microM), a reversible proteasome inhibitor, blocked the degradation of Bad by EGCG. The present study reveals a novel pathway in the neuroprotective mechanism of EGCG, which involves a rapid PKC-dependent degradation of Bad protein by the UPS.

Differential Intrinsic Neuronal Plasticity in Epilepsy

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Temporal lobe epilepsy (TLE), the most common epilepsy in adults, is associated with structural and functional alterations in hippocampus and related structures, which lead to hyperexcitability and recurrent seizures. In a widely studied rat model of TLE, similar changes can be seen a few weeks after a single episode of status epilepticus (SE) induced by injecting pilocarpine. In this model, ex-vivo recordings from CA1 pyramidal cells (PCs) have revealed several changes in intrinsic excitability. The most dramatic change was increase in the fraction of bursting cells. This burst-firing was abolished by low Ni2+ concentration (100 *f*YM), implicating low voltage-activated T-type Ca2+ current (ICaT) in its generation. To test whether TLE associated changes in intrinsic excitability are unique to CA1 PCs, we recorded similarly in CA3 PCs using standard current-clamp intracellular recording techniques. In control rats, CA3 PCs fired either regularly or in bursts in response to long (180 ms) and strong depolarizing current stimuli. Low-intensity or brief stimuli did not induce bursting. In contrast, 20% of CA3 PCs in pilocarpine-injected rats fired an all-or-non bursts spontaneously or in response to just-threshold stimuli. This de novo bursting was unaffected by 100 *f*YM nickel, but was blocked by the persistent Na+ current (INaP) blocker riluzole (10 *f*YM), implicating the latter current, rather than ICaT, in its generation. This data, together with our previous study in CA1, suggest that upregulation of intrinsic bursting in experimental TLE is wide spread, but the ionic mechanisms underlying aberrant intrinsic bursting may vary across different types of neurons.

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Acute brain neuroprotection by scavenging blood glutamate

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Abnormally high Glutamate (Glu) levels in brain interstitial and cerebrospinal fluids are the hallmark of several neurodegenerative conditions that result from acute insults, such as stroke, traumatic brain injury or meningitis. As a novel neuroprotective strategy, we have established that a decrease of deleterious Glu in brain fluids can be achieved by accelerating the naturally occurring brain-to-blood Glu efflux. This is produced by decreasing blood Glu levels upon intravenous (IV) administration of pyruvate (Pyr), and/or oxaloacetate (OxAc). These compounds act as blood Glu scavengers since they activate respectively, together with their co-substrate Glu, the blood resident enzymes Glu- Pyr transaminase and Glu- OxAc transaminase with transform Glu into 2-ketoglutarate. We have investigated the acute neuroprotective effects of Pyr and OxAc in rat models of closed head injury and of global ischemia. In the rat model of closed head injury, the IV administration of Pyr and/or OxAc performed 1 hour after head trauma was found to dramatically improve the neurological status determined after 48 hours. OxAc was superior to Pyr while the neuroprotective effects of OxAc were abolished when the rats were treated with OxAc + Glu suggesting that the beneficial effects of OxAc are likely to be due to its blood Glu scavenging property. This suggestion is supported by the observation that rats treated with IV Glu have a worse outcome than control rats. In the rat model of transient global ischemia, the 30 min long IV administration of Pyr and OxAc, overlapping the 10 min long ischemia, was found after 7 days to cause the preservation of the vast majority of brain neurons in comparison to the death of 60 70% of neurons in control animals. We conclude that scavengers that reduce blood Glu levels cause brain neuroprotection by increasing the brain-to-blood Glu efflux decreasing thereby the excitotoxic and deleterious effects of the high Glu levels in brain fluids.

The effect of magnetic field on olfactory processing

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Functional magnetic resonance imaging is increasingly used as a tool to elucidate the neural substrates of olfaction. However, it is possible that the magnetic field used in functional imaging may itself affect olfaction. It is known that the direction and strength of a magnetic field have an effect on visual perception tasks. Likewise, the strong magnetic field of an MRI scanner can induce phantom gustatory perception. Anecdotal observations in our laboratory suggested that olfactory intensity perception was enhanced under a strong magnetic field. To address this possibility, the University of Pennsylvania Smell Identification Task (UPSIT) was administered to 9 subjects both in the MRI scanner (4 Tesla Varian) and out of the magnetic field in a mock scanner. In addition to identification, subjects rated stimulus intensity and pleasantness on a visual analog scale. The order of field strength conditions (IN/OUT of the magnet) and UPSIT booklets (1 through 4) were counterbalanced across subjects. There was no significant difference in identification accuracy (mean OUT = 37, SD = 2.027; mean IN = 33, SD = 2.179) or hedonic rating (mean OUT = 43.97, SD = 17.402; mean IN = 45.86, SD = 17.7) in and out of the magnetic field. By contrast, there was a trend towards greater intensity rating IN as compared to OUT of the magnetic field (mean OUT = 0.480, mean IN = 0.523, $t(8) = 2$, $p < 0.07$). A post-hoc examination of identification accuracy for the 40 odorants that comprise the UPSIT identified a trend towards a magnetic field effect for the odorant cinnamon. Whereas only one subject failed to identify cinnamon in the field, five subjects failed to identify it out of the field. This difference ($p < 0.02$) does not meet the bonferroni corrected criteria of $p < 0.001$. Further investigation of these results will determine whether these effects result from a change in peripheral or central level olfactory processing.

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Anatomical and Functional Consequences of Blood-Brain Barrier disruption in human Cerebral Cortex

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The blood brain-barrier (BBB) protects the brain from circulating xenobiotic agents. Disruption of the BBB is known under many pathological conditions. However, the pathophysiology, time span, spatial pattern and consequences of BBB disruptions are unknown. In animals, several invasive methods have been developed to quantitatively measure BBB permeability. However, most of these methods are not applicable to humans. We have developed an image analyses program for quantifying BBB permeability to contrast agents injected during routine brain images procedures- computerized tomography (CT) and magnetic resonance imaging (MRI). By image analyses we were able to make a statistical comparison between brain images taken before and after the injection of the contrast material as well as measure % enhancement values. In a group of patients BBB disruption, detected by CT or MRI, was verified by single photon tomography (SPECT) following the injection of 99mTc-diethylenetriaminepentaacetic acid (Tc-DTPA) or by albumin concentrations in the cerebrospinal fluid. BBB disruption was found to be either diffuse or focal, and in most cases (>90%, n=101) was found to be confined to the cerebral cortex. In some cases focal disruption of the BBB persisted over long periods of time (weeks-years). While various pathologies were found to present with changes in BBB permeability, no single pathological process was found to underlie disruption in all patients. Two sub-groups of patients with focal, long-lasting BBB disruption were subjected to quantitative electroencephalographic recordings. These included 18 patients after mild head trauma and 12 patients post surgical removal of a benign meningioma. In both groups, spatial correlation was found between areas of BBB disruption and slow-wave abnormal cortical activity. We conclude that BBB disruption is a common disorder in the diseased cerebral cortex, and when persistent may be associated with abnormal cortical function.

Effects of pleasant and unpleasant gustatory stimuli in anorexia nervosa as revealed by spectral and dimensional EEG changes.

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Anorexia nervosa (AN) is considered a multi-factordetermined disease, with biological and environmental factors contributing to its evolution. The pathologically altered processing of gustatory stimuli could be an important factor in the development of AN. The aim of the present study was to investigate the effects of pleasant (chocolate) and unpleasant (bitter tea) gustatory stimuli on the EEG in both a healthy control group and in a group of AN patients by linear (frequency spectral analysis, Omega complexity) and nonlinear (PD2, characterizing dimensional complexity) EEG complexity analysis. The subjects were exposed for two minutes to pleasant (sweet chocolate) and unpleasant (bitter tea) gustatory stimuli. The EEG was recorded right after taste exposure followed by mouthwash. The EEG was recorded by the NeuroScan system. The EEG recorded by 12 electrodes (Fp1, Fp2, F3,

F4, C3, C4, T3, T4, T5, T6, P3, P4) was selected for further off-line analysis. In AN patients lower dimensional complexity and higher amount of relative theta power was observed than that seen in controls, independent of taste conditions. Higher Omega complexity was seen in control subjects in the left side irrespective of taste effects. No such hemispheric difference was observed in AN. The lack of a significant Omega complexity change in response to exposure of sweet taste in the left side in AN patients may correspond to a decreased sensitivity to such stimuli in these subjects. Since all the patients who participated in the present study had episodes of abnormal wasting prior the investigation it seems reasonable to suppose that a long-lasting effects of malnutrition could be manifested in low dimensional EEG and higher amount of relative theta (4-8 Hz) activity.

"Juvenile" stress as a risk factor for impaired coping behavior in adulthood - A rat model.

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Epidemiological studies indicate that early life stress constitutes a risk factor for developing mood and anxiety disorders in adulthood. While most studies focus on pre-weaning exposure, this study examined the consequences of stress during the post-weaning period Experiment 1 examined the effects of mild juvenile stress (days 27-29) on coping with stress in adulthood (Day 56), measuring exploratory behavior and avoidance learning. Experiment 2 evaluated the duration and magnitude of juvenile stress (28 days) effects on anxiety indices in adulthood. Experiment 3 sought after a 'critical developmental window' during the post-weaning period, i.e. rats underwent mild stress at either 27-29 days (juvenile) or 33-35 days (pre-adolescence) and their exploring and avoidance learning were assessed in adulthood.

Learning Deficits and Neuronal Degeneration in Male Mice Harboring One Copy of the Gene Encoding Activity-Dependent Neuroprotective Protein (ADNP)

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Vasoactive intestinal peptide (VIP), a brain extracellular signaling molecule, has been implicated in neuroprotection, learning and memory as well as in sexual behavior in genetically manipulated animals. Activity-dependent neuroprotective protein (ADNP), a homeobox-profile containing gene, was recently identified as a VIP-responsive gene (J Neurochem. 1999, 72(3):1283-93. J Biol Chem. 2001 276, 708). The current study was set out to investigate the role of ADNP in brain function using homologous recombination. ADNP knockout embryos die in uteri (Brain Res Dev Brain Res. 2003 144,83), while ADNP+/- heterozygous mice that show a 50% reduction in brain ADNP mRNA expression, exhibit growth restriction (7-20%) and learning deficits. Learning deficits in the Morris water maze were observed at one month of age and were enhanced at two months of age in the ADNP+/- heterozygous males. Assessment of motor activity did not reveal a difference up to 2 month of age. The learning deficits may stem from defective brain development during embryogenesis coupled to deficits in ADNP in adulthood. Cresyl Violet staining revealed degenerative neurons in the hippocampus and the cortex of 9-12 months old ADNP+/- mice and these results were corroborated by staining with a polyclonal antibody against the C-terminus of the beta-APP (beta amyloid precursor protein). Further studies identified hyper tau phophosphorylation in the ADNP+/- mice In conclusion, ADNP is identified here as a new key gene essential for normal brain function.

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Prenatal immune activation in rats: mimicking abnormalities relevant to schizophrenia

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Prenatal exposure to infection is associated with increased liability to schizophrenia, and it is believed that such an association is mediated by the maternal immune response, in particular the pro-inflammatory cytokines released by the maternal immune system, which may disrupt fetal brain development. We induced maternal immune activation by peripheral administration of the synthetic cytokine releaser Polyriboinosinic-Polyribocytidilic acid (poly I:C) to pregnant dams, and assessed in the offspring several indices considered relevant to schizophrenia, pre- and post-puberty. Consistent with the characteristic maturational delay of schizophrenia, prenatal immune activation led to post pubertal emergence of disrupted capacity to ignore irrelevant stimuli, one of the central cognitive deficits in schizophrenia, which was normalized by haloperidol and clozapine, as well as increased sensitivity to the locomotor-stimulating effects of amphetamine and increased *in-vitro* striatal dopamine release. Morphological alterations in the hippocampus and the entorhinal cortex were evident at both ages. These results are consistent with the well documented mesolimbic dopaminergic and temporolimbic pathology in schizophrenia, and further suggest that the latter precedes the former. Importantly, prenatal poly I:C administration did not lead to a general learning deficit. Our findings suggest that prenatal administration of poly I:C may provide a neurodevelopmental model of schizophrenia which: 1. reproduces a putative inducing factor; 2. mimics the characteristic maturational delay of the clinical disorder; 3. mimics a central cognitive, neurochemical, and neuropathological abnormality of the disorder; and 4. predicts responsiveness to antipsychotic drugs. This in turn supports the hypothesis that immune activation during pregnancy may in part be responsible for the interaction between maternal infection during pregnancy and schizophrenia.

Frequency MMN is impaired in dyslexics with learning difficulties

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Frequency discrimination findings in dyslexic research vary extensively, perhaps due to the variability in behavioral paradigms applied, and in the heterogeneity of the dyslexic groups. Previous findings in our lab have shown that the majority of dyslexic individuals who suffer from additional learning disabilities (D-LD) perform poorly in simple psychoacoustic tone discriminations. On the other hand – their basic speech perception seems adequate.We now asked whether it is the requirement of explicit stimulus comparison, in simple psychoacoustic tasks, which poses the difficulty for this group. A group of D-LD teenagers and a group of education and age-matched controls were administered an odd-ball paradigm with graded changes in tone frequency. In the first phase, subjects ignored the auditory stimuli and mismatch-negativity (MMN) was recorded. Afterwards a behavioral active discrimination task was administered. We found diminished MMN amplitudes in the D-LDs' group compared to controls. A particularly large difference was found for the larger deviance. Moreover, whereas MMN amplitude and latency for controls was graded according to the degree of deviance presented, no such gradation was found for D-LDs. This pattern of results was mirrored in the behavioral performance. Response time and accuracy for all deviants were worse in D-LDs, and showed no gradation for the different deviants, whereas controls showed better performance as the deviance increased. Thus, D-LDs have impaired behavioral and brain responses even when no explicit comparison is required. MMN stems from an implicit form of perceptual memory, i.e. specific adaptation to repetitive sequences of stimuli. We thus propose that the source of D-LDs' deficit is impaired implicit memory, apparent as adaptation. Since specific adaptation leads to encapsulated representation of consistently concurring stimuli, its malfunction hampers formation of adequate auditory representations, as is the case in D-LDs.

Examining effects of postnatal maternal care on offspring phenotype by "switching" the pups between dams of one line and another

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The relative contribution of postnatal maternal care to the offspring's phenotype can be partially analyzed by studying pups from one line/genotype that are placed with a mother from another line/genotype and comparing them with pups raised by same-line dams. Benefits and limitations of this approach will be discussed, together with findings from our labs, using several rat models and assessing isolation-induced ultrasonic vocalizations (USV; a measure of "infant separation-anxiety"), body-weight gain and immobility in the swim-test (a measure of "behavioral despair"). We found that cross-fostering rat pups from a line that emits a high amount of USV to low-USV-line dams did not affect the pups' high vocal response. Pups from a different line ("OLETF"), lacking type-A receptors for the neuropeptide cholecystokinin, also were found to emit many USV compared to their control line (LETO). This was further found whether the OLETF pup was interacting with a LETO or an OLETF dam. OLETF pups also gain weight more than their controls. Preliminary results suggest that this holds even when the OLETF pups are raised by a LETO dam. In the Flinders-Sensitive Line (FSL), an animal model of depression, we found that nursing dams and weaned, prepubertal pups, exhibit greater durations of immobility in the swim-test compared to Sprague-Dawley (SD) controls. Maternal behavior patterns of FSL dams were also abnormal. Cross-fostering SD pups to FSL mothers increased the prepubertal pups' immobility duration, while immobility of FSL pups was not significantly changed by cross-fostering by a SD dam. To the extent that the "switching" method can represent postnatal environmental influences, the results above suggest that factors beyond postnatal care (i.e., genetic, and prenatal environmental factors) may provide most of the influence on USV and weight gain, at least in these particular rat lines. However, other postnatal manipulations may nevertheless affect the infant's phenotype.

Interleukin-1 (IL-1) Plays a Role in Stress-Induced Analgesia (SIA)

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Several lines of evidence indicate that the proinflammatory cytokine IL-1 is involved in the neural, endocrine and behavioral responses to stress. For example, exposure to various stressors was found to increase the production and secretion of IL-1, in the periphery and within the brain, and this increase was associated with activation of the hypothalamic-pituitary-adrenal axis. We have recently shown that mice with impaired IL-1 signaling display diminished corticosterone secretion after exposure to mild stress compared with their wild type (WT) controls. A prominent consequence of exposure to stressful stimuli is reduced pain sensitivity, termed "stress-induced analgesia (SIA)". Since IL-1 plays a role not only in stress responsiveness but also in pain modulation (under both inflammatory and non-inflammatory conditions), we hypothesized that it is involved in the pain modulatory effect of stress. To test this hypothesis we used two mouse models of impaired IL-1-signaling: Targeted deletion of the IL-1 receptor type I (IL-1rKO), or transgenic overexpression of the IL-1 receptor antagonist within the CNS (IL-1raTG). Mutant mice were compared with their WT controls. Mice swam for 2 min at 32°C, allowed to dry for 2 min, and tested for pain sensitivity using the hot-plate test immediately after drying. Two-way ANOVA revealed a significant strain by treatment interaction: The two WT strains displayed marked analgesia following exposure to the swim-stress, while both mutant strains did not display stress-induced analgesia. These results suggest that IL-1 plays an important role in SIA. Since this effect was also observed in IL-1raTG mice, which overexpress IL-1ra only in the CNS, it appears that this role of IL-1 is mediated via the CNS.

Impairment of Interleukin-1 (IL-1) Signaling Attenuates Neuropathic Pain and Spontaneous Ectopic Neuronal Activity Following Nerve Injury

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Neuropathic pain is a chronic pain state resulting from peripheral nerve injury, characterized by both hyperalgesia and allodynia. In view of the known pain facilitatory role of IL-1 in various inflammatory conditions, these findings suggest that over-production of IL-1 may underlie the hyperalgesia and allodynia seen in neuropathic pain. In the present study, we tested the hypothesis that impaired IL-1-signaling influences neuropathic pain, using two mouse models: mice with targeted deletion of the IL-1 receptor type I (IL-1rKO) and mice with transgenic overexpression of the IL-1 receptor antagonist (IL-1raTG), and their WT controls. Neuropathy was induced by cutting the L5 spinal nerve on one side, and mechanosensitivity was measured for 7 successive days. Neuropathic pain was also assessed by cutting the sciatic nerve, measuring the autotomy score for 35 days. We report here that WT mice developed neuropathic pain, as reflected by significant allodynia in the hindpaw ipsilateral to the injury compared with the contralateral hindpaw. The mutant strains, however, did not display increased pain sensitivity in either hindpaw. Spontaneous ectopic neuronal activity of these strains was recorded in the dorsal root ganglion (DRG), 1, 3, and 7 days following nerve injury. In WT mice a significant proportion of the axons (10.3-18.0%) exhibited spontaneous ectopic neuronal activity at all time points, whereas in mutant mice only minimal number of axons exhibited such activity (1.3-1.6%). WT mice developed progressive autotomy following sciatic denervation, while both IL-1rKO and IL-1raTG mice displayed delayed onset and reduced scoring. Taken together, these results suggest that IL-1 signaling plays an important role in the altered neuronal activity that underlies the development of neuropathic pain. *Gilly Wolf and Eran Gabay contributed equally to this research.

D-Serine as a Physiological Activator of NMDA Receptors: Implications for Stroke and Psychiatric Diseases.

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NMDA receptor plays a major role in excitatory neurotransmission, displaying a unique requirement of two distinct agonists to mediate calcium influx. In addition to glutamate, it requires binding of either glycine or D-serine to the "glycine site" of the receptor. Recent data indicate the presence of high levels of D-serine in the brain of higher organisms, raising the possibility that this unusual D-amino acid may be involved in the physiological regulation of NMDA receptors. We will present data demonstrating the biosynthesis, metabolism, uptake and release of D-serine from astrocytes, neurons and brain slices. We report that NMDA-elicited neurotoxicity in different experimental systems requires endogenous D-serine, indicating that D-serine physiologically interacts with the "glycine site" of NMDA receptors. In this framework, D-serine is proposed to be a novel neurotransmitter in the brain. Drugs that affect D-serine synthesis and degradation might be useful in several pathological conditions, including overstimulation of NMDA receptors in stroke and neurodegenerative diseases, and NMDA receptor hypofunction in schizophrenia.

Scaffolding of Fyn kinase to the NMDA receptor determines brain region sensitivity to ethanol

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Alcohol abuse is a major societal problem. Although ethanol is a structurally simple, diffusible molecule, its sites of action are surprisingly selective and the molecular mechanisms underlying specificity in ethanol actions are not understood. The N-Methyl D-Aspartate (NMDA) receptor channel is one of the main targets for ethanol in the brain. We found that the brain region-specific compartmentalization of Fyn kinase determines NMDA receptor sensitivity to ethanol. We demonstrate that in the hippocampus but not in the cerebral cortex, Fyn is targeted to the NR2B subunit of the NMDA receptor by the scaffolding protein RACK1. Upon acute exposure to ethanol, RACK1 is dissociated from the complex thereby facilitating Fyn-mediated phosphorylation of NR2B, which enhances channel activity and thereby counteracts the inhibitory actions of ethanol. In this way, the selective scaffolding can account for the ethanol-induced acute tolerance of NMDA receptor activity that is detected in the hippocampus but not in the cerebral cortex. The phosphorylation-dependent, region-specific activities of ethanol on the NMDA receptor provides a compelling molecular explanation that accounts for the selective activities of ethanol and may have important implications for elucidating pathways leading to alcohol addiction.

Delay activity neurons in monkey prefrontal cortex

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We trained a macaque monkey on a behavioral task that requires holding several visual images simultaneously in working memory. In each trial, a sequence of 1-4 different images served as samples. These were followed by a match stimulus, which was a repetition of one of the samples, (called the cue). The length of the sequence and the position of the cue in the sequence were chosen at random on each trial. The monkey's task was to recognize the appearance of a repetition of any one of the samples and therefore, for best performance, it needed to hold in working memory (selective delay activity) all of the images of the sequence. We recorded from prefrontal cortex, understood to be the most appropriate cortical area for involvement in such a task. A quarter of the recorded cells (45/168) exhibited delay activity. We found that delay activity initiated by presentation of one stimulus could survive through presentation of a few other images, as well as the inter-image-intervals. As expected, we found that the longer the trial, i.e. the more intervening stimuli, the less was the chance of survival of the image's delay activity. These results are in good agreement with our behavioral results and model, proposing delay activity reflecting active working memory, maintaining storage of multiple images (ISF, 2002, 2003; Amit et al., Cerebral Cortex 2003; Yakovlev et al., Cerebral Cortex 2004).

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A possible antagonism between norepinephrine and glucocorticoids induced signaling pathways: relevance to the etiology and treatment of major depression.

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Substantial clinical and preclinical evidence implicates alterations of the stress hormones and an impairment of the HPA axis in the etiology and development of depression. In the past decade, research has focused on long term intracellular processes in depression and stress leading to abnormal neuronal plasticity. To examine a role for the glucocorticoid on neuronal morphology and plasticity, human neuroblastoma SH-SY5Y cells were treated with repeated doses of 10-5M dexamethasone (DEX) for 24 48 or 72 hours. DEX treatment induced a time dependent decrease of cell number after 24h while an increase in cell division was observed following daily treatment with DEX for 72 hours. Moreover, cells treated with 10-5M showed a transient decrease in neurite number when compared with non treated cells. These changes were accompanied by time dependent decreases in CREB and ATF-2, transcription factors involved in plasticity and implicated in stress and depression. Concomitantly, mRNA levels of CAM-L1, a neurite-outgrowth promoting genes, and Gap-43, a synaptic marker, were decreased after 24 and 72 hours, respectively. The alterations in cell number together with the changes in morphology and the expression of plasticity related genes suggest a role for glucocorticoids in cell differentiation. In a previous study we have shown that the expression of ATF-2, CAM-L1 and Gap-43 were increased following a single treatment with norepinephrine. The opposite effects of DEX, acting as a model for stress and depression, and NE, a substrate of anti-depressant drugs, point to a possible convergence of signaling pathways and may explain the etiology and treatment of depression.

The effects of acute stress on local circuit activity in the rat dentate gyrus

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Studies have shown that, depending on its severity and contex, emotional stress can impair learning. Most related studies concentrate on synaptic plasticity and long-term potentiation (LTP) of principle cells. However, it has become clear that modifications also take place at the level of complex interactions with the principle cells within the dentate gyrus, i.e. at the local circuit level. So far though, no research has been done to establish the possible effects of stress on local circuit activity and plasticity. We set out to examine possible alterations in local circuit activity and plasticity following exposure to stress. Local circuit activity and plasticity were measured by using frequency dependent inhibition (FDI) and commissural modulation protocols following an exposure to a 15 minute- forced swim stress. Commissural induced inhibition was significantly higher in stressed rats both before and after applying high frequency stimulation. Exposure to stress did not alter FDI. The application of high frequency stimulation reduced FDI in both groups, but this type of plasticity was greater in the stressed rats. These findings indicate that the exposure to acute stress affects aspects of local circuit activity and plasticity in the dentate gyrus. It is possible that these alterations underlie some of the behavioral consequences of the stress experience.

The soma of pyramidal cells is noisier than its dendrites

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Neurons are noisy elements. A quantitative understanding of neuronal noise along with a qualitative understanding of its origins is necessary for understanding the constraints under which the neural code operates. In a previous study, using current clamp recordings from layer IV-V pyramidal neurons in slice preparation of rats' neocortex, we demonstrated that voltage noise increases as the cell depolarizes. This increase was mostly due to the negative slope of persistent Na+ conductance in the subthreshold voltage regime, which acts as a voltage dependent amplifier of low frequency transients. In a recent study using simultaneous recordings we compared the noise in the soma to that of a dendrite in the same neuron. As in the soma, noise in dendrites also increased with depolarization. Unexpectedly, the magnitude of noise in the soma was always larger than that in the dendrite. The difference increased with the distance from the soma and was eliminated by blocking the Na+ conductance using tetrodotoxin. We conclude that the source of this noise is

the persistent Na+ current which is located at the soma; the lower noise level at the dendrites is due to electrotonic attenuation of the noise from the soma to the dendrites. These results further support the existence of a tetrodotoxin-dependent noise source near the soma and suggest that Na+ dependent noise plays a major role in the integration of synaptic inputs and determination of the neuronal output.

The hippocampus and insular cortex are differentially activated in novel taste learning

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We are interested in understanding the neural mechanisms which underlie the formation of long-term memory. Towards that end, we investigate the activity of ERKI/II, phosphorylation of Akt/protein kinease B(PKB) and cAMP respons element binding protein (CREB), and expression levels of C/EBP in the hippocampus and the insular cortex following novel taste learning. We compare between novel (saccharin 0.3%) and familiar taste (water) in the following time points: 2min, 20min, 30min, 3hr, 6hr, 14hr, 18hr, 24hr (n>7 for each time point). ERKI/II, CREB, actin and Akt expression levels are not changed in the cortex or the hippocampus following learning. ERKI/II activation is increased in the insular cortex 20 minutes following learning but not in any other time point (as published before). However, ERKI/II is not activated in the hippocampus in the same time point. In contrast to ERKI/II, Akt and CREB are phosphorylated (CREB on ser 133 and Akt on ser 473) in the hippocampus of the trained but not control animals 20 minutes following learning but not in any other time point (169%, $p<0.01$ 427%, $P<0.05$ respectively). We next measured the expression level of C/EBP, protein known to be down stream of CREB and involved in learning and memory process. We detect an increase in C/EBP expression 18hr following learning both in the hippocampus and insular cortex (37%, $p< 0.05$). We concluded that both the hippocampus and the insular cortex are working in concert to form novel taste learning. In addition, different biochemical pathways are activated in the two brain structures in a similar time frame.

Learning to adapt: adaptation of the visual system to monocular optical-distortions.

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The visual system is capable of adapting to optical distortions caused by the eyes optics or by added lenses. Astigmatism is an optical error that distorts the visual input along one axis of the visual image due to the cylindrical shape of the lens (which is spherical in the standard eye). Here we study the time course of adaptation to cylindrically distorted visual inputs given to one eye (as in amblyopia). Methods: We used a matrix of 10x10 dots as a target to test grouping by proximity. Subjects wore on one eye a cylindrical lens of +1.00 D, to create an optical distortion. which changed the proximity between the dots along one direction and thus the directionality of the perceived pattern. Subjects task was to distinguish between horizontal and vertical groupings without feedback. The other eye was either covered (monoptic) with or was open (dichoptic). Perceived grouping before, after, and throughout the adaptation period was measured. Results: (1) Without the cylinder lens no bias was found (N=12). There was a match between proximity bias in the stimulus and the subjects' report, with a sharp transition between vertical and horizontal groupings. (2) Tests with the cylindrical lens (N=12) showed a bias in the perceived orientation, in accordance with the distortion axes. (3) After 2 hours with the cylindrical lens (N=12) there was no sign for adaptation but only for an after-effect when the lens was removed (reversed bias). (3) After 4 hours, the monoptic group (N=6) showed adaptation (reduced bias) while the dichoptic group (N=3) showed an opposite effect (increased bias). (4) For both groups (N=12) the adaptation effects were preserved when the lens was re-applied the next day. Discussion: The results suggest that the site of adaptation is at a binocular level. The transfer across days implies that the recalibration process underlying visual adaptation can be learned and efficiently reactivated when a previously experienced distortion reappears.

Stretch Injury to Cells Causes Changes in GSH/GSSG ratio (Redox status) in in-vitro Model.

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Background: Astrocytes are the most abundant glial cells in the brain. They provide neurons with a supportive environment by exchanging products which are essential for the normal neuronal function and protect them against toxic mediators and hostile environment. Glutathione is one of the products which is exchanged between astrocytes and neurons. It is sensitive to oxidative stress and protects the brain from reactive oxygen species (ROS) which are massively produced in trauma. Objective: To evaluate changes in the levels of reduced (GSH) and oxidized (GSSG) glutathione in response to stretch injury of different severities in astrocytes and in epithelial cell-line, in correlation with cell death. Methods: Primary astrocytes cultured from newborn mice and HaCaT, transformed epithelial cell-line, were grown in wells on a flexible silastic bottom. A cell injury controller was used to produce a rapid pressure of known amplitude and duration leading to a stretch injury, which deforms the cells and serves as our model system. Cells were collected 1, 4 and 24 hours after the trauma and injected into HPLC-ECD. Cell survival was measured by MTT method. Results and discussion: The survival of both cell types decreased with increased degree of trauma. In parallel, a decrease in GSH was found in both cell types 1 and 4 hours after trauma. Thus the redox potential calculated by the Nernst equation was found to be less negative in severe trauma as compared to control. No changes in the potential were observed in HaCaT 24 hours after trauma Addition of NAC or BSO prior to the trauma affected significanly the results. Our results indicate that mechanical injury leads to changes in redox state reflecting oxidative stress, which in turn correlates with cell death. Thus, the ratio GSH/GSSG can serve as a sensitive cellular marker for oxidative stress after injury, and as a tool to evaluate novel antioxidant therapies.

Hill Coefficient for Estimating the Magnitude of Cooperativity in Gating Transitions of Voltage-Dependent Ion Channels

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A frequently used measure for the extent of cooperativity in ligand binding by an allosteric protein is the Hill coefficient, obtained by fitting data of initial reaction velocity (or fractional binding saturation) as a function of substrate concentration to the Hill equation. Here, it is demonstrated that the simple two-state Boltzmann equation that is widely used to fit voltage-activation data of voltage-dependent ion channels is analogous to the Hill equation. A general empiric definition for a Hill coefficient (nH) for channel gating transitions, that is analogous to the logarithmic potential sensitivity function of Almers, is derived. This definition provides a novel framework for interpreting the meaning of the Hill coefficient. In considering three particular and simple gating schemes for a voltage-activated cation channel, the relation of the Hill coefficient to the magnitude and nature of cooperative interactions along the reaction coordinate of channel gating is demonstrated. A possible functional explanation for the low value of the Hill coefficient for gating transitions of the Shaker voltage-activated K+ channel is suggested. The analogy between the Hill coefficients for ligand binding and for channel gating transitions further points to a unified conceptual framework in analyzing enzyme and channel behavior.

Illuminating Vesicle Priming with live-cell TIRF microscopy

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Vesicles in neurons and neurosecretory cells undergo multiple steps of maturation in order to become fusion competent and eventually undergo exocytosis. The first requirement for fusion-competence is morphological docking of the vesicle at the plasma membrane. A docked vesicle is then primed for exocytosis by a series of molecular steps. A key step in vesicle priming is the formation of the SNARE complex between Syntaxin, SNAP25 and VAMP (Synaptobrevin). Formation of this complex has been shown to be a crucial step in neurotransmitter release and as such it is regulated by numerous protein-protein interactions. It was suggested that the degree of "release-readiness" of different vesicle populations is defined by the molecular machinery that regulates docking and priming. We have used total internal reflection fluorescence microscopy (TIRF) to track single large dense-core vesicles (LDCV's) inside living chromaffin cells and analyze their mobility. Using a custom-written software we have obtained trajectories of individual vesicles within control cells and cells overexpressing the inhibitory protein Tomosyn. Tomosyn was shown to form SNARE complexes with Syntaxin and SNAP25 and inhibit the association of Synaptobrevin with these two proteins. We have previously shown that Tomosyn dramatically reduces the amount of fusion-competent vesicles in chromaffin cells but does not affect the amount of docked vesicles. In the present study we examined whether the inhibition of priming is correlated with changes in vesicle mobility. We observe that in control cells, 50% of the vesicles detected near the plasma membrane are virtually immobile. However, when tomosyn is overexpressed, the size of this pool is reduced by 50% and overall vesicle mobility is increased. This is the first evidence for a correlation between vesicle priming and mobility. Using the TIRF system, we will be able to better understand the molecular mechanisms underlying vesicle docking, priming and fusion.

The novel anti-Alzheimer-antiParkinson drug, ladostigil (TV3326) and rivastigmine, prevent apoptosis and regulates holo-APP processing in SK-N-SH cells.

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The colinesterase (ChE)- monoamine oxidase (MAO)-inhibitor, ladostigil (TV3326) has been developed as an anti-Alzheimer drug from the anti-Parkinson drug, rasagiline. We have previously shown that ladostigil regulates amyloid precursor protein (APP) processing by a protein kinase C activation (PKC)-dependent mechanism, in cell culture and in vivo. Since programmed cell death may play an integral role in Alzheimer's disease (AD), we investigated whether ladostigil exerts neuroprotective activity and regulate the levels of the holo-APP and its fragments, using high-density apoptotic neuroblastoma SK-N-SH cells in long-term culture. Ladostigil (0.1-10 μM) dose-dependently decreased apoptosis via inhibition of the cleavage and prevention of caspase3 activation. Furthermore, it decreased apoptosis through the Bcl-2 family protcins regulation, resulting in reduced the levels of pro-apoptotic Bad and Bax and induction of anti-apoptotic Bcl-2. In addition, long-term culture of induced-apoptotic SK-N-SH cells resulted in elevation of holo-APP levels, whereas in this model, treatment with ladostigil markedly decreased the levels of holo-APP, as well as stimulated the release of the non-amyloidogenic α-secretase form of soluble APP (sAPPα) in the medium. Similar to ladostigil, its S-isomer, TV3279, which is a ChE inhibitor but lacks MAO inhibitory activity, exerted similar neuroprotective properties and APP processing, suggesting that the mode of action is independent of MAO inhibition. The ChE inhibitor drug, rivastigmine, also prevented neuronal apoptosis, as well as affected APP regulation/processing. Our data demonstrate that ladostigil neuroprotective properties, via the Bcl-2 family proteins, together with its effect on holo-APP and sAPPα levels, might reduce the amyloidogenesis in AD and thus make ladostigil a potentially drug for the treatment of the AD and Lewy body disease.

Proximal Persistent Na+ Channels Underlie Spike Afterdepolarization and Burst Generation in Adult Rat CA1 Pyramidal Cells

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It is firmly established that the fast, all-or-none spike in principal brain neurons is driven by voltage-gated Na+ currents and is initiated at the axon initial segment or proximal nodes. In contrast, not much is known about the identity of the ion channels that generate the slow and graded spike afterdepolarizing potential (ADP) and the subcellular sites at which this potential originates. CA1 pyramidal cells manifest a conspicuous somatic spike ADP that causes some of them to burst-fire when strongly depolarized. Here, we show that CA1 neurons possess a persistent Na+ current (INaP) that gives rise to a substantial inward current within the voltage range of the spike ADP. In contrast, inward Ca2+ currents deactivate rapidly, with persistent Ca2+ currents within the voltage range of the ADP being about tenfold smaller. The somatic spike ADPs and associated bursting were potently suppressed by a battery of drugs that blocked INaP. These effects of INaP blockers were replicated when the drugs were applied locally to the somatic region, but not following local application to distal dendrites. Additionally, spike ADPs were preserved in CA1 neurons in which the dendritic tree had been severed close to the soma, and were similarly sensitive to blockers of INaP. Collectively, these data suggest that the somatic spike ADP, which is a crucial determinant of CA1 neuron excitability, is generated locally by activation of persistent Na+ channels in the proximal portions of the neuron.

Brain activation during recognition of sparse, camouflaged figures – an fMRI study

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We used fMRI to study the brain areas involved in the process of perceiving a figure from a sparse, camouflaged input. Two paradigms were used. In the first, four subjects viewed camouflaged images displayed for 7 or 20 sec, and were asked to indicate if and when they recognized the figure. fMRI data were taken throughout the viewing period. We explored the changes in the BOLD signal around recognition time. Comparing activation patterns before and after recognition, with activation seen when the subject failed to recognize the image, revealed areas that responded more strongly during recognition in the middle temporal gyrus while in early and mid-level visual areas activation was similar for both conditions. The second experiment used the fMR adaptation method to test whether common or distinct neural populations respond to a camouflaged picture in comparison with grayscale photographs of the same figures. Stimuli were displayed in a block design paradigm, with repeating (adaptive) or different (non adaptive) figures. The results indicate that in higher brain areas there are regions containing different population that are sensitive to grayscale pictures and to camouflaged ones although the figures in both cases are the same. Our results may help to explore the network involved in the act of transforming seemingly random spatial cues into a meaningful, informative object.

The influence of NAPSVIPQ pre-treatment on the induction and severity of experimental autoimmune encephalomyelitis

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Activity-dependent neuroprotective protein (ADNP) was shown to be essential for brain formation (Pinhasov et al., Brain Res, 2003). Peptide scanning identified a motif on ADNP, NAPSVIPQ (NAP), that provides femtomolar neuroprotection (Bassan et al., J. Neurochem,1999). Multiple sclerosis (MS) is a chronic disabling disease of the CNS. It is believed that immunological mechanisms are involved in MS. The influence of NAP was checked on C57BL/6 female mice, in which experimental autoimmune encephalomyelitis (EAE), a model for multiple sclerosis was induced by immunization with a peptide derived from myelin oligodendrocyte glycoprotein (MOG). Intra-nasal daily treatment with NAP, that started 10 days before MOG immunization and continued for 40 days, significantly reduced the number of mice suffering from EAE. Furthermore, the severity of the disease, represented by the degree of motor dysfunction was reduced in the NAP treated mice. In order to asses, whether NAP effect was related to neuroprotective, neurotrotrophic or immunoregulatory activities, the expression of 1,176 genes was compared, using Clontech Atlas Array, between spinal cords of MOG immunized mice, MOG immunized mice treated with NAP and non-immunized (or treated) mice (naive mice). Spinal cords of NAP-treated mice showed an increased mRNA expression of genes associated with neuro/glia protection, genes related to neurite outgrowth and synapse formation and genes associated with the reduction of inflammatory activity related to EAE. In contrast, the mRNA levels of genes associated with inflammation or CNS cells injury, were increased in spinal cords of MOG-immunized mice and decreased following NAP treatment dramatically.

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Transcranial Magnetic Stimulation of Deep Brain Regions: Evidence for Efficacy of the H-Coil

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Objective: Standard coils used in research and the clinic for noninvasive magnetic stimulation of the human brain are not capable of stimulating deep brain regions directly. As the fields induced by these coils decrease rapidly as a function of depth, only very high intensities would allow functional stimulation of deep brain regions and such intensities would lead to undesirable side effects. We have designed a coil based on numerical simulations and phantom brain measurements that allows stimulation of deeper brain regions, termed the Hesed H-coil. In the present study we tested the efficacy and some safety aspects of the H-coil on healthy volunteers. Methods: The H-coil was compared to a regular figure-8 coil in six healthy volunteers by measuring thresholds for activation of the abductor pollicis brevis (APB) representation in the motor cortex as a function of distance from each of the coils. Results: The rate of decrease in the coil intensity as a function of distance is markedly slower for the H-coil. The motor cortex could be activated by the H-coil at a distance of 5.5cm compared to 2cm with the figure-8 coil. Conclusions: The present study indicate that the H-coil is likely to have the ability of deep brain stimulation and without the need of increasing the intensity to extreme levels that over-stimulate cortical regions. Significance: The ability of non-invasive deep brain stimulation opens a wide range of both research and therapeutic applications.

Cloning, Overexpression and Purification of the Cholinesterase Domain of Neurotactin and its Interacting Partner Amalgam

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Studies during the last decade have identified five proteins with substantial sequence similarity to cholinesterases (ChEs). The regions of sequence similarity correspond to only part of the complete sequences of these proteins, thus establishing the ChE domain as a modular domain incorporated into different proteins. One of these proteins is neurotactin. Neurotactin is a Drosophila transmembrane glycoprotein that is dynamically expressed in neuronal and epithelial tissues during embryogenesis and in the late larval period. In in vitro assays, neurotactin promotes heterophilic cell aggregation through interaction of its extracellular ChE domain with a secreted immunoglobulin-like protein called amalgam. We have sub-cloned, separately, the genes of neurotactin and amalgam into a P. Pastoris expression vector. Stable transformants of P. Pastoris with the gene of neutrotactin and amalgam was achieved by electroporation followed by metabolic selection. Screen for colonies with multi copies of the genes was performed by selection on increasing concentration of the antibiotic G418. Expression of the proteins was induced with methanol for 6 days, resulted in secretion of the corresponding proteins into the growth medium from which they were collected. Separation of the proteins from the medium components and other P. pastoris proteins was in two steps first, affinity chromatography and then size exclusion chromatography in the presence of a detergent.

Discriminating Deuterated from Undeuterated Acetophenone: Comparing Humans and a Dog

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To determine if deuterated compounds are distinguishable from their undeuterated counterparts through smell, we set out to replicate a previous report: 31 subjects performed a one-trial same/different discrimination on two jars containing deuterated (D) and undeuterated (H) acetophenone. 24 subjects correctly chose different. However, when performing the same task using two identical samples of H, 23 subjects erroneously chose different. Thus, a bias existed toward answering different. To avoid this we used an olfactometer to test 38 subjects in a 32 trial same/different forced choice design. Mean accuracy was not different from chance (52.5% ± 3.5, NS). To eliminate possible habituation effects, we repeated the task in 14 subjects with only 8 trials. Although mean accuracy was not different from chance (60% ± 23, NS), 3 subjects did get all 8 trials correct. To test a different paradigm we then tested an additional 65 subjects on a 14-trial two-alternative forced choice identification task again with jars. Mean accuracy was not different from chance (51.2% ± 16, $p>.1$), but 5 subjects performed significantly greater then chance (one subject at 100% $p< .00006$, two subjects at 93% $p< .0009$, one subject at 86% $p < .006$, and one at 78.5% $p < .03$) while no subject performed significantly below chance. Humans mostly unsuccessful, we set out to see if dogs could do it. A German Shepard was trained to recognize H. He then did 7 trials of a three-alternative forced-choice identification task at 100% accuracy ($p<.001$). To address the concern that the dog was making an intensity rather than identity judgment, we conducted an additional 12 trials using different intensities of the target and distracters. The dog was at 100% accuracy ($p<.0001$). Thus we conclude dogs can distinguish deuterated from undeuterated acetophenone.

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Enahnced neural exciatbility of hippocampal neurons is related to acquisition olfactory rule-learning

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Rule learning of an olfactory discrimination task in rats is accompanied by reduction in the post-burst after-hyperpolarization (AHP) in piriform cortex pyramidal neurons. The purpose of the present study was to examine whether such reduction occurs also in hippocampal neurons. Water deprived rats were trained in a 4-arm maze to discriminate positive cues in 2 pairs of odors for a water reward. We examined the AHP amplitude in CA1 hippocampal neurons recorded in brain slices at different time intervals after the beginning of training. To standardize AHP recordings, neurons were depolarized to holding potential of –60 mV by current application via the recording electrode. Post-burst AHP amplitude was then measured following a 100 ms depolarizing current step with intensity that generates 6 action potentials. Olfactory learning-induced reduction in post-burst AHP was observed in CA1 neurons as soon as 5 days after the rats began their training (e.g. during the time in which they are learning the rule). Post burst AHP was reduced in neurons from trained rats: In the 5-7 days of training, the averaged AHP amplitude (in mV) was 2.92+1.32, n=38, in neurons from trained rats, 3.65+1.35, n=17 in neurons from naïve rats and 3.96+1.51, n=36 in neurons from pseudo trained rats ($p<0.05$, one way ANOVA). Notably, three days after rule learning, the averaged AHP value in CA1 neurons form trained rats was significantly higher than observed during learning (4.53+1.64 mV, n=6) even if training was continued with a new pair of odors. This value does not differ from that observed in neurons from control rats, suggesting that the time course of post-burst AHP reduction and its subsequent return to control values differs between piriform cortex and hippocampal neurons. We suggest that olfactory learning-related post-burst AHP reduction in CA1 hippocampal neurons may represent a mechanism that enables rule learning, but is nor related to its maintenance.

Adaptive immunity is needed to maintain hippocampal neurogenesis in adulthood

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Studies from our laboratory over the last few years have shown that the controlled activity of T cells directed to autoantigens in the central nervous system (CNS) is needed for postinjury survival and repair and their action is part of the body's physiological response to CNS injury. Recently we showed that spatial learning/memory is impaired in immune-deficient mice and restored by T cells. In this study we tested whether under normal (non-pathological conditions) at adulthood, T cells have a role in regulating hippocampal neurogenesis. Here we show that in adult mice with severe immunodeficiency (SCID or nude), hippocampal neurogenesis was significantly impaired relative to their wild-type counterparts. Reduced hippocampal neurogenesis in SCID mice relative to wild-type mice was correlated with reduced levels of brain derived neurothrophic factor in the dentate gyrus, as well as lower density of capillary vessels in the dentate gyrus,. These results might shed light on age-related cognitive loss and hint at a novel means of maintaining neurogenesis.

Functional organization of motor centers in the octopus brain

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The nervous system of the octopus is uniquely divided into a centralized brain and an elaborated peripheral nervous system of the arms that contains 2/3 of the total 500 million nerve cells. Several lines of evidence suggest that a significant part of the arm functions are rather autonomous; both in processing sensory information and in executing stereotypical arm movements. To understand the control relationships between the central brain and the peripheral nervous system, a micro-wire electrode was implanted and glued to the brain capsule allowing recording of single units activity and micro-stimulation in freely behaving animals. The electrodes were positioned to obtain recordings from higher motor centers (basal lobes), and the exact site was determined by establishing histologically the location of electro-lesions. Stimulation initiated a variety of whole body movements. The kinematic analysis of the evoked movements did not reveal areas within the higher motor centers where specific stereotypical movements, such as arm extensions, could be triggered nor movements of a specific arm. These higher motor centers have strong sensory inputs from the entire body. Analysis of the responses evoked by stimulating different body parts shows that as in the motor case, there is no central spatial representation of the arms or other body parts within the basal lobe. Thus, a site that responds to tactile stimulation usually responds to stimulating all eight arms with no preference to any certain location along the arm. In addition, different sensory modalities (e.g. visual and tactile) were found to converge to the same recording site. All these findings fit the idea that in contrast to vertebrates, in the octopus brain there is no somatotopic sensory or motor organization. This may reflect an adaptation for the inherent complexity in representing eight flexible arms in a relatively small brain.

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Dependence of gamma-oscillatory synchronization on selective visual attention in awake behaving monkey

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Several recent models of psychopathological disorders that are thought to be related to abnormal interaction of distributed brain processes have focused on the meaning of oscillatory gamma synchronization. It was argued that the visuoperceptual anomalies associated with weak central coherence in autism may be due to the reduction of gamma-frequency synchronization between local networks. Recent advances in schizophrenic research also relate specific symptoms of schizophrenia to a dysfunction of gamma-oscillatory activity, especially in the context of attention, which in schizophrenia is seriously affected. Some recent results have indicated a general relationship between attention and gamma-band synchronization, but there is only little experimental data about the influence of attention on synchronized activity at the single cell level. To test this hypothesis further we carried out multi-electrode recordings in macaque motion-sensitive area MT while the animals did a demanding visual attention task. The results of two experimental variants indicate that correlated responses to the attended stimulus were always found to have their strongest oscillatory modulation within the gamma band of the frequency range. In contrast, if cells were driven by the non-attended stimulus we found a shift of oscillatory power towards lower frequency components. In particular, with enhanced spatial competition between objects the most prominent oscillatory modulation of synchronized activity elicited by the distracter bar was found in the alpha range. Thus, the spectral analysis of crosscorrelated spike patterns not only revealed prominent gamma power in response to attended objects, but also demonstrated a frequency shift towards the alpha band for the non-attended condition. This result indicates that the attended and the non-attended stimuli are represented by neuronal assemblies which are distinguished by the different temporal structure of their synchronized neuronal activity.

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