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Scaling Brain Size, Keeping Timing: Evolutionary Preservation of Brain Rhythms

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Abstract

Despite the several-thousand-fold increase of brain volume during the course of mammalian evolution, the hierarchy of brain oscillations remains remarkably preserved, allowing for multiple-time-scale communication within and across neuronal networks at approximately the same speed, irrespective of brain size. Deployment of large-diameter axons of long-range neurons could be a key factor in the preserved time management in growing brains. We discuss the consequences of such preserved network constellation in mental disease, drug discovery, and interventional therapies.

Introduction

Vertebrate brains are among the most sophisticated scalable architectures in nature. Scalability refers to a property that allows the system to grow and perform the same desired computations, often with increased efficacy. In scalable systems, certain aspects of the system must be constrained if the same computational goals are to be achieved in the face of increasing organismal complexity. In this essay, we submit that temporal organization of neuronal activity, represented by the system of rhythms, is one of the fundamental constraints in scaling brain size.

When *Neuron* got its start 25 years ago, the study of neuronal oscillations was largely confined to clinical electroencephalography, invertebrate physiology, sleep research, and a few laboratories devoted to the study of the relationships between specific local-field-potential rhythms and behavior or perceptual processes. Today, the study of brain rhythms is

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SUPPLEMENTAL INFORMATION

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an intertwined part of systems neuroscience and among its fastest growing fields. This shift is largely due to the recognition that the multifarious rhythms of the brain form a hierarchical system that offers a syntactical structure for the spike traffic within and across circuits at multiple time scales. The constellation of network rhythms is characteristic of individual brains, and their alterations invariably lead to mental and neurological disease. In today's world of the "connectome," it is worth reiterating that network oscillations are among the most conservatively preserved phenotypes in mammalian evolution. What are the structural and physiological solutions that allow the preservation of the syntactical rules of spike communication in the face of rapidly growing brain size? Answering this question is among the most critical in neuroscience and amounts to an understanding of the neuronal "code."

Brains, small and large, are predictive devices that exploit regularity and recurrence as a fundamental property of the surrounding world and apply effective heuristics acquired through phylogenetic and individual experience for problem solving. The brain's ability to work both as a subsumption and as a prediction device relies on a set of complex properties, including self-organized information retention and local-global integration. The former refers to the brain's capacity to preserve a lasting trace long after the input has already vanished. This is achieved over short time scales by persistent activity or, over long time scales, by use-dependent modifications of synaptic transmission. The latter pertains to the ability to integrate a large number of distributed local processes into globally ordered states (Tononi et al., 1998; Dehaene et al., 1998) whereby the results of local computations are broadcast to widespread brain areas so that multiple structures are simultaneously informed about any given local effect. In the reverse direction, local computations and the flow of signals to multiple downstream targets are under the control of global brain activity, usually referred to as "executive," "attentional," or "top-down" control (Engel et al., 2001; Varela et al., 2001). Naturally, a critical requirement for effective local-global communication is that the results of local computations in multiple areas are delivered within the integration time window of downstream "observer" mechanisms (Buzsáki, 2010). In growing interconnected systems, the building blocks are inevitably placed farther apart from each other. For integration to be possible across the entire system, either the integration time window should widen (slowing down the speed of operations) or other mechanisms should be in place to compensate for the longer distances of transmission.

We hypothesize below that the aforementioned essential features of brain organization, the activity-information retention and the local-global integration, are maintained by a hierarchical system of brain oscillations (Buzsáki, 2006), and we demonstrate that despite a 17,000-fold variability in brain volume across mammalian species (See Note 1 in the Supplemental Information available with this article online), the temporal dynamics within and across brain networks remain remarkably similar. It follows that, irrespective of brain size, the management of multiple time-scales is supported by the same fundamental mechanisms, despite potential adaptive changes in network connectivity.

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Hierarchical Organization of Brain Rhythms

Rhythms are a ubiquitous phenomenon in nervous systems across all phyla and are generated by devoted mechanisms. In simple systems, neurons are often endowed with pacemaker currents, which favor rhythmic activity and resonance in specific frequency bands (Grillner 2006; Marder and Rehm, 2005). In more complex systems, oscillators are usually realized by specific microcircuits in which inhibition plays a prominent role (Buzsáki et al., 1983; Buzsáki and Chrobak, 1995; Kopell et al., 2000; Whittington et al., 1995, 2000). As a result of selective reciprocal coupling via chemical and electrical synapses, several classes of specific networks of inhibitory interneurons are formed (Klausberger and Somogyi, 2008). These tend to engage in synchronized rhythmic activity and generate rhythmic IPSPs in principal cell populations. This in turn provides windows of alternating reduced and enhanced excitability (Bishop, 1933; Lindsley, 1952) and offers natural temporal frames for grouping, or “chunking,” neuronal activity into cell assemblies and sequences of assemblies for the effective exchange of information among cortical networks (Destexhe and Sejnowski, 2003; Wilson and McNaughton, 1994; Steriade et al., 1993a; Fries, 2005; Buzsáki, 2010). This temporal parsing function of neuronal oscillators can be used for dynamic gating of communication between distributed nodes, which is an important function for the task-dependent formation of functional networks and coherent cell assemblies on the backbone of a relatively fixed anatomical connectome.

Brain rhythms cover more than four orders of magnitude in frequency, from the infraslow (<0.01 Hz) to ultrafast rhythms, and include at least ten interactive oscillation classes (Figure 1A). Integrated over a long temporal scale, the power distribution of the various frequencies has the appearance of $1/f^n$ “noise” (Nunez, 1981), partly reflecting the fact that slow oscillations generate large, synchronous membrane-potential fluctuations in many neurons in brain-wide networks (He et al., 2008), whereas faster oscillations are associated with smaller changes in membrane potential in a limited number of cells, that are synchronized only within a restricted neural volume (Figure 1B). Nonetheless, when the brain engages in specific functions such as processing sensory stimuli, directing attention to particular features, orienting in space, engaging working memory, or preparing movements, the dynamics of the involved structures changes and particular oscillation frequencies become dominant. In these cases the frequency-power relationship deviates from the 1/f statistics, and a peak (bump) appears in the respective frequency band (Singer, 1999; Gray and Singer, 1989; Singer and Gray, 1995).

Notably, the mean frequencies of neuronal oscillators form a linear progression on a natural logarithmic scale (Buzsáki and Draguhn, 2004). Unfortunately, the taxonomy of brain oscillations is poorly developed, and existing terms typically refer to the frequency band that the rhythm occupies rather than its mechanism. As a result, different frequency bands can refer to the same mechanisms and vice versa (e.g., the mechanism underlying hippocampal theta occupies both the traditional theta and alpha bands: 5–10 Hz), and the same name (e.g., alpha) might refer to entirely different mechanisms and the functions they support. Induced gamma oscillations can also vary over a wide frequency range (30–80 Hz) depending on the features of the inducing stimuli (Lima et al., 2010; Ray and Maunsell, 2010; Belluscio et al., 2012).

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Many oscillations often co-occur in the same brain state and interact with each other either within the same or across different structures. The nature of interaction is usually hierarchical and universal, so that the phase of the slower oscillation modulates the power of the faster ones (Figure 1B; Bragin et al., 1995; Chrobak and Buzsáki, 1998; Leopold et al., 2003; Schroeder and Lakatos, 2009; Canolty et al., 2006; Buzsáki and Wang, 2012; Fell and Axmacher, 2011). Slower rhythms can reset and temporally bias local computation in multiple cortical areas via such cross-frequency phase and amplitude coupling. For example, hippocampal-entorhinal theta oscillations can modulate locally emerging neocortical gamma patterns (Sirota et al., 2008). The temporal bias brought about by the slower rhythm can induce comodulation of the power of faster oscillations even in nonconnected brain regions ("power-power coupling"; Buzsáki and Wang, 2012). In this case, the power (amplitude) envelopes of the oscillators are correlated (e.g., Leopold et al., 2003) even though phase constancy (i.e., coherence) between the faster waves is present.

Cross-frequency coupling across the various rhythms, which have a typically noninteger, irrational relationship with each other (Figure 1A), creates an oscillatory interference, and this interaction is most likely responsible for the brain's perpetually changing activity patterns (Buzsáki and Draguhn, 2004). It seems that the dynamics emerging from the complex interactions between local processors, many of which are tuned to generate oscillations in specific frequency bands, have a very high dimensionality (Shew et al., 2009). Such a hierarchical cross-frequency-coupled organization can support the encoding of nested relations, which is crucial for the representation of composite objects, and it can encompass syntactical rules, known to both sender and receiver, and thus make communication more straightforward than interpreting long uninterrupted messages (Buzsáki, 2010) or stochastic patterns of spikes.

Preservation of Brain Rhythms in Mammals

Every known pattern of local field potential, oscillatory or intermittent, in the human brain is present in other mammals investigated to date. Not only the frequency bands but also the temporal aspects of oscillatory activity (such as duration and temporal evolution) and, importantly, their behavioral correlations are conserved (Figure 2). The various rhythms shown in Figure 2 are discussed in Supplemental Notes 2 and 3 (see also Buzsáki and Watson, 2012). Below, we will focus only on the special requirements needed to maintain timing within and across brain regions, irrespective of brain size.

The preservation of cortical rhythms reflects widespread neural-processing strategies requiring distinct time parsing, rather than an inability of the brain to change its timing mechanisms. For example, central pattern generators for respiratory rhythms vary according to species needs from 0.5/min in large aquatic mammals to 100/min in mice. Thus, the relative constancy of the many brain oscillations and their cross-frequency coupling effects across species appear to reflect functional requirements needed for effective time processing independent of brain volume and anatomical connectivity. Although we are still at the beginning of understanding the complex dynamics of brain processes, some constraints related to the biophysical properties of neurons and microcircuits can be identified. For example, the time constants of dendritic integration determine the intervals of effective

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temporal and spatial summation of synaptic inputs, and these in turn set the limits within which synchrony enhances the saliency of input signals. Likewise, the rules for synaptic plasticity (e.g., the STDP rule) define the precision of temporal relations between presynaptic and postsynaptic firing that needs to be maintained independent of the distance between the locations of the somata of the participating neurons to allow the expression of unambiguous semantic relations between cause and effect. Constraints for timing and the minimal duration of structured activity patterns can also arise from the second-messenger processes that translate correlated activity patterns into lasting changes of synaptic efficacies (Morishita et al., 2005). Finally, it is to be expected that brain rhythms need to be adapted to the mechanics of the effector systems, including the skeletal muscles. The fundamental properties of myosin and actin, including their contraction speed, have remained largely conserved across mammals. All of these timing constraints had to be reconciled with the complexity imposed by the growing size of the brain. The most obvious problem imposed by large brains is increasing distances among the neuronal somata of homologous regions and the inevitable lengthening of their essential communication lines, the axons. Importantly, the axonal length and volume increase much more rapidly than the number of neurons. Furthermore, a proportional increase of neurons and connections would inevitably lead to a rapid increase of “synaptic path length,” defined as the average number of monosynaptic connections in the shortest path between two neurons (Watts and Strogatz, 1998; Sporns et al., 2005; Buzsáki et al., 2004). So that the path length can be maintained, “short cut” connections can be inserted, resulting in “small-world”- and “scale-free”-type networks (Albert and Barabási, 2002). Although such a solution can effectively decrease path length within the neocortex, the increased lengths of the axons and the associated increased travel time of the action potentials still pose serious problems. As compensation for these excessive delays, axon caliber and myelination should be increased (Innocenti et al., 2013; Houzel et al., 1994). An indication that larger brains deploy both more shortcuts (long-range connections) and larger-caliber axons is that the volume of the white matter increased at 4/3 power of the volume of gray matter during the course of evolution. Although the white matter occupies only 6% of the neocortical volume in hedgehogs, it exceeds 40% in humans (Allman, 1999). Another indication of time-preservation mechanisms is that the latency increase of sensory evoked responses in humans compared with rodents is only modestly increased in comparison to differences in brain size (Supplemental Note 4).

Below, we discuss examples which illustrate that such compensatory properties are indeed in place. Within the same hemisphere, slow oscillations typically originate in prefrontal–orbitofrontal regions and propagate in a fronto-occipital direction at a speed of 1.2–7.0 m/sec in humans (Massimini et al., 2004) but only at 0.02–0.1 m/sec in rats (Luczak et al., 2007). The faster propagation of slow waves in the human brain presumably secures that homologous brain regions in both species are timed similarly and, as a consequence, can address their targets within the approximately same temporal windows, irrespective of brain size. Importantly, homologous brain regions in the left and right hemispheres synchronize together in both species, irrespective of the physical distance between the structures. In contrast, slow oscillations occur largely independent of each other in the two hemispheres in

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acallosal mice and after callosotomy in cats, indicating a critical role of the interhemispheric fiber tracks in sustaining synchrony (Singer and Creutzfeldt, 1969; Mohajerani et al., 2010).

The preservation of the frequency of sleep spindles as brain size increases can, in principle, be explained by preserved channel, cellular, and synaptic mechanisms in the thalamus (Steriade et al., 1993b), whereas the duration (i.e., initiation and termination) of spindles might depend on the neocortex (Bonjean et al., 2012). However, the coordination of spindle waves across large areas of the cortex and between the cortex and thalamus still remains a problem (Contreras et al., 1996). Compensatory mechanisms for the size increase might include the deployment of more rapidly conducting axons in more complex brains. Alternatively or in addition, the solution might reflect counter-intuitive synergistic properties of coupled oscillators. For instance, analysis of the synchronization behavior of coupled oscillators (Fischer et al., 2006) and simulation studies on delay-coupled networks with spiking neurons (Vicente et al., 2008) have demonstrated that phase synchronization can be achieved despite variable conduction times of the coupling connections provided that the oscillators have similar preferred frequencies and the intrastructure connectivity matrix comprises at least three reciprocally coupled oscillators.

Alpha oscillations also arise in the thalamocortical system, and their synchronization between the thalamus and vast areas of the neocortex faces challenges similar to those of sleep spindles. As the neocortex grows, the cortical modules of different modalities are displaced progressively more distantly from each other and from their thalamic input neurons. Despite the increasing axonal lengths of both thalamocortical and corticothalamic axons and the growing complexity of cortical circuits in large-brained animals, thalamocortical rhythms are essentially identical across species (Figures 2A and 2B).

Beta oscillations largely serve to coordinate the timing of action potentials of neurons in the motor systems, and the large distances of the motor areas and their distances from the muscles they control must have special solutions. One well-known adaptation to the timing problem is the giant layer V corticospinal (Betz) cells that are located in primary motor cortex of primates and have fast-conducting, large-diameter, myelinated axons (Stanfield, 1992). However, the anatomical substrates and temporal coordination mechanisms that exist between motor cortex, basal ganglia, and cerebellum and keep the beta frequency coherence similar in brains of very small and large animals remain to be discovered.

Theta oscillations represent a consortium of mechanisms, supported by various intracellular and circuit properties of the septo-hippocampal-entorhinal system (Buzsáki, 2002). Despite their common relevance to behavior, hippocampal theta oscillations have perhaps the most frequency variation across species (Figure 2B). Rodents show 6–10 Hz theta oscillations (Vanderwolf, 1969), whereas these oscillations are 4–6 Hz in carnivores (Grastyan et al., 1959; Arnolds et al., 1979). Out of all investigated species, humans have the slowest theta frequency (1–4 Hz; Arnolds et al., 1980; Kahana et al., 2001). A potential argument for the decreasing frequency and irregularity of hippocampal theta oscillations in mammals as brain size increases is that the hippocampus is a single cortical module (Wittner et al., 2007) and its growth is limited by the axon conduction delays. Pyramidal neurons of the CA3 region innervate a very large volume of the hippocampus (Ishizuka et al., 1990; Li et al., 1994;

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Wittner et al., 2007); they connect distant peer neurons and require long axonal lengths and, consequently, have longer delays. A further difficulty is that the theta rhythm is not globally synchronous; rather, each cycle is a traveling wave that undergoes a half cycle (180°) phase shift from the septal to the temporal poles in the rat (Lubenov and Siapas, 2009; Patel et al., 2012). Assuming a phase shift of similar magnitude in the much larger primate hippocampus requires a mechanism that can significantly speed up the wave propagation. With increasing hippocampal volume, keeping the speed of communication across the large cortical module requires the deployment of large-caliber axons. The fast increase of the share of the axon volume in a relatively randomly connected graph might explain why the scaling in the hippocampus during evolution was left behind the modularly organized neocortex. One can only speculate that the ensuing increasing delays might contribute to the slowing of the theta rhythm.

Gamma oscillations emerge from local networks of reciprocally coupled, parvalbumin-containing basket cells and pyramidal cells (Buzsáki and Wang, 2012), but the locally generated gamma rhythms can become synchronized over surprisingly long distances in a context-dependent way, e.g., between hemispheres (Engel et al., 1991, 2001; Buzsáki et al., 2003), between entorhinal cortex and hippocampus (Chrobak and Buzsáki, 1998), and between remote regions of the cerebral cortex (Gregoriou et al., 2009; Melloni et al., 2007). Candidates for the mediation of these synchronization phenomena are (1) reciprocal fast-conducting glutamatergic projections that originate from pyramidal cells and impinge on both inhibitory and excitatory neurons in the respective target structure and (2) long-range inhibitory projections that directly link the inhibitory network in one region with that in another (Buzsáki et al., 2004; Jinno et al., 2007; Caputi et al., 2013). In addition to implementing fast-conducting synchronizing connections, nature seems to rely also on counter-intuitive properties of nonlinear dynamical systems that permit such synchronization by reciprocal coupling despite conduction delays (Vicente et al., 2008).

The most precisely synchronized cortical rhythm is the fast “ripple” oscillation of the hippocampus (130–160 Hz in rats; Buzsáki et al., 1992; O’Keefe and Nadel, 1978). The frequency of the ripple decreases somewhat from approximately 160–180 Hz in mice (Buzsáki et al., 2003) to 110 Hz in humans (Bragin et al., 1999; Supplementary Note 2); ripples can arise at any site along the septo-temporal axis of the hippocampus and can remain either localized or spread to the septal or temporal direction (Patel et al., 2013). The ripple-related synchronous hippocampal output can exert a powerful influence on widespread cortical and subcortical structures in both rats and monkeys (Siapas et al., 2005; Logothetis et al., 2012), and appropriate timing of these widespread regions demands structural support. It is not known though whether hippocampal ripples activate their different cortical and subcortical targets by delays, in which case their synchrony would not be guaranteed, or whether their target “hot spots” are coactivated to form a specific engram. Under the latter scenario, one might expect special constraints on the transmission pathways and mechanisms, both of which should scale with brain size.

In summary, the preservation of temporal constants that govern brain operations across several orders of magnitude of time scales suggests that the brain’s architectural aspects, such as scaling of the ratios of neuron types, modular growth, system size, inter-system

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connectivity, synaptic path lengths, and axon caliber, are subordinated to a temporal organizational priority. Of these components, the changing features of axons across species are best documented. Although the brains of mammals and birds evolved independently, it is possible that the topics discussed here also apply to the conservation of timing mechanisms in bird brain evolution (Northcutt and Kaas, 1995; Balanoff et al., 2013).

Scaling of Axon Calibers Supports Preservation of Timing

Size-invariant time parsing in neural networks strongly depends on neuronal conduction velocity. As an example, for gamma oscillation to be synchronous in both hemispheres of the mouse brain, at an interhemispheric distance of ~5–10 μm, a conduction velocity of 5 m/s is sufficient (Buzsáki et al., 2003). Maintaining coherent oscillations at the same frequency in the human brain, with a 70–140 μm interhemispheric distance (Varela et al., 2001), requires much more rapidly conducting axons.

Of the various structural-anatomical possibilities, evolutionary adaptation of axon size and myelination appear to be most critical for a brain-size-invariant scaling of network oscillations because they both determine the conduction velocity of neurons. The benefits of increased brain size should therefore be offset by the cost of larger-caliber axons (Figure 3; Aboitiz et al., 2003; Wang et al., 2008) so that signals can travel longer distances within approximately the same time window. The scaling laws of axons support this hypothesis. Indeed, axon calibers in the brain vary by several orders of magnitude (Swadlow, 2000). An important evolutionary strategy is the myelination of axons and saltatory conduction; the speed of conduction along a myelinated axon scales relatively linearly with axon diameter (Hursh, 1939; Tasaki, 1939). In humans, the great majority of callosal axons, which connect approximately 2%–3% of cortical neurons, have diameters <0.8 μm, but the thickest 0.1% of axons can exceed 10 μm in diameter (Aboitiz et al., 2003). The calibers of axons emanating from the same neurons but targeting different brain regions can vary substantially, exemplifying a complex system of lines of communication with different geometrical and time-computing properties (Innocenti et al., 2013). However, a proportional increase of axon caliber in larger brains would enormously increase brain size. Instead, a minority of axons with a disproportionally increased diameter might be responsible for keeping the timing relatively constant across species. Indeed, it is the thickest diameter tail of the distribution that scales best with brain size (Figure 3), whereas across species the fraction of thinner fibers/total numbers of cortical neurons decreases (Swadlow, 2000; Wang et al., 2008; Olivares et al., 2001; Aboitiz et al., 2003). Although adding a small fraction of giant axons to the neuropil still demands increased volume and an increasing share of the white matter in larger brains, the metabolic costs and the needed volume are still orders of magnitude less than would result from the proportional increase of axon calibers of all neurons. Adding a very small fraction of very-large-diameter axons might guarantee that the cross-brain conduction times increase only modestly (Figure 3B) across species (Wang et al., 2008). The host neurons of the giant axons still need to be identified. At least a fraction of them are inhibitory neurons; the myelinated axon diameter of long-range inhibitory neurons in the rat can reach 3 μm (Jinno et al., 2007). In turn, theoretical and modeling studies suggest that long-range interneurons are critical for brain-wide synchronization of gamma, and potentially other, oscillations (Buzsáki and Chrobak, 1995; Buzsáki et al., 2004). In

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summary, preservation of timing in increasingly large brains might be secured by the disproportional increase of larger-diameter axons with fast conduction velocities.

Brain Rhythms Are Robust and Heritable Phenotypes

If the temporal management of the brain depends strongly on its structural organization, one might expect to see variations among individuals of the same species. This is indeed the case. Whereas brain oscillations undergo dramatic changes during development (Matousek and Petersen, 1973; Gou et al., 2011; Khazipov et al., 2004; 2008), power spectral patterns in the alpha-beta band during sleep are remarkably stable in adults and allow for up to 90% correct discrimination among individuals (Gasser et al., 1985; Buckelmüller et al., 2006; De Gennaro et al., 2008), independent of the level of education or general intelligence (Posthuma et al., 2001). When the entire spectra are considered, monozygotic twins show high similarity in all brain areas; correlation levels are close to $r = 0.9$ across pairs, and the largest part of the EEG variance can be explained by additive genetic factors. The concordance within heterozygotic twins is less but still higher than between nontwin siblings (Anokhin et al., 1992; van Beijsterveldt et al., 1996; Smit et al., 2006; De Gennaro et al., 2008; Linkenkaer-Hansen et al., 2007). These finger prints of intrinsic, or “spontaneous,” patterns are also reflected in stimulus-induced changes, such as the high index of heritability (0.9 in twins) of visually induced gamma-band (45–85 Hz) activity (Figure 4; van Pelt et al., 2012).

Brain rhythms in rodents are also under strong genetic control. For example, thalamocortical μ rhythm is sex and strain dependent in both rats and mice (Peeters et al., 1992; Marescaux et al., 1992; Vadász et al., 1995; Noebels 2003). A study of REM sleep in numerous strains of mice indicated the presence of a gene with a major effect on theta frequency, which could explain more than 80% of the total variability among strains (Franken et al., 1998). Analysis of quantitative traits in recombinant inbred strains identified several candidate genes responsible for various patterns of sleep (Tafti, 2007). Although the molecular genetics of brain oscillation patterns are way behind the impressive progress in the genetic analysis of circadian rhythms, the existing knowledge clearly reveals that brain rhythms are among the most heritable traits in mammals (Vogel, 1970; van Beijsterveldt et al., 1996), leading to the suggestion that EEG patterns could be used for “fingerprinting” individuals (De Gennaro et al., 2008). It should be mentioned that previous studies typically analyzed individual frequency bands separately and have not yet exploited the high sensitivity of cross-frequency phase coupling and other hierarchical features among the various oscillations.

Dysrhythmias and Oscillopathies

The data reviewed so far indicate that temporal parsing of neuronal activity in different frequency ranges is extremely well conserved across the evolution of mammalian brains. This suggests that temporal coordination of distributed brain processes, as reflected by oscillatory patterning, synchronization, phase locking, and cross-frequency coupling, might have important functions and not be epiphenomenal. In this case, one expects that disruption of these dynamic processes would lead to specific disturbances of cognitive or executive functions. Possibilities are numerous. Changes in the subunit composition of ligand- and

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voltage-gated membrane channels can alter the time constants and resonance properties of neurons and microcircuits, and hence such “channelopathies” lead to changes in oscillatory behavior. Similar changes would result from alterations in modulatory systems that are known to regulate network dynamics by controlling cell excitability and channel kinetics. Moreover, temporal coordination can be jeopardized by connectome abnormalities that alter path lengths or conduction velocities in communication channels critical for timing. In all of these cases one expects to find alterations in variables reflecting brain dynamics; for example, such variables include the power of particular oscillations and the extent and precision of synchronization in the various frequency ranges and their cross-frequency relationships. Extracting some of these variables of brain dynamics from electroencephalograms (EEGs) and magnetoencephalograms (MEGs) allows fingerprinting of individuals and could also provide a promising way to characterize neurological and mental diseases from the perspective of brain activity. Such “oscillopathies” or “dysrhythmias” could reflect malfunctioning networks and, as endophenotypes, could assist in specifying diagnosis (Llinás et al., 1999; Uhlhaas and Singer, 2012).

For a number of diseases, such as the various forms of epilepsy, chorea, and Huntington and Parkinson’s diseases, the relation between the clinical symptoms and abnormalities in brain dynamics is obvious. One might also speculate that the sometimes severe but reversible cognitive deficits in multiple sclerosis are not due solely to severe destruction of axons but also to increased conduction delays caused by demyelination, which precedes axonal degeneration or can even be reversible. If precise timing matters, disseminated alterations of conduction times would jeopardize temporal coordination of distributed processes.

Over the last decade considerable evidence has been accumulated for a relation between psychiatric conditions and disturbed brain dynamics (Uhlhaas and Singer, 2006, 2012). Here we shall focus on schizophrenia because this disease has been studied most thoroughly with methods suitable for the analysis of brain dynamics (Figure 5). The cognitive abnormalities in schizophrenic patients include fragmented perception, erroneous binding of features, deficits in attention, impaired working memory, and the inability to distinguish contents of imagery from external stimulation, delusions, and hallucinations. Because of the evidence that feature binding (Gray et al., 1989), perceptual closure (Varela et al., 2001; Rodriguez et al., 1999; Grützner et al., 2010; Tallon-Baudry and Bertrand, 1999), focus of attention (Bosman et al., 2012; Fries et al., 2001), and maintenance of contents in working memory (Haenschel et al., 2009; Tallon-Baudry et al., 2004) are closely associated with increased beta- and gamma-band oscillations and enhanced synchronization, numerous studies have attempted to establish relations between mental diseases and signatures of brain dynamics. This search has been surprisingly successful and has revealed a number of close correlations between clinical markers and abnormal brain dynamics.

A consistent finding across numerous studies is that induced gamma oscillations are reduced during tasks probing perceptual closure and working memory, and recent investigations demonstrate that this reduction is already present in untreated patients upon admission (Grützner et al., 2013) and, in an attenuated form, also in nonaffected siblings of patients; therefore, such a reduction could be a traceable endophenotype (Herrmann and Demiralp, 2005). In schizophrenic patients, the GABA synthesizing enzyme GAD 65 and the calcium-

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binding protein parvalbumin are downregulated in basket cells, which are crucial for the generation of gamma rhythms (Lewis et al., 2005). The former change reduces GABA release, whereas the latter might enhance it, suggesting the action of some compensatory process (Rotaru et al., 2011). Other evidence supports disturbances of NMDA-receptor-mediated functions. A number of studies have provided evidence for NMDA receptor hypofunction, especially in prefrontal cortical regions (Javitt, 2009), and further support for this hypothesis comes from the fact that administration of ketamine mimics the clinical symptoms of schizophrenia in great detail (Javitt and Zukin, 1991). The finding that blockade of NMDA receptors enhances gamma oscillations suggests that NMDA action dampens fast oscillations (Hong et al., 2010; Roopun et al., 2008). It is also unclear to which extent NMDA receptor hypofunction could contribute to the disturbance of long-range synchrony. Here, more likely candidates are the established abnormalities in the connectome of brains of schizophrenic patients. Although postmortem studies have provided robust evidence for white-matter abnormalities (shrinkage with enlarged ventricles) and changes in the white/gray matter ratio, it was only after the application of probabilistic diffusion tensor imaging that rather specific abnormalities of network features became evident. Application of graph analytical methods to these data showed changes in path length and centrality of strategic nodes as well as hyperconnectivity in some regions and hypoconnectivity in other regions (Fornito et al., 2012). It is possible that these abnormalities of the connectome impair precise temporal coordination of distributed brain processes.

Schizophrenic patients also show a reduction of theta-gamma phase coupling (Lisman and Buzsáki, 2008) and sleep spindles (Ferrarelli et al., 2010). Compared to that in healthy controls, beta coherence is also diminished, and the degree of reduction correlates with the severity of several clinical symptoms (Uhlhaas et al., 2006). As reviewed in detail elsewhere (Uhlhaas and Singer, 2012), many of the putatively disease-related genetic, structural, and functional abnormalities target mechanisms that are more or less directly involved in the generation of oscillations and/or their synchronization.

Alterations in brain dynamics have also been observed in association with other mental diseases and are discussed elsewhere (cf., Buzsáki and Watson, 2012). In conclusion, signatures of brain dynamics have proven extremely useful as functional markers of mental disease. Because much is known already from animal research about the mechanisms supporting oscillations and synchrony in the various frequency bands, the numerous correlations between brain dynamics and disease now enable more targeted searches for disturbances of distinct mechanisms and ultimately might suggest new avenues for therapeutic interventions. Albeit that we are only at the beginning of the research on the temporal deficits in mental disease, analysis of oscillations, coherence, cross-frequency coupling, and dynamic synchronization now allows us to identify the formation of distinct functional networks and their interactions and to thereby obtain the first insights into principles of distributed coding and temporal coordination of parallel processing.

Tasks for Today and Tomorrow

We have reviewed three inter-related topics in this perspective: evolutionary preservation of brain rhythms, the stability of the constellation of the oscillation system in individual (adult)

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brains, and the mental consequences of perturbing the syntactical structure supported by rhythms.

It is generally accepted that increased performance of the brain in higher mammals is a result of the increased complexity of brain structure. The modular organization of the cerebrum and cerebellum can amply serve that goal simply through the addition of new modules. Another way of increasing complexity is to diversify the components of the system. A clearly definable component of the brain is the neuron. The cerebral cortex has at least five principal cell types, and it is quite likely that numerous subtypes or a continuous distribution of neurons with various features (Nelson et al., 2006) exists. The versatility of the principal neurons can be further increased by the inhibitory cells that innervate the principal cells. Hyperpolarization or shunting inhibition of the apical dendritic shaft or other major dendrites of pyramidal cells amounts to a temporary conversion of a pyramidal neuron into a stellate cell. There are at least 20 different types of inhibitory neurons, which target specific domains of the principal cells and also innervate each other in a complex yet mostly unknown manner (Freund and Buzsáki, 1996; Klausberger and Somogyi, 2008). However, it is unlikely that each principal cell is innervated by all 20 inhibitory interneuron types. More likely, different sets and combinations of interneurons innervate members of the same type of principal cells, thus diversifying their performance. Whereas in “simpler” brains principal cells might send axon collaterals to numerous targets, in “smarter” brains the division of labor might allow different neurons to innervate fewer targets, thus permitting more complex local computation and more selective temporal targeting of downstream partners via fewer axons. Furthermore, the firing rates of principal cells span at least four orders of magnitude, and within in each “class” only a minority of cells is most active under various conditions (Mizuseki and Buzsáki, 2013). In addition to the diversifications of components and enrichment of local connectivity, local-global communication requires that the various regions remain sufficiently interconnected despite the rapidly growing demand on wiring, space, and energy support. All these changes come about in brains of growing complexity without affecting the individual oscillation families and their cross-frequency relationships. The preservation of temporal scales of rhythms suggests that all of the brain’s architectural aspects, including component enrichment, modular growth, system size, inter-system connectivity, synaptic path lengths, and axon caliber, are subordinated to a temporal organizational priority.

The preservation of temporal management is needed for a number of known physiological processes. Spike-timing-dependent plasticity operates in limited time windows, and it is therefore critical that timing of presynaptic and postsynaptic neurons be activated in a similar time window, irrespective of the spatial distances of their cell bodies. The membrane time constants of the neurons are also preserved, and therefore carrying out similar operations requires that the downstream observer neurons receive similarly synchronized inputs from their afferents in both small and large brains. Oscillation is the most efficient mechanism by which to achieve synchrony (Buzsáki, 2006; Singer and Gray, 1995).

Unfortunately, the rules and principles that allow for the preservation of temporal scales in brains of different sizes and complexity are largely unknown. Currently, only limited information is available about how long-range wiring and a selective increase of axons with

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larger calibers can contribute to the constancy of rhythms. If scientists are to gain insights into the structural rules of scaling, detailed information about local cortical circuits in multiple species are needed. How are interneurons connected to the principal cells and to each other? How many types of pyramidal cells exist? What are the connection probabilities between different pyramidal cell types in different layers? What are the patterns of connectivity within local circuits (Song et al., 2005)? How are the modules connected with each other? These critical mesoscopic questions will require anatomical methods for labeling multiple identified neurons and high-density, large-scale physiological methods capable of resolving single neurons at the speed of spike communication. Currently, there is a rapid development of electrode technology permitting long-term recordings of large numbers of neurons in awake, behaviorally trained animals. These approaches can be enhanced by optogenetic identification of neurons and by their selective perturbation (Cardin et al., 2009; Sohal et al., 2009; Stark et al., 2012), complemented with high spatial-resolution imaging (Svoboda and Yasuda, 2006) and computational modeling (Wang, 2010) to aid in our understanding of the mechanisms and utility of oscillations. The technical and intellectual challenges ahead are enormous, but the quest to understand how time management and the fundamentals of information processing can be preserved in growing brains with ever more complex architectures is one of the greatest challenges in neuroscience.

Despite the surprisingly small variability of individual rhythms across species, their frequency ranges within species and the unique constellations of their cross-frequency interactions are sufficiently broad to characterize individual brains. If we work under the principle that cognition and perception are supported by brain-generated ensemble patterns in cortical networks and that impairment of proper temporal organization underlies the various deficits associated with psychiatric disorders, targeting network oscillations is a promising and effective method for both furthering our understanding of the basis of disease and for finding new treatments. Brain rhythms are robust phenotypes and, therefore, are particularly appropriate targets for further mechanistic and therapeutic research. Network oscillations and their cross-frequency interactions can be measured and quantified in resting, sleeping, and task-solving animals. Oscillations of resting state and sleep faithfully reveal individual-specific brain dynamics without the problems of interpreting complex stimulus- and environment-induced effects. Because rhythms and their interactions are specifically and differentially affected by a large spectrum of psychotropic drugs (Buzsáki 1992; Agid et al., 2007; Alhaj et al., 2011), they can be used in early screening. Unlike the widely varying drug responses between humans and animal models across many measures (Nestler and Hyman, 2010), the pharmacological profiles of network oscillations are most likely identical in all mammalian species. For indepth and targeted analysis, large-scale recordings of multiple single neurons in the behaving animal can be used both for assessment of the mechanistic network-level effects of existing drugs that are already known to be effective in humans and for discovery of novel agents.

The rhythm-focused approach also offers an alternative to drug-based interventions; for example, such alternatives include pattern-guided, closed-loop deep-brain stimulation, sensory feedback, and transcranial magnetic and electrical stimulation. In summary, we submit that approaching psychiatric disease from the perspective of brain dynamics and, in

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particular, oscillations will lead to new understandings of the underpinnings of psychiatric symptoms and represent an alternative road to novel therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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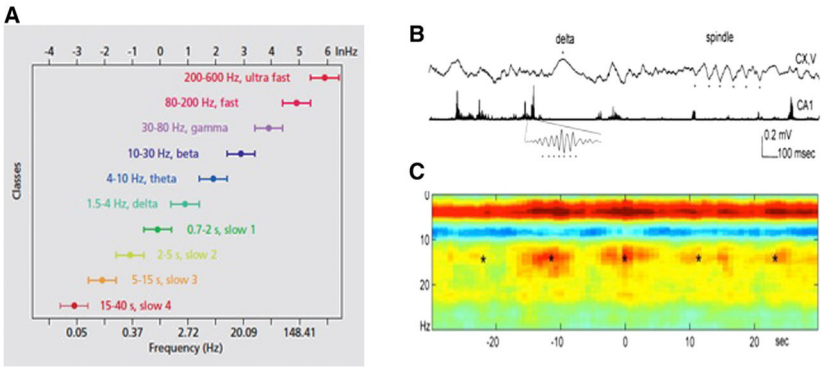

Figure 1. Hierarchical System of Brain Oscillations

(A) A system of interacting brain oscillations. Oscillatory classes in the cortex. Note the linear progression of the frequency classes, together with its commonly used term, on the natural log scale. Note also that the log-frequency variance relative to that of the band frequencies remains constant.

(B and C) Cross-frequency coupling contributes to the hierarchy of brain rhythms. (B) Local-field-potential trace from layer 5 of the rat neocortex (1–3 kHz) and a filtered (140–240 Hz) and rectified derivative of a trace from the hippocampal CA1 pyramidal layer, illustrating the emergence of "ripples." One ripple event is shown at an expanded time scale. The peak of a delta wave and troughs of a sleep spindle are marked by asterisks.

(C) Hippocampal ripple-triggered power spectrogram of neocortical activity centered on hippocampal ripples. Note that ripple activity is modulated by the sleep spindles (as revealed by the power in the 10–18 Hz band), both events are modulated by the slow oscillation (strong red band at 0–3 Hz), and all three oscillations are biased by the phase of the ultraslow rhythm (approximately 0.1 Hz; asterisks).

Panel (A) is reproduced from Penttonen and Buzsáki (2003); panels (B) and (C) are reproduced from Sirota et al. (2003).

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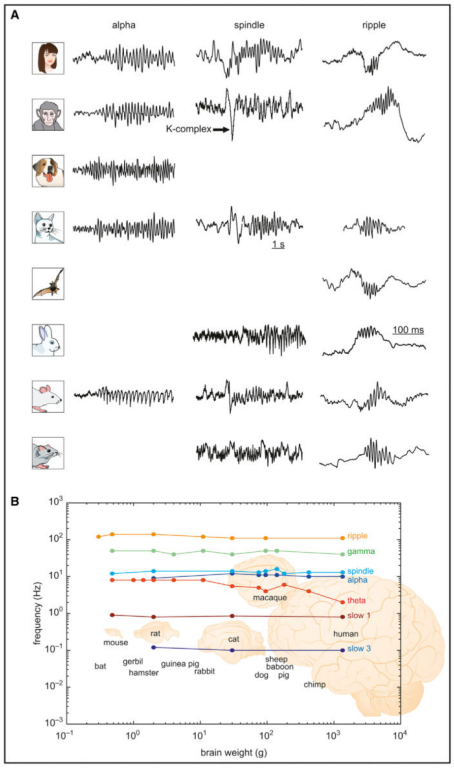

Figure 2. Preservation of Brain Rhythms in Mammals

(A) Illustrative traces of neocortical alpha oscillations, sleep spindles, and hippocampal CA1 ripples in various species. An arrow points to a K complex preceding the spindle. Note the similarity of frequency, evolution, and waveforms of the respective patterns across species.

(B) Relationship between brain weight and frequency of the various rhythm classes on a log-log scale. Note the small variation of frequency changes despite increases in brain weight of several orders of magnitude. Extensive literature sources for data shown here are listed in Supplemental Note 3. The human alpha trace is courtesy of Wolfgang Klimesch (Klimesch, 1997); macaque alpha is courtesy of Charles Schroeder (Bollimunta et al., 2008); dog alpha is from da Silva et al., 1973; human spindle is from Nir et al., 2011; cat spindle is from Hughes et al., 2004; rabbit spindle is from Bereshpolova et al., 2007; rat spindle is from Peyrache et al., 2011; human ripple is from Bragin et al., 1999; macaque spindle is from Skaggs et al., 2007; cat ripple is from Kanamori, 1985; bat ripple is reprinted from Ulanovsky and Moss, 2007; and rabbit ripple is reprinted from Nokia et al., 2010.

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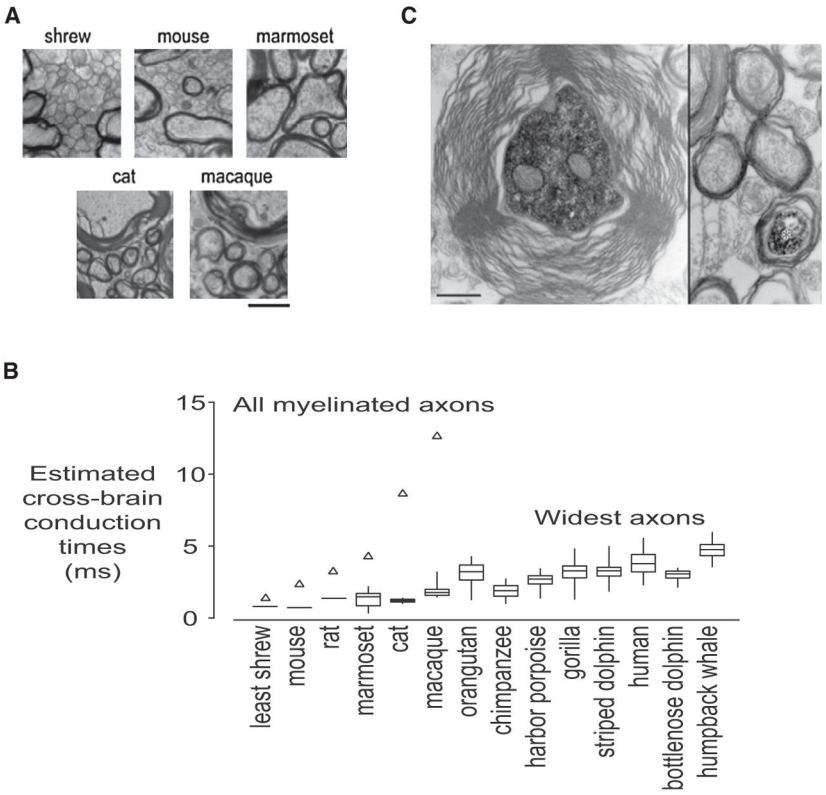

Figure 3. Evolution of Axon Caliber

(A) Representative micrographs of callosal tissue in different species. The scale bar represents 1 μm.

(B) Estimated cross-brain conduction times for myelinated axons (average values; open triangles) and the widest axons (box plots). The widest axons were taken to be the widest 10 axons per 10,000 μm^2, except for shrew, mouse, and rat, in which case the widest observed axon was used. Note only a few-fold change of the fastest cross-brain conduction time across species and compare this to the rapidly increasing conduction times for all myelinated axons. (C) Some of the large-caliber axons might belong to long-range inhibitory neurons. (Left) Cross-section of the neurobiotin-labeled main axon of an intracellularly filled hippocamal CA1 interneuron. (Right) A neurobiotin-labeled main axon of a CA1 pyramidal cell (asterisk) is surrounded by similar axons. Note the difference in diameter and myelin thickness between the axons of the interneuron and pyramidal cell. (A and B) Reproduced from Wang et al., 2008.

(C) Reproduced from Jinno et al. (2007).

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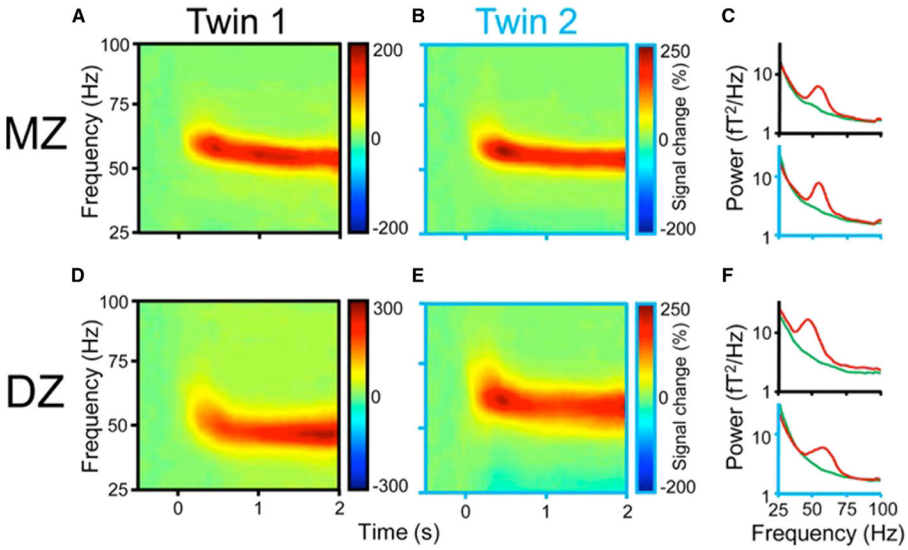

Figure 4. Brain Rhythms Are Specific to Individual Brains

(A and B) Time-frequency display of visually induced gamma-band activity in a monozygotic (MZ) twin pair. (C) Average spectral power of magnetoencephalogram activity during control (green) and visual stimulation (red) epochs. (D–F), same as (A–C) but in a dizygotic (DZ) twin pair. Note the stronger similarity of frequency and temporal dynamic changes of the MEG in the MZ pair relative to the DZ pair. Reproduced from van Pelt et al. (2012).

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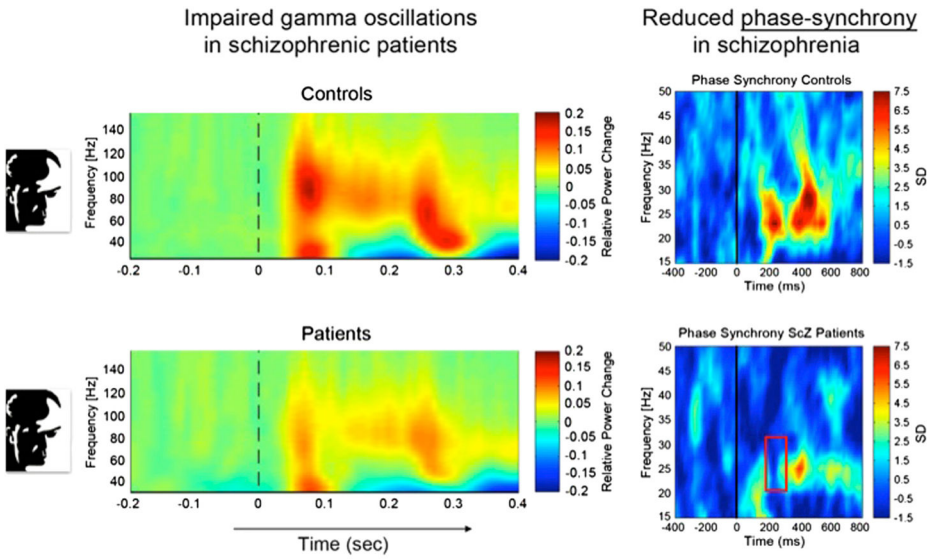

Figure 5. Gamma Oscillations and Phase Synchrony in Schizophrenic Patients

Subjects were presented with Moony faces (left inserts) and were asked to report recognition. Left panels: Time-frequency plots of the power (color scale) of gamma oscillations (frequency on ordinate) after presentation of the stimulus (T0 on abscissa). Right panels: Precision of phase locking of beta oscillations (frequency on ordinate) across sensors (color scale) after stimulus presentation (T0 on abscissa). Upper panels: Healthy control subjects. Lower panels: Schizophrenic patients. Note the reduced power of gamma oscillations induced by the cognitive task (perceptual closure) and the drastically reduced phase synchronization in patients. Adapted from Uhlhaas et al., 2006.