NORMAL AND PATHOLOGICAL OSCILLATORY COMMUNICATION IN THE BRAIN

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Abstract | The huge number of neurons in the human brain are connected to form functionally specialized assemblies. The brain's amazing processing capabilities rest on local communication within and long-range communication between these assemblies. Even simple sensory, motor and cognitive tasks depend on the precise coordination of many brain areas. Recent improvements in the methods of studying long-range communication have allowed us to address several important questions. What are the common mechanisms that govern local and long-range communication and how do they relate to the structure of the brain? How does oscillatory synchronization subserve neural communication? And what are the consequences of abnormal synchronization?

FREQUENCY BANDS
Neural oscillations have been classified into different frequency bands (delta, 1–3 Hz; theta, 4–7 Hz; alpha, 8–13 Hz; beta, 14–30 Hz; gamma, 30–80 Hz; fast, 80–200 Hz; ultra fast, 200–600 Hz).

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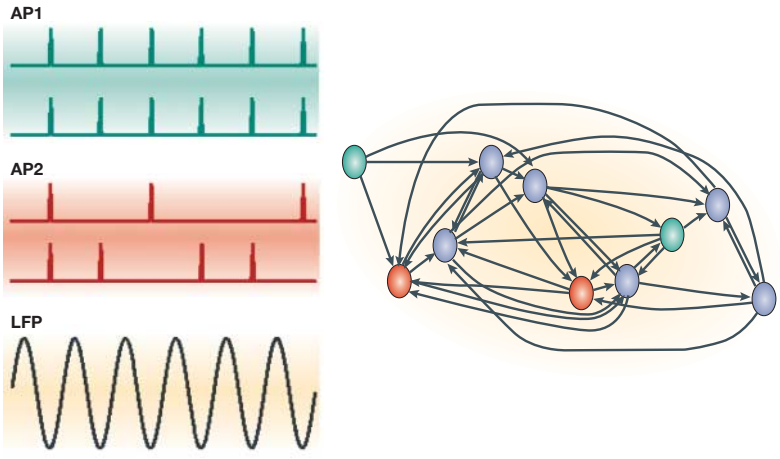
The human brain has remarkable processing capabilities. Consider, for example, a badminton player preparing to defend a smash by his opponent. During a jump smash, the shuttlecock can reach up to 300 km h^{-1}, which bridges the few metres distance between the opponents in less than 300 ms. However, it is often possible to return the shuttlecock. So, how are the ~10^{11} neurons in the human brain organized to support these computations? As no behaviourally relevant task is performed independently by a single neuron, communication is of the utmost importance and, ultimately, optimal computational performance relies on optimal communication. Here we use a broad definition of neural communication, in which a neural element (a single neuron or a population of neurons) conveys certain aspects of its functional state to another neural element. Neural communication depends on the anatomical components that connect individual neurons (structure) and the process of transmitting information (function). Both aspects affect the overall performance of the system.

Structurally, the most striking neuroanatomical feature of the brain is the abundant connectivity between neurons, which reflects the importance of neural communication. Functionally, oscillations are a prominent feature of neuronal activity (BOX 1) and the synchronization of oscillations — which reflects the temporally precise interaction of neural activities — is a likely mechanism for neural communication (BOX 2).

Previously, oscillatory synchronization in the gamma band has been proposed to be a binding mechanism that subserves perceptual and cognitive functions[1–5]. Recent findings have led to an extension of the concept of synchronization by showing that oscillatory networks in the motor system emerge from long-range synchronization in distinct FREQUENCY BANDS — often below the gamma range — between cortical and subcortical areas and the spinal cord in various motor tasks. Importantly, evidence is emerging that a delicately balanced pattern of synchronization and desynchronization in space and time is fundamental to the functional consequences of synchronization. For example, an abnormal pattern of synchronization in parts of the motor system seems to be a key pathophysiological mechanism that underlies motor symptoms, such as tremor and poverty of movement, in Parkinson's disease[6]. Similarly, a balanced and temporally-precise pattern of synchronization and desynchronization is pertinent to cognitive function[7]. Synchronized oscillatory networks can be identified and dynamically characterized in humans by applying new methods of analysis to non-invasive whole-head magnetoencephalographic (MEG) recordings[8] (BOX 3).

Box 1 | **Neural oscillations**



Neural oscillations refer to periodic variations in the recordings of neural activity (left panel). Activity measures are related to the membrane potential of single neurons or populations of neurons (right panel) and thereby encompass action potentials (APs) and LOCAL FIELD POTENTIALS **(LFPs). LFPs represent extracellularly-recorded voltage fluctuations in the membrane potentials of a local neuronal population. LFPs originate from** EXCITATORY AND INHIBITORY POSTSYNAPTIC POTENTIALS **(EPSP/IPSP), mainly as a result of action potential input. As LFPs represent a population measure (spatial average across many neurons), consistent effects across a local population of neurons are enhanced. Oscillations in LFPs often represent regularities in the input to local neurons. These oscillations might have different relations to neuronal firing. They might result from a population of neurons, each firing consistently at every cycle of the oscillation (AP1, see panel). They could also be caused by neurons for which the firing probability is modulated at the frequency of the LFP oscillations. These neurons could fire at a different frequency from that of LFP oscillations, or at no particular frequency (AP2, see panel). Nevertheless, the modulation of firing probability leads (as a population effect) to oscillatory LFPs (see panel). LFP oscillations might be due to regularities in the firing of only a subset of neurons in a local area, as LFPs represent a spatial average. The members of the subset might even change over time. This has important implications for identifying correlated neural firing. Because, technically, only a few neurons can be recorded simultaneously, it might be difficult to identify neurons that participate in correlated activity.**

The emergence of oscillations and the frequencies of these oscillations depend on cellular pacemaker mechanisms and neuronal network properties[25,129]. In general, higher frequency oscillations originate from a smaller neuronal population, whereas low frequency oscillations encompass larger populations. Furthermore, in a given network, the frequency of inhibition-based oscillations might depend on the strength of the driving input and on the magnitude and timecourse of the IPSP[26].

This article reviews recent findings and perspectives on the emerging concept of long-range neural synchronization and desynchronization in motor control and cognition under physiological and pathological conditions. These findings indicate that long-range oscillatory synchronization implements coordinated communication between various areas in the brain. In the first section, we summarize the basic structural and functional neuronal properties that subserve neural communication, and describe possible mechanisms for long-range communication. The second section covers new findings about the functional roles of long-range communication in cognition and motor control. The consequences of disturbed long-range communication and its involvement in clinical symptoms are presented in the final section.

LOCAL FIELD POTENTIAL (LFP). LFPs represent extracellularly recorded voltage fluctuations of a local neuronal population.

EXCITATORY (INHIBITORY) POSTSYNAPTIC POTENTIAL Membrane depolarisation (hyperpolarization) of the postsynaptic neuron following excitatory (inhibitory) input.

Mechanisms of neural communication

The specific cytoarchitectonic structure and connectivity of individual brain areas endow each region with the ability to perform specific tasks. This specialization is important for optimal information processing, but necessitates integration through long-range communication between neural assemblies.

The exact mechanisms of long-range interactions are poorly understood. However, recent findings point towards some general principles that have been elegantly shown in studies of the insect olfactory system. Although it is not yet clear to what extent these results apply to mammals, this system, owing to its relatively small size and reduced complexity, is ideal for studying the mechanisms that underlie oscillatory communication, and their functional consequences, in detail[9,10]. The interactions between the antennal lobe, the mushroom body and the inhibitory neurons in the lateral horn are of particular interest[11–13]. The antennal lobe receives input from olfactory receptor neurons; it then transforms and reformats this input for transfer through projection neurons to the mushroom body, which is responsible for memory encoding and retrieval, and to the lateral horn (FIG. 1). In turn, inhibitory interneurons in the lateral horn project to the mushroom body. Odours elicit global oscillatory activity of 20–30 Hz in the antennal lobe network (which is composed of local and projection neurons), and this, in turn, is reflected in the local field potentials (LFPs) of the antennal lobe, mushroom body and lateral horn. The action potentials of projection neurons are PHASE-LOCKED to the LFP oscillations in a neuron-, odour- and time-specific manner, such that the antennal lobe output is an evolving 20–30 Hz sequence of synchronized projection neuron spikes. Interestingly, the preferred firing time, relative to the oscillating field potential (taken, for example, from the mushroom body), is different in all three networks. Lateral horn inhibitory interneurons fire about half a period after the phase-locked projection neurons. Consequently, inhibitory postsynaptic potentials (IPSPs) to mushroom body neurons that arise from input from the lateral horn occur half an oscillation cycle after the excitatory postsynaptic potentials (EPSPs) that arise from direct input from the antennal lobe. The strong IPSPs lead to collective inhibition of mushroom body neurons during half the oscillation cycle. Therefore, mushroom body neurons can only integrate their input briefly once per oscillation cycle. The functional consequence of the oscillatory interactions of excitatory drive (from the antennal lobe) and phase-shifted inhibition (from the lateral horn) in this particular case is a spatial and temporal sparsening of the odour representation[11], which is a prerequisite for fine odour discrimination[9,10,14]. This example illustrates the following rules, which govern interneuronal communication on different spatial scales.

Filtering and resonance. The effect of the action potentials that are generated in the antennal lobe on the neurons in the mushroom body depends on their timing relative to the global LFP oscillations. The oscillations add relevance

Box 2 | **Neural oscillatory communication**

Long-range interareal communication can be best investigated at the level of population activity as local field potentials (LFPs) and spatially summated LFPs. Long-range communication describes a process in which an area, A, conveys certain aspects of its current functional state to another area, B. The transmission of this information relies on action potentials. The action potential input to area B results in excitatory and inhibitory postsynaptic potentials, which, if temporally overlapping across a neuronal population, would give rise to LFPs that could be measured extracellularly. So, in addition to local processes that affect membrane potential, long-range input from other brain areas also affects locally measured LFPs.

Inhibitory interneurons provide an important mechanism for synchronization of the LFP oscillations of remote neural populations[28,29]. According to the network model of Bibbig and co-workers[28], synchronization can be mediated by a pair of action potentials per oscillation cycle (long-interval doublets). The first spike of the doublet originates from excitatory input from local principal cells; the second is caused by excitation from distant principal cells. The timing between the doublets in a given cycle provides the feedback required to synchronize the oscillations of distant networks.

Although a clear separation is difficult, it is useful to distinguish two effects of area A on area B — A can drive B or A can modulate B. Driving input is mostly excitatory in nature and usually leads to direct activation of B. Modulating input modifies the state of neural populations in a way that affects the processing of driving input[130]. A typical example of driving is the bottom-up input from peripheral receptors to primary sensory cortices, whereas the top-down attentional control of early sensory processing usually reflects modulating input. The different effects of driving and modulating input are evident in the insect olfactory system (see main text).

Functional consequences of oscillatory driving input to the motoneurons that relate to breathing have also been shown in rats *in vitro*[58]. First, similar to the effect of correlated presynaptic inputs on other neurons, the timing of action potentials in motor neurons is crucially affected by oscillatory modulations of input. Motor neuron spike trains are much less variable and more consistent during oscillatory input. Second, increased synchronization in the oscillatory input increases the gain — that is, an increase in the number of action potentials that are elicited by a given input[58] augments the force output in a computer simulation of a motor neuron pool[131]. Given that about 50% of the brain's energy is used for signal transmission[23], efficient interactions are important. Third, synchronization increases the robustness of the input–output relationship for motor neurons against changes in neurotransmitter level[58]. Finally, recent studies indicate that oscillatory communication subserves gating of information processing and modulates the effects of spike trains, and so shows a strong dependence on the behavioural state[11,12,132–134].

to the spike train; they gate information processing. Therefore, "macroscopic oscillations may indicate the existence of neural filters whose properties will determine the interpretation of a spike train."[11]

Filtering and resonance phenomena indicate the dependence of neuronal activity on the frequency content of the input, and are implemented at the level of synapses[15], single neurons[11,16,17] and neuronal populations[18]. They result in the transmission of selected features of the information, enhance the sensitivity of neurons to a certain input frequency, and are subject to plastic changes.

Structural connectivity. The particular variant of oscillatory communication seen in the insect olfactory system relies on a specific connectivity of the three neuronal populations described above. Neurons in the mushroom body receive excitatory input from the fraction of projection neurons that show odour-specific excitation. By contrast, inhibitory interneurons in the lateral horn respond to any odour and project to many neurons in the mushroom body (nonspecific inhibition). Therefore, this particular structural connectivity implements specific excitation and nonspecific inhibition, and subserves sparsening of odour representation.

In general, neurons in the brain are tightly interconnected. The abundance of short-range connections is the structural basis for the development of local functional networks. A small percentage of long-range connections greatly reduces the minimal path length between any two neurons[19–21]. This pattern of structural connectivity is optimal for selectively biasing the communication of local and global networks[22,23]. Changes in communication demands might lead to changes in anatomical connectivity[24].

Spatiotemporal pattern of excitation and inhibition. The example of the insect olfactory system shows the importance of excitation and inhibition for efficient information processing. The excitatory input from the antennal lobe to the mushroom body is counterbalanced by inhibition from the lateral horn, which leads to a temporally sparse odour representation.

Overall, inhibition is important for the emergence of oscillations in networks of principal cells and interneurons[25,26]. The output of neurons that have balanced excitatory and inhibitory inputs is particularly sensitive to correlated input[27]. Furthermore, inhibitory interneurons provide a possible mechanism by which the LFP oscillations of remote neural populations could be synchronized[28–30] (BOX 2).

Physiological relevance

Relation to cognitive functions. The phenomenon of neural oscillations and synchronization has received considerable attention in neuroscience since it was shown to correlate with perceptual binding[31]. In particular, gamma-band oscillatory synchronization has been associated with cognitive functions such as attention, arousal, object recognition and top-down modulation of sensory processes[1,2]. To some extent, specific oscillations have been identified that are associated with particular cognitive processes[4].

Three lines of evidence provide experimental support for extending the concept of gamma-band synchronization as a mechanism for binding. First, there is new experimental evidence that beta oscillations are important in long-range synchronization[32–35], which is further supported by computational modelling[29]. Second, the importance of desynchronization, or, more specifically, the spatiotemporal balance of synchronization and desynchronization, is increasingly being recognized[36–39]. Third, there is new evidence that specific synchronization patterns are directly related to behaviour[32,39–41].

All three of these were shown by a recent whole-head MEG study, in which participants had to detect and report two predefined target letters in a rapid serial visual-presentation protocol[7,42]. Fifteen single letters were presented in rapid succession (7 letters per second). If the two target letters were separated by only

PHASE-LOCKED
Phase locked action potentials occur at specific times in the oscillatory cycle of a local field potential.

Box 3 | **Non-invasive investigation of oscillatory communication**

The non-invasive study of long-range neural communication requires neural activity to be recorded at high temporal resolution and with whole-scalp coverage — conditions that can currently only be met by magnetoencephalography (MEG) or electroencephalography (EEG). These techniques non-invasively record a spatial summation of local field potentials (LFPs) with a temporal resolution of milliseconds. The amplitude of MEG/EEG signals is affected by the size of the activated neuronal population, the degree of synchronization of the LFPs, the strengths of these LFPs and their spatial orientations. The MEG/EEG signal reflects suprathreshold and subthreshold oscillations, the latter of which are not accompanied by action potentials.

We propose three steps for the analysis of neural communication based on non-invasive electrophysiological recordings. First, suitable transformations of the recorded signals are carried out to localize the corresponding neural generators. Second, statistically significant dependencies between the recorded signals are identified. Third, significant dependencies are further characterized and task-specificity is analysed.

- **For noninvasive MEG recordings, tomographic coherence analysis has been introduced by establishing the method dynamic imaging of coherent sources (DICS[8]). (For recently developed alternative approaches see REFS 135–137.) DICS uses a spatial filter in the frequency domain to estimate power or coherence in a specified frequency band. Coherence to a reference signal is computed for a large number of voxels that cover the entire brain. The reference signal could be an electromyographic recording of muscle activity (cerebro-muscular coherence map) or the activity at a reference voxel in the brain (cerebro-cerebral coherence map). The functional tomographic connectivity maps can be overlaid on anatomical MRI images.**
- **With DICS, the coherence spectra between brain areas are computed using Welch's method. Coherence is sensitive to phase and amplitude dynamics, whereas phase synchronization analysis (for example, using the Hilbert transform) can be used to quantify dependencies of phase dynamics only[3,138–140].**
- **Further characterization of dependencies comprises the quantification of directionality in the interaction[141,142]. Another important point is to distinguish the case in which area A interacts with area B from the case in which both areas interact with a third area, C. Both cases could yield the same coherence spectrum between A and B. Partial coherence is an extension of the classical coherence measure that distinguishes between these cases[143,144]. This allows the computation of coherence between A and B, taking into account the common effect of C.**

It is important to note that the identification of significant dependencies, as such, is not very informative. Instead, the aim should be to identify task-specific effects and/or transient changes in dependencies. In the studies that are presented here this has been achieved either by relating synchronization results directly to behavioural phenomena (like movement) or by identifying differences between experimental conditions.

one distractor, participants were unable to report the second target in ~40% of the trials. This reduced ability to detect the second of two targets is called the attentional blink[43]. Target processing was associated with increased power in the beta band at around 400 ms compared with distractor processing. The brain areas responsible for target processing were identified using a technique called DYNAMIC IMAGING OF COHERENT SOURCES (DICS)[8] (BOX 3). Phase synchronization was computed for all area combinations, and this revealed a specific functional network in which synchronization was modulated by targets but not distractors. The strongest synchronization was observed between the right posterior parietal and the left frontal cortices (FIG. 2a). Specifically, the processing of two targets that were separated by a distractor was associated with an increase in synchronization about 260 ms after the presentation of each target, followed by active desynchronization below the baseline level. Interestingly, changes in synchronization were different for the trials in which the second target could not be reported (FIG. 2b). Synchronization to the first target did not differ between trials in which the second target was or was not detected. However, the subsequent desynchronization and the synchronization to the second target were significantly smaller when participants were not able to report the second target. The smaller desynchronization might reflect less efficient suppression of distractor processing or a less efficient transition between processing states. The enhanced synchronization seen when the second targets were correctly reported might indicate preferred processing of the target due to top-down mechanisms. So, this study substantiates a prominent role for beta oscillations in long-range cortico-cortical synchronization, the functional importance of active desynchronization processes and the behavioural relevance of a specific pattern of long-range synchronization.

Relation to motor function. The behavioural effects of oscillatory synchronization are more evident in the motor system, where they can become visible as peripheral oscillations in movement kinematics, and in the ELECTROMYOGRAM (EMG).

During slow finger movements, a common modulation of motor unit firing can be seen at 6–9 Hz[44–46], which results in oscillations of finger velocity at the same frequency (FIG. 3a). The underlying synchronized oscillatory network in the brain was identified in a recent MEG study[47]. Cerebro-muscular coherence between EMG recordings and MEG signals of the contralateral sensorimotor cortex showed significant COHERENCE in the 6–9 Hz frequency range. In a directionality analysis, coupling between muscle and the postcentral somatosensory cortex was found to be mainly afferent. The afferent input to the primary somatosensory cortex is expected, as the pulsatile velocity changes are detected by peripheral receptors and fed back along sensory pathways to the cortex. Most importantly, however, the primary motor cortex showed an efferent directionality, which provides direct evidence that the peripheral movement discontinuities have a central origin.

As the primary motor cortex is part of an extended network of areas that are involved in motor control, subsequent analysis was carried out to identify areas that communicate with the primary motor cortex. This analysis led to the identification of a network that consists of the contralateral primary motor cortex, the premotor cortex, the thalamus and the ipsilateral cerebellum (FIG. 3b). Although these areas are known to be part of a cerebellothalamocortical loop, this study showed, for the first time, an oscillatory interaction, at 6–9 Hz, within this loop. These interactions are likely to reflect discrete movement control. As a part of the cerebellothalamocortical loop, the cerebellum has specifically been associated with the optimization and correction of ongoing

DYNAMIC IMAGING OF COHERENT SOURCES (DICS). Analysis technique that can compute tomographic functional maps of oscillatory power and coherence.

ELECTROMYOGRAM
Recording of electrical muscle activity.

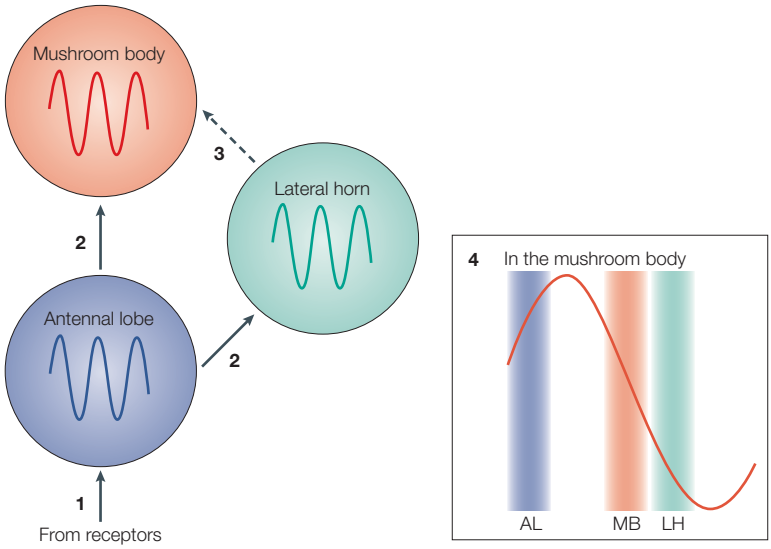


Figure 1 | **Oscillatory communication in the insect olfactory system.** Schematic illustration of interactions between the antennal lobe (AL), the mushroom body (MB) and inhibitory neurons in the lateral horn (LH) during odour processing. Solid arrows represent excitatory influence and the dashed arrow represents inhibitory influence. Odours induce local field potential (LFP) oscillations at a frequency of `~20–30 Hz in AL, MB and LH (**1**). The firing of some (odour-specific) projection neurons in AL is phase-locked to the oscillations (that is, firing takes place at a specific time in a cycle) in a certain (odour-specific) time window. Spike trains from AL are transmitted to MB and LH (**2**). LH output to MB leads to global inhibition for about half the LFP cycle (**3**). Illustration of the firing probability for neurons in AL, MB and LH relative to a LFP oscillation in MB (**4**). During each oscillation cycle, nonspecific but phase-delayed inhibitory postsynaptic potentials (IPSPs) quickly follow the volley of direct and neuron-specific excitatory inputs from the AL, which generally prevents any response from the MB neuron. If the MB neuron reaches spike threshold, the IPSP prevents the generation of further action potentials.

movements. In order to perform this task, sensory information from the periphery is integrated with the efference copy from the motor cortex, which allows the required corrections to be computed. In addition, cerebellar activity is known to directly affect the amplitude and timing of AGONIST AND ANTAGONIST muscle activities. As the peripheral discontinuities are caused by an alternating pattern of agonistic and antagonistic bursts, the results indicate that continuous finger movements are implemented as repeatedly performed micro-movements (at 6–9 Hz), each of which consists of a short, accelerating burst of agonist followed by a short, decelerating burst of antagonist. By controlling the amplitude (and perhaps the timing) of this possibly preprogrammed pattern, the cerebellothalamocortical loop might implement a flexible control of ongoing movements that is robust in the presence of conduction delay.

A common modulation of motor unit firing can be seen not only at 6–9 Hz during slow finger movements, but also in the beta band during ISOMETRIC CONTRACTIONS[48–50]. MEG and electroencephalography (EEG) have been used to trace the common modulation back to the primary motor cortex. This phenomenon is evident as CORTICOMUSCULAR COHERENCE, which can be seen between EMG and neuromagnetic recordings (for reviews, see REFS 51,52). So, there are oscillations in muscle activity that represent the reverberations of synchronized oscillations of neuronal populations in the primary motor cortex. Indeed, multi-electrode recordings in the monkey primary motor cortex revealed not only the presence of abundant beta LFPs at rest[53–55] but also synchrony between neurons that have the same output connectivity to muscles[56]. Although corticomuscular coherence shows task-related modulations[57], its functional significance is still unclear. However, recent findings from the rat respiratory motor system indicate that corticomuscular coherence might enhance the precision, efficacy and robustness of information processing[58] (BOX 2).

In the motor system, beta oscillations are not only restricted to the primary motor cortex, but also occur in premotor areas[55,59], parietal areas[53,60], the cerebellum[61], the subthalamic nucleus[62] and the striatum[61]. In addition to simple coexistence, there is evidence for long-range synchronization of cerebral areas that oscillate at the beta frequency. Thalamocortical coherence occurs in the beta band during movement preparation[63], isometric contraction and at rest[64]. Brovelli *et al.* recorded LFPs in the beta frequency range during isometric contraction in monkeys[60], and showed beta synchronization between the primary somatosensory, primary motor and inferior posterior parietal cortices (FIG. 4). The direction of information flow in this network supports the hypothesis of a sensorimotor sampling loop, which was previously proposed to rely on a periodic sampling of the state of the periphery[65] to achieve optimal motor control.

Pathological significance

Abnormal synchronization processes have been associated with several neuropsychiatric disorders, including epilepsy[66,67], schizophrenia[68], dementia[69] and, in particular, basal ganglia disorders such as Parkinson's disease[70].

In the past few years, electrophysiological studies of the normal functioning of basal ganglia-thalamocortical circuits (FIG. 5a) and the pathophysiology of Parkinson's disease[6,71] (BOX 4) have provided new insights into the functional roles of oscillations and oscillatory synchronization. Because animal models of Parkinson's disease are available[72], as are new therapeutic approaches in patients, including DEEP BRAIN STIMULATION by chronically implanted electrodes in the basal ganglia[73], unique opportunities have emerged in this area of research, providing access to many levels of neurophysiological data. Recordings of single and multi-unit activity, as well as LFPs from the subthalamic nucleus (STN), the globus pallidus internus (GPi) and the thalamus can be obtained from normal animals, animal models of Parkinson's disease and patients with Parkinson's disease, both during awake neurosurgery and for a couple of days after surgery. Furthermore, non-invasive MEG/EEG recordings from patients with Parkinson's disease and healthy individuals yield complementary information on large-scale neural activity and synchronization between brain areas. In addition, the effects of pharmacological interventions and of therapeutic electrical

COHERENCE
A frequency-domain measure of neuronal interaction normalized between 0 and 1. High values indicate dependence of two oscillations.

AGONIST AND ANTAGONIST
The antagonist is a muscle that counteracts the effect of another muscle, the agonist.

ISOMETRIC CONTRACTION
Static muscle contraction that occurs without movement.

CORTICOMUSCULAR COHERENCE
Coherence between cortical activity and muscle activity.

DEEP BRAIN STIMULATION
Continuous therapeutic electric stimulation of subcortical areas at high frequencies (~130 Hz) using chronically implanted electrodes.

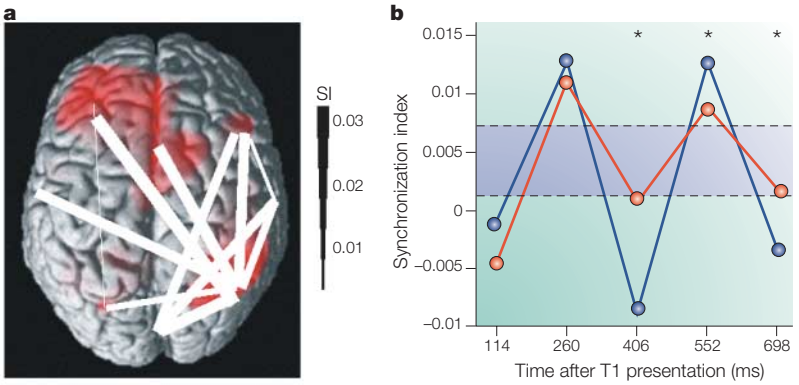


Figure 2 | **Long-range synchronization in a visual attention-related network detected with whole-head magnetoencephalography (MEG). a** | The target-related network is shown in lines. The width of the lines indicates the strength of synchronization at 260 ms after onset of the first target. The strongest connection is between the right posterior parietal cortex and left frontal cortex. **b** | The synchronization index (SI), which quantifies phase synchronization, shown for five successive stimuli. The x-axis specifies time after presentation of the first target. Each point represents the mean SI in a 60-ms-window centred at 260 ms after the respective stimulus. Values at 260 ms quantify the network synchronization to the first target (T1), whereas values at 114 ms represent the network synchronization that corresponds to the distractor preceding the first target. The blue line represents the response seen when both targets were correctly reported and the red line the response seen when the second target was missed. The dashed lines mark the extent of the SI in trials that contained only distractors. Asterisks indicate significant differences between conditions ($p<0.05$, Kruskall-Wallis test). Negative values arise from the filtering of the SI time courses. Modified, with permission, from REF. 7 © (2004) National Academy of Sciences USA.

stimulation of specific basal ganglia target areas are being studied. Rapidly growing evidence from this exciting field of research indicates that oscillatory synchronization within the basal ganglia and between subcortical and cortical structures is of particular significance in the pathophysiology of Parkinson's disease.

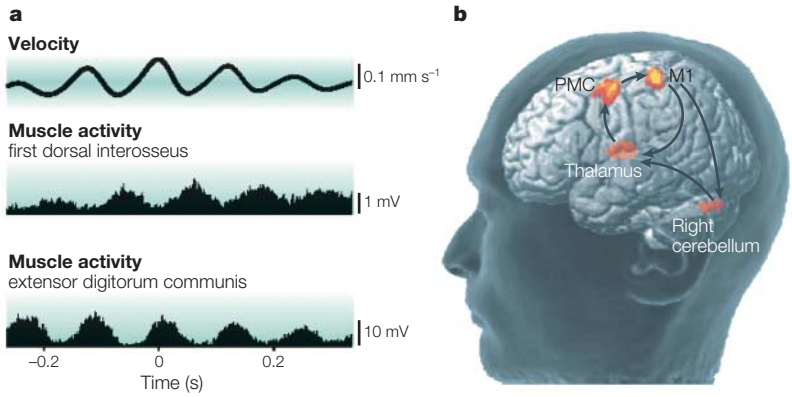


Figure 3 | **Long-range oscillatory network that underlies 6–9 Hz movement discontinuities. a** | Averaged finger velocity and electromyogram of first dorsal interosseus and extensor digitorum communis muscles during a slow index finger extension movement in a typical human subject. The trigger points for averaging were 300 maxima of the velocity signal, which were found by band-pass filtering the signal at 6–9 Hz and performing a Hilbert transformation to obtain the instantaneous phase and amplitude. The averaging was done on unfiltered traces. The average represents the part of the signal that is time-locked to discontinuities in the finger velocity. **b** | The spatial distribution of coherence with the left primary motor cortex (M1) as a reference region. Only areas with $p<0.05$ (corrected, one-sample t-test) are shown. Note that the left thalamus and right cerebellum are projected to the left surface for easier visualization. The dominant coupling direction (mean directionality index[141]) is indicated by arrows. PMC, premotor cortex. Modified, with permission, from REF. 47 © (2002) National Academy of Sciences USA.

Abnormal synchronization in Parkinson's disease. Studies of neuronal firing in both human patients and animal models of Parkinson's disease have provided evidence of an increase in oscillatory activity in the globus pallidus externus (GPe), the GPi and the STN[74,75]. The excitatory STN and inhibitory GPe form a feedback system that engages in synchronized bursting[76]. Interestingly, lesions or high frequency stimulation of the GPi or STN are effective in treating the symptoms of Parkinson's disease, probably because they reduce or abolish abnormally synchronized basal ganglia output. These findings indicate that changes in oscillatory discharge patterns and synchronization between basal ganglia neurons and abnormal long-range network interactions are important in the pathophysiology of Parkinson's disease. Frequency domain analysis of LFP recordings from patients with Parkinson's disease has revealed oscillations in three main frequency bands in the basal ganglia: 3–10 Hz, 11–30 Hz and 60–80 Hz. The occurrence and synchronization of these oscillations have been associated with either preventing or supporting normal motor behaviours (FIG. 5b).

Relation to movement execution. In patients with Parkinson's disease who have been treated with dopaminergic drugs, coherence of LFPs between the STN and GPi occurs at ~60–80 Hz, which resembles the normal state[77]. Before and during voluntary movement, the STN–GPi coherence and the coherence between the STN and the cortex are increased[78], with STN and GPi oscillations leading (and so probably driving) the cortical activity[79]. These findings indicate that the STN, GPi and cortex form a long-range functional network that resonates at 60–80 Hz, and that they are prokinetic[6] (supporting normal movement) (FIG. 5b). In line with this concept, stimulation of the STN or GPi at frequencies that are likely to cause 60–80 Hz resonance in this network improves AKINESIA in patients with Parkinson's disease[80,81]. However, these oscillations are unlikely to be directly linked to the execution of movement, because they occur both during movement and at rest. Interestingly, with drowsiness they disappear in the STN[77]. As such, it has been suggested that they might be related to attentional processes in the motor domain rather than to the actual execution of movement, possibly acting through the thalamus to favour cortico-cortical interactions[82,83].

By contrast, the frequencies of about 11–30 Hz and 3–10 Hz are considered to be predominantly antikinetic[6] (FIG. 5b). Observations in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) MODEL of Parkinson's disease (BOX 4) indicate that, in the diseased state, beta oscillatory activity is enhanced and gamma activity depressed[84]. Indeed, synchronous oscillations at 11–30 Hz in single units and LFPs in the STN and GPi have also been shown in patients with Parkinson's disease[62,85,86]. Furthermore, there is coherence between the motor cortex EEG and LFP beta oscillations in the STN and GPi of untreated patients with Parkinson's disease, which is decreased after the administration of dopaminergic drugs[77,86] and by

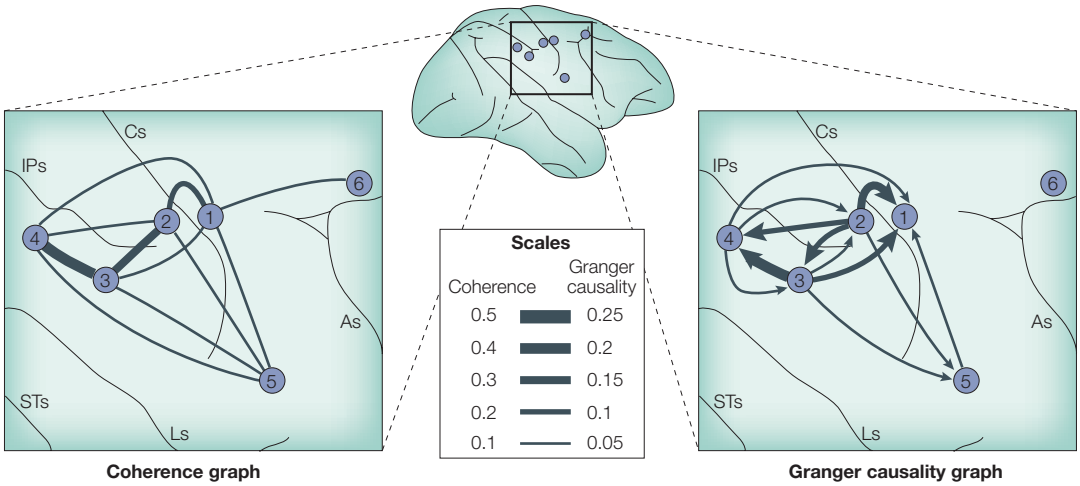


Figure 4 | **Oscillatory interactions in the beta band in the monkey cortex during an isometric contraction task.** Line thickness indicates the degree of coherence (left) and Granger causality (right) found between recording sites (labelled 1–6) when a monkey performs a contraction task. Granger causality quantifies the directionality of information flow. Only significant interactions are shown. As, arcuate sulcus; Cs, central sulcus; IPs, intraparietal sulcus; Ls, lateral sulcus; STs, superior temporal sulcus. Modified, with permission, from REF. 60 © (2004) National Academy of Sciences USA.

voluntary movement[78]. Interestingly, these drug- and task-induced effects on the beta band are essentially reciprocal to those of the gamma band. Because of this functional reciprocity, and as estimates of phase relations indicate that beta LFP oscillations in the STN and GPi are driven by the cortex[79,86], it has been proposed that, as a result of dopamine depletion in patients with Parkinson's disease, antikinetic beta oscillatory input from the cortex suppresses prokinetic gamma oscillations in the basal ganglia[62,77]. Together, these findings indicate that, in patients with Parkinson's disease, an increased tendency of the basal ganglia to oscillate in the beta frequency range interferes with the brain's ability to execute movement, which leads to the akinesia that is associated with the disease. The symptom of akinesia seems to reflect an abnormally held 15–30 Hz oscillatory state, which is usually observed in healthy humans during normal position-holding through the provision of a 15–30 Hz motor-cortex drive to muscle.

Although these results support the prevailing idea that the occurrence of beta oscillations and synchrony in basal ganglia circuits is important in the pathophysiology of akinesia, there is also evidence for a more differentiated view. It might not be the presence of beta oscillations *per se*, but the amount and synchrony of oscillations that determine whether the behavioural consequence is normal or pathological. Courtemanche and co-workers[61] recently showed that synchronized beta oscillations occur globally in the striatum of healthy monkeys at rest. Interestingly, focal sites in the striatum that were engaged in an oculomotor task showed decreased beta power and, most importantly, became disengaged from the general LFP synchrony during the eye movement. So, although LFP oscillations can normally filter striatal input–output transmission[61], beta oscillations in patients with Parkinson's disease might be enhanced to the extent that voluntary movements are impeded because the motor command for initiation cannot overide the enhanced oscillatory state[6,70]. The desynchronization that is required in the beta band for the initiation of movement[85] might be unable to traverse the elevated threshold, which could lead to the movement deficits that are seen in patients with Parkinson's disease. In line with this pathophysiological model of Parkinson's disease, driving the STN by electrical stimulation at 20 Hz was shown to increase synchrony in the GPi[87]. Conversely, stimulation of the STN at frequencies above 70 Hz has been shown to suppress LFP beta oscillations in the GPi[87] and can markedly relieve the symptoms of Parkinson's disease[80], whereas low-frequency STN stimulation at ~10–15 Hz results in worsening of akinesia[88]. These findings provide further support for the concept that a delicate balance of synchronization and desynchronization is functionally and behaviourally important.

Relation to tremor. Oscillations in the low-frequency range (3–10 Hz) are frequently in synchrony with tremor, another clinical hallmark of Parkinson's disease. In both patients with Parkinson's disease and animal models, tremor-correlated neurons are found in the STN, GPi and the thalamus[89]. Simultaneous microelectrode recordings have shown that oscillatory bursting is synchronized in different GPi neurons of tremulous MPTP-treated monkeys and patients with Parkinson's disease[75,90–92]. Similar findings have been reported in the STN of patients with Parkinson's disease-associated tremor[74]. These observations support the hypothesis that synchronized oscillations are related to the pathogenesis of limb tremor[90,93]. Tremor-related oscillations in the STN, GPi and thalamus are an integral part of an oscillating network that includes both the basal ganglia-thalamocortical and the cerebellothalamocortical

AKINESIA
Poverty and slowness of movement.

MPTP MODEL
Animals treated with the neurotoxic substance MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) develop symptoms of Parkinson's disease.

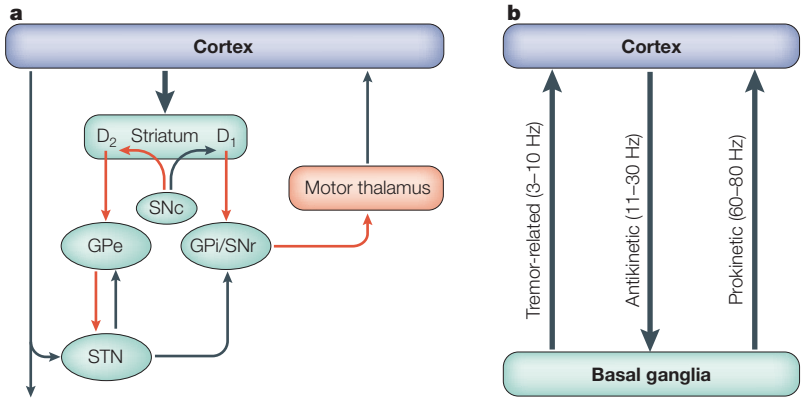


Figure 5 | **The basal ganglia circuit. a** | The basal ganglia are a group of subcortical nuclei that are involved in many segregated parallel loops that modulate cortical activity and subserve motor, oculomotor, associative and emotional functions[145–147]. The nuclei involved in the motor loop include the striatum (consisting of the caudate nucleus and putamen), globus pallidus (GP), substantia nigra (SN), subthalamic nucleus (STN) and the motor nuclei of the thalamus. The GP is further subdivided into the GP externus (GPe) and GP internus (GPi). The SN can be divided into two parts: the SN pars compacta (SNc) and the SN pars reticulata (SNr). The striatum receives most of the input from the cerebral cortex; in this sense, it is the doorway to the basal ganglia. The GPi and SNr are the output nuclei of the basal ganglia and send the main inhibitory output from the basal ganglia back to the thalamus. The striatum sends its output to the GPi/SNr through a direct dopamine D1-receptor-mediated pathway and through an indirect dopamine D2-receptor-mediated pathway involving the GPe and STN. The direct pathway is thought to facilitate movement, whereas the indirect pathway is thought to suppress movement[148,149]. There is a delicate balance between these two pathways that is partly maintained by dopamine release from the SNc to the striatum. Dopamine release inhibits the indirect pathway by stimulating dopamine D2 receptors and excites the direct pathway by stimulating the dopamine D1 receptors. Black arrows indicate excitatory pathways; red arrows indicate inhibitory pathways. **b** | The akinetic and prokinetic effects of the different frequency bands of oscillations in the basal ganglia–cortical network[70].

loop[94,95]. A recent MEG study[95] investigated the large scale synchronization between brain areas and tremor EMGs in patients with Parkinson's disease-associated resting tremor (FIG. 6). Tremor-related oscillatory activity and synchronization was shown in an extended network, which comprises the basal ganglia-thalamocortical loop, cerebellothalamocortical loop, primary and non-primary cortical motor and sensory areas contralateral to the tremor hand. Interestingly, the frequency of coupling between brain areas is approximately twice as high as the tremor frequency. So, the frequency of the rest tremor in Parkinson's disease probably reflects a 2:1 transformation of cerebral network oscillations. Compatible with this hypothesis, in MPTP-treated vervets tremor episodes were associated with 10–15 Hz oscillatory activity in the GPi and 5–7 Hz oscillations in the motor thalamus[96]. The occurrence and possible mechanisms of such a non-linear entrainment have recently been shown in the response of the olivocerebellar system to rhythmic input from the motor cortex[18]. The mechanism and origin of the transformation in Parkinson's disease are, as yet, unknown.

Interestingly, the oscillatory network that was shown by Timmermann *et al.*[95] is not only involved in tremor generation but also in controlling physiological repetitive movements[97,98]. In a study of healthy subjects who voluntarily imitated the rest tremor of Parkinson's disease, Pollok *et al.*[98] showed that the tremor of Parkinson's disease and a voluntary tremor share the same oscillatory network. However, there are characteristic differences in the coupling strengths between areas in the network that distinguish the two conditions. Patients with Parkinson's disease who exhibit rest tremor show a stronger coherence between the thalamus and the primary motor cortex. By contrast, healthy individuals show a stronger coherence between the primary motor cortex and premotor cortex. These results are consistent with the idea that the resting tremor of Parkinson's disease arises from abnormal thalamocortical synchronization that drives the primary motor cortex, whereas in voluntary tremor the motor cortex is primarily driven by premotor areas. So, once again, it is the relative amount of long-range synchronization between constituents of the oscillatory network that determines the network's functional state and behavioural output.

Accordingly, the beneficial effects of high frequency stimulation of various target areas within this network on the tremor of Parkinson's disease might be due to a partial desynchronization of the abnormally rhythmic activity within the oscillating loops. Interestingly, and in agreement with the results of Timmermann *et al.*[95], the tremor of Parkinson's disease can be successfully treated, not only by targeting the basal ganglia–thalamocortical network through stimulation of the STN or GPi, but also by modulating the cerebellothalamocortical loop through stimulation of the ventralis intermedius nucleus[89,95]. As the basal ganglia–thalamocortical projection and the cerebellothalamocortical projection are thought to remain separate until they reach the cortex, an interaction between the two projections might take place at the cortical level, most probably in the primary motor cortex. Several lines of evidence support this idea.

First, the primary motor cortex is involved in the tremor-generating network[94,95,99,100]. Second, motor cortical oscillations are coherent with oscillations in the thalamus, basal ganglia and the cerebellum[95]. Third, rhythmic cortical activity has been shown to be transmitted to the STN and STN–GP network[101]. Finally, if the motor cortex is the convergent structure of the two oscillating networks, the hypothesis must be that cortical stimulation would also ameliorate the tremor of Parkinson's disease. Indeed, it has recently been shown, in a baboon model of Parkinson's disease, that high-frequency motor cortex stimulation effectively alleviates the symptoms of Parkinson's disease, including tremor, and reduces oscillatory synchronization in the STN and GPi[102].

Together, these findings corroborate the significance of long-range cortico-subcortical synchronization phenomena in the generation of the tremor of Parkinson's disease. They also exemplify how analysis of oscillatory synchronization could contribute to our understanding of the pathophysiology of abnormal motor behaviour, and might help in the development of novel treatment strategies.

Box 4 | **Parkinson's disease and the MPTP animal model**

Parkinson's disease is characterized by poverty and slowness of movement (akinesia), muscle stiffness (rigidity) and tremor. In Parkinson's disease, the dopaminergic neurons of the substantia nigra pars compacta (SNc) degenerate, which leads to increased neuronal firing and enhanced oscillatory and synchronized activity of the subthalamic nucleus (STN), and results in excessive inhibition of the thalamocortical drive. In the early 1980s, several users of an illegal drug developed parkinsonian symptoms that were caused by toxic contamination with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).

In animals, MPTP results in the selective loss of dopaminergic neurons in the SNc and a subsequent reduction in dopamine levels in the striatum, which leads to the development of parkinsonian symptoms. It has been proposed that dopamine depletion might lead to a breakdown in the segregation of parallel subcircuits in the basal ganglia and an increase in synchronized neuronal activity. This hypothesis is based on the results of studies that used simultaneous microelectrode recording techniques to show that oscillatory firing rate fluctuations are abnormally synchronized in pallidal neurons in tremulous MPTP-treated monkeys and in the pallidal and STN neurons of patients with Parkinson's disease. The oscillatory activity recorded in these cases is in the 15–30 Hz beta range and/or the 3–10 Hz range. Both ameliorating the dopaminergic deficits with dopaminergic drugs and disrupting the pathological STN or globus pallidus internus activity by electrical high-frequency stimulation alleviate the symptoms of Parkinson's disease in patients and in MPTP-treated monkeys.

Synchronization in other movement disorders. Recently, the long-range synchronization of neural activity in humans has been studied for other tremor disorders, such as postural tremor in Wilson's disease[103], essential tremor[104,105], physiological tremor[106,107] and mini-asterixis in hepatic encephalopathy[108,109]. It seems that oscillatory networks that underlie the various tremor disorders partially overlap in space, and show distinct features with regard to oscillation frequencies, oscillatory power and/or oscillatory coupling.

Recent evidence indicates that the degree of synchronization of neural activity in basal ganglia circuits is also of pathophysiological or adaptive relevance to other movement disorders, such as dystonia[110,111], drug-induced dyskinesias[112] and TOURETTE SYNDROME[113]. Silberstein *et al.*[110] found decreased LFP power in the 11–30 Hz band and increased power in the 4–10 Hz band in the globus pallidus of patients with dystonia compared with untreated or treated patients with Parkinson's disease. In keeping with these findings, coherence analysis between different muscles — an indirect measure of corticomuscular drive — revealed a pathological 4–7 Hz drive in patients with cervical[114,115] and limb[116] dystonia. The reciprocal pattern of synchronization in the globus pallidus and the fact that pallidal functional neurosurgery improves the symptoms of both dystonia and Parkinson's disease indicate that, in both conditions, oscillatory activity is pathological, and its suppression is, therefore, therapeutically successful.

The pathophysiological role of oscillatory synchronization in Tourette syndrome is largely unexplored. However, high frequency electrical stimulation of medial thalamic nuclei greatly reduced motor tics in three severely affected patients[117]. Whether this beneficial effect was due to a modulation of oscillatory synchronization and whether it can be substantiated in a larger number of patients will have to be clarified in further investigations. As patients with Tourette syndrome often show psychiatric symptoms, such as obsessive-compulsive behaviour, it will also be interesting to study their relation to synchronization processes in non-motor basal ganglia loops.

TOURETTE SYNDROME
A childhood-onset disorder that is characterized by irregular motor tics and vocalizations. It is often accompanied by obsessive-compulsive behavioural disturbances.

Synchronization in neuropsychiatric diseases. Since complex cognitive functions particularly require the coordination of large-scale processing by sets of distributed, interconnected areas, and local processing within areas[118], the investigation of long-range synchronization has become a main focus of scientific interest in neuropsychiatric diseases[119]. Recent evidence indicates that cognitive deficits seen in Alzheimer's disease are associated with a functional disconnection of neuro-cognitive networks. Analyses of global EEG synchronization reveal a widespread reduction in the alpha-, beta- and gamma-band synchronization[120], concomitant with an increase in the delta-band synchronization[121]. In patients with mild Alzheimer's disease, a loss of beta-band synchronization has been shown to correlate with cognitive impairment[122]. A decline in interhemispheric functional connectivity in patients with Alzheimer's disease seems to result, at least in part, from a specific loss of cortical association neurons projecting through the corpus callosum, as a reduction in interhemispheric coherence correlates with corpus callosum size in a region-specific manner[123].

Neurochemically, Alzheimer's disease is characterized by cholinergic hypofunction. Interestingly, acetylcholine has been shown to have a crucial role in oscillatory patterning and synchronization in the gamma band[124]. So, this study[124] provides a possible link between neurochemical alteration, oscillatory synchronization and the cognitive dysfunction that is seen in Alzheimer's disease.

Abnormalities in neural synchronization have also been reported in schizophrenia, in which a failure of stimulus-locked and a reduced frequency of response-locked gamma-band oscillations have been observed [125,126], with the latter being correlated with the symptomatology of the disorder[126]. A number of possible causes have been suggested for this inability to synchronize at high frequencies, including white matter abnormalities, reduced excitatory input to pyramidal cells, disfacilitation from reduced thalamic inputs and a reduction in inhibitory neurotransmisson[126]. Together,

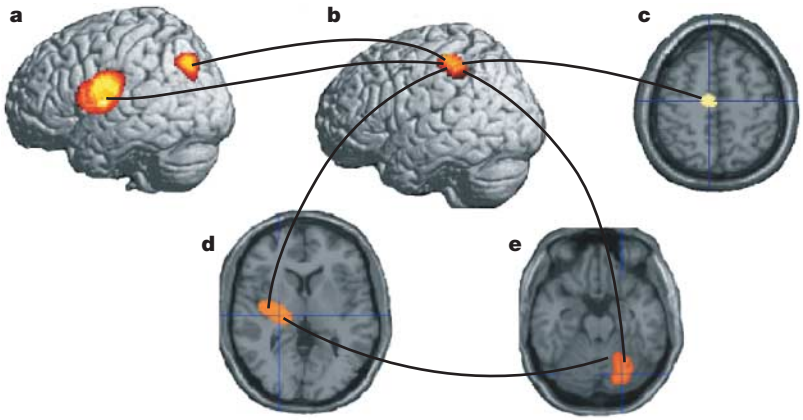


Figure 6 | **Long-range synchronization in Parkinson's disease.** Maps of spatially normalized cerebro-muscular and cerebro-cerebral coherence averaged across 4 patients with right-sided rest tremor. Cerebro-muscular coherence at double tremor frequency occurs in the contralateral primary motor cortex (**b**). Cerebro-cerebral coherence was computed with the reference region in the primary motor cortex and averaged for all patients. Areas of consistent coherence are the lateral (**a**) and medial (**c**) premotor areas, secondary somatosensory cortex (**a**), posterior parietal cortex (**a**) as well as the thalamus/basal ganglia (**d**) contralateral to the tremor hand and the cerebellum (**e**) ipsilateral to the tremor hand. Note that because of the large distance to the magnetoencephalogram (MEG) sensors, localization in both subcortical areas is not as precise as at the cortical level.

studies on dementia and schizophrenia have clearly shown abnormalities in long-range synchronization in these disorders. However, further investigation is required to clarify which anatomical structures are involved, and the specificity and pathophysiological relevance of the findings.

Conclusions and future perspectives

The data that we have reviewed here indicate that long-range oscillatory synchronization constitutes a fundamental mechanism for implementing coordinated communication between spatially distributed local networks in the brain. It rests on optimal structural connectivity patterns and is pertinent to almost all domains of brain function. On the basis of the reviewed data, we suggest a broadening of the concept of neural synchronization, from a mechanism of perceptual binding to a more general role of synchronization in mediating coordinated communication within and across different neural subsystems. Although the bulk of the evidence for the behavioural relevance of synchronization is still correlative, recent studies, particularly those on the insect olfactory system[12] and the human motor system[6], strongly indicate that changes in synchronization lead to changes in behaviour. Altering the pattern of synchronization in the olfactory bulb affects odour discrimination. Modifying abnormal synchronization in the basal ganglia of patients with Parkinson's disease using high-frequency electrical stimulation effectively alleviates the symptoms of Parkinson's disease that are associated with abnormal synchronization patterns. Therefore, important advances have been made with regard to the functional significance of neural synchronization. Furthermore, recent progress in methodological developments[8] now allows the non-invasive investigation of long-range synchronization in healthy human individuals and patients with brain disorders, thereby providing exciting future perspectives in this research area.

At present, our knowledge about the detrimental effects of abnormal synchronization in patients with Parkinson's disease and experiences with deep brain stimulation demand further study in order to characterize the role of synchronization in other movement disorders and neuropsychiatric disorders, in which disturbances in neural communication are likely to occur. By improving our understanding of the pathophysiological mechanisms, these studies might eventually lead to predictions about target areas for deep brain stimulation or substances for specific pharmacological treatment.

Controlled perturbations of long-range communication by pharmacological intervention, invasive electrical stimulation, transcranial magnetic stimulation or behavioural interventions are promising approaches that might be used to further advance our understanding of the role of long-range neural communication under physiological and pathological conditions. Future developments might enable us to perform non-invasive real-time measurements of synchrony that can be used as feedback signals to modify behaviour.

On methodological grounds, statistical procedures are currently being developed (often based on permutation techniques) that subserve identification of task-specific functional connectivities. This will be important in supplementing information about the specific and unique structural connectivity pattern of a cortical area ('connectional fingerprint'[127]), with a more detailed description of its task-related functional connectivity. Combining information about anatomical connectivity from diffusion tensor imaging with MEG/EEG synchronization analysis could offer a powerful approach for achieving this goal. Similarly, simultaneous EEG/functional MRI measurements provide the opportunity to explore the non-trivial relationship between electrophysiological and functional connectivity measures[128].

Due to the nonlinear nature of brain signals, it is likely that signal transmission measures of nonlinear interactions will have an important role in the future. Investigating the interplay between different frequencies adds another dimension to the already complex identification of spatiotemporal and frequency-specific neuronal networks and require appropriate techniques for dimensionality reduction. The current linear analysis approaches are likely to allow us to see only the tip of the iceberg of the oscillatory neural communication processes.

The functional significance of brain oscillations remained a tantalizing mystery for many decades after their discovery. Now, the available evidence indicates that not only does oscillatory synchrony represent a mechanism for binding, but that it is also important for neural communication in general.

1. Singer, W. Neuronal synchrony: a versatile code for the definition of relations? *Neuron* **24**, 49–65, 111–125 (1999).
2. Engel, A. K., Fries, P. & Singer, W. Dynamic predictions: oscillations and synchrony in top-down processing. *Nature Rev. Neurosci.* **2**, 704–716 (2001).
3. Varela, F., Lachaux, J. P., Rodriguez, E. & Martinerie, J. The brainweb: phase synchronization and large-scale integration. *Nature Rev. Neurosci.* **2**, 229–239 (2001).
4. Ward, L. M. Synchronous neural oscillations and cognitive processes. *Trends Cogn. Sci.* **7**, 553–559 (2003).
5. Buzsaki, G. & Draguhn, A. Neuronal oscillations in cortical networks. *Science* **304**, 1926–1929 (2004).
6. Brown, P. Oscillatory nature of human basal ganglia activity: relationship to the pathophysiology of Parkinson's disease. *Mov. Disord.* **18**, 357–363 (2003).
7. Gross, J. *et al.* Modulation of long-range neural synchrony reflects temporal limitations of visual attention in humans. *Proc. Natl Acad. Sci. USA* **101**, 13050–13055 (2004).
8. Gross, J. *et al.* Dynamic imaging of coherent sources: studying neural interactions in the human brain. *Proc. Natl Acad. Sci. USA* **98**, 694–699 (2001).
9. MacLeod, K., Backer, A. & Laurent, G. Who reads temporal information contained across synchronized and oscillatory spike trains? *Nature* **395**, 693–698 (1998).
10. Stopfer, M., Bhagavan, S., Smith, B. H. & Laurent, G. Impaired odour discrimination on desynchronization of odour-encoding neural assemblies. *Nature* **390**, 70–74 (1997).
11. Perez-Orive, J. *et al.* Oscillations and sparsening of odor representations in the mushroom body. *Science* **297**, 359–365 (2002).
Direct experimental evidence for the functional significance of oscillatory synchronization.
12. Laurent, G. Olfactory network dynamics and the coding of multidimensional signals. *Nature Rev. Neurosci.* **3**, 884–895 (2002).
13. Friedrich, R. W., Habermann, C. J. & Laurent, G. Multiplexing using synchrony in the zebrafish olfactory bulb. *Nature Neurosci.* **7**, 862–871 (2004).
14. Sivan, E. & Kopell, N. Mechanism and circuitry for clustering and fine discrimination of odors in insects. *Proc. Natl Acad. Sci. USA* **101**, 17861–17866 (2004).
A modelling study complementing the work on synchronization in the insect olfactory system and providing important information on the functional consequences of oscillatory synchronization.
15. Abbott, L. F. & Regehr, W. G. Synaptic computation. *Nature* **431**, 796–803 (2004).
16. Izhikevich, E. M., Desai, N. S., Walcott, E. C. & Hoppensteadt, F. C. Bursts as a unit of neural information: selective communication via resonance. *Trends Neurosci.* **26**, 161–167 (2003).
17. Hutcheon, B. & Yarom, Y. Resonance, oscillation and the intrinsic frequency preferences of neurons. *Trends Neurosci.* **23**, 216–222 (2000).
18. Marshall, S. P. & Lang, E. J. Inferior olive oscillations gate transmission of motor cortical activity to the cerebellum. *J. Neurosci.* **24**, 11356–11367 (2004).
The authors studied the resonance properties of rat inferior olives to afferents from the motor cortex at varying frequencies and observed nonlinear effects.
19. Strogatz, S. H. Exploring complex networks. *Nature* **410**, 268–276 (2001).
20. Sporns, O., Chialvo, D. R., Kaiser, M. & Hilgetag, C. C. Organization, development and function of complex brain networks. *Trends Cogn. Sci.* **8**, 418–425 (2004).
21. Buzsaki, G., Geisler, C., Henze, D. A. & Wang, X. J. Interneuron diversity series: circuit complexity and axon wiring economy of cortical interneurons. *Trends Neurosci.* **27**, 186–193 (2004).
22. Chklovskii, D. B., Schikorski, T. & Stevens, C. F. Wiring optimization in cortical circuits. *Neuron* **34**, 341–347 (2002).
23. Laughlin, S. B. & Sejnowski, T. J. Communication in neuronal networks. *Science* **301**, 1870–1874 (2003).
24. Chklovskii, D. B., Mel, B. W. & Svoboda, K. Cortical rewiring and information storage. *Nature* **431**, 782–788 (2004).
25. Wang, X. J. in *Encyclopedia of Cognitive Science* 272–280 (MacMillan, London, 2003).
26. Whittington, M. A., Traub, R. D., Kopell, N., Ermentrout, B. & Buhl, E. H. Inhibition-based rhythms: experimental and mathematical observations on network dynamics. *Int. J. Psychophysiol.* **38**, 315–336 (2000).
27. Salinas, E. & Sejnowski, T. J. Impact of correlated synaptic input on output firing rate and variability in simple neuronal models. *J. Neurosci.* **20**, 6193–6209 (2000).
Neurons with balanced excitatory and inhibitory input are very sensitive to correlations in the input.
28. Bibbig, A., Traub, R. D. & Whittington, M. A. Long-range synchronization of gamma and beta oscillations and the plasticity of excitatory and inhibitory synapses: a network model. *J. Neurophysiol.* **88**, 1634–1654 (2002).
29. Kopell, N., Ermentrout, G. B., Whittington, M. A. & Traub, R. D. Gamma rhythms and beta rhythms have different synchronization properties. *Proc. Natl Acad. Sci. USA* **97**, 1867–1872 (2000).
Based on computational models, the authors describe properties of different frequencies of neuronal oscillations and the consequences for synchronization.
30. Fellous, J. M. & Sejnowski, T. J. Cholinergic induction of oscillations in the hippocampal slice in the slow (0.5–2 Hz), theta (5–12 Hz), and gamma (35–70 Hz) bands. *Hippocampus* **10**, 187–197 (2000).
31. Gray, C. M., König, P., Engel, A. K. & Singer, W. Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties. *Nature* **338**, 334–337 (1989).
32. Tallon-Baudry, C., Mandon, S., Freiwald, W. A. & Kreiter, A. K. Oscillatory synchrony in the monkey temporal lobe correlates with performance in a visual short-term memory task. *Cereb. Cortex* **14**, 713–720 (2004).
33. Tallon-Baudry, C., Bertrand, O. & Fischer, C. Oscillatory synchrony between human extrastriate areas during visual short-term memory maintenance. *J. Neurosci.* **21**, RC177 (2001).
34. von Stein, A., Rappelsberger, P., Sarnthein, J. & Petsche, H. Synchronization between temporal and parietal cortex during multimodal object processing in man. *Cereb. Cortex* **9**, 137–150 (1999).
35. Gail, A., Brinksmeyer, H. J. & Eckhorn, R. Perception-related modulations of local field potential power and coherence in primary visual cortex of awake monkey during binocular rivalry. *Cereb. Cortex* **14**, 300–313 (2004).
36. Breakspear, M., Williams, L. M. & Stam, C. J. A novel method for the topographic analysis of neural activity reveals formation and dissolution of 'dynamic cell assemblies'. *J. Comput. Neurosci.* **16**, 49–68 (2004).
37. Friston, K. J. The labile brain. I. Neuronal transients and nonlinear coupling. *Phil. Trans. R. Soc. Lond. B* **355**, 215–236 (2000).
38. Rodriguez, E. *et al.* Perception's shadow: long-distance synchronization of human brain activity. *Nature* **397**, 430–433 (1999).
This study shows enhanced long-range gamma synchronization during perception and the importance of desynchronization.
39. Fell, J. *et al.* Human memory formation is accompanied by rhinal-hippocampal coupling and decoupling. *Nature Neurosci.* **4**, 1259–1264 (2001).
40. Hummel, F. & Gerloff, C. Larger interregional synchrony is associated with greater behavioral success in a complex sensory integration task in humans. *Cereb. Cortex* 1 Sep 2004 (doi:10.1093/cercor/bhh170).
41. Fries, P., Schroder, J. H., Roelfsema, P. R., Singer, W. & Engel, A. K. Oscillatory neuronal synchronization in primary visual cortex as a correlate of stimulus selection. *J. Neurosci.* **22**, 3739–3754 (2002).
42. Tallon-Baudry, C. Attention and awareness in synchrony. *Trends Cogn. Sci.* **8**, 523–525 (2004).
43. Raymond, J. E., Shapiro, K. L. & Arnell, K. M. Temporary suppression of visual processing in an RSVP task: an attentional blink? *J. Exp. Psychol. Hum. Percept. Perform.* **18**, 849–860 (1992).
44. Vallbo, A. B. & Wessberg, J. Organization of motor output in slow finger movements in man. *J. Physiol. (Lond.)* **469**, 673–691 (1993).
45. Kakuda, N., Nagaoka, M. & Wessberg, J. Common modulation of motor unit pairs during slow wrist movements in man. *J. Physiol. (Lond.)* **520**, 929–940 (1999).
46. Wessberg, J. & Kakuda, N. Single motor unit activity in relation to pulsatile motor output in human finger movements. *J. Physiol. (Lond.)* **517**, 273–285 (1999).
47. Gross, J. *et al.* The neural basis of intermittent motor control in humans. *Proc. Natl Acad. Sci. USA* **99**, 2299–2302 (2002).
48. Gross, J. *et al.* Cortico-muscular synchronization during isometric muscle contraction in humans as revealed by magnetoencephalography. *J. Physiol. (Lond.)* **527**, 623–631 (2000).
49. Salenius, S., Portin, K., Kajola, M., Salmelin, R. & Hari, R. Cortical control of human motoneuron firing during isometric contraction. *J. Neurophysiol.* **77**, 3401–3405 (1997).
50. Conway, B. A. *et al.* Synchronization between motor cortex and spinal motoneuronal pool during the performance of a maintained motor task in man. *J. Physiol. (Lond.)* **489**, 917–924 (1995).
51. Hari, R. & Salenius, S. Rhythmical corticomotor communication. *Neuroreport* **10**, R1–R10 (1999).
52. Salenius, S. & Hari, R. Synchronous cortical oscillatory activity during motor action. *Curr. Opin. Neurobiol.* **13**, 678–684 (2003).
53. Murthy, V. N. & Fetz, E. E. Coherent 25- to 35-Hz oscillations in the sensorimotor cortex of awake behaving monkeys. *Proc. Natl Acad. Sci. USA* **89**, 5670–5674 (1992).
54. Donoghue, J. P., Sanes, J. N., Hatsopoulos, N. G. & Gaal, G. Neural discharge and local field potential oscillations in primate motor cortex during voluntary movements. *J. Neurophysiol.* **79**, 159–173 (1998).
55. Sanes, J. N. & Donoghue, J. P. Oscillations in local field potentials of the primate motor cortex during voluntary movement. *Proc. Natl Acad. Sci. USA* **90**, 4470–4474 (1993).
56. Jackson, A., Gee, V., Baker, S. & Lemon, R. Synchrony between neurons with similar muscle fields in monkey motor cortex. *Neuron* **38**, 115–125 (2003).
57. Kilner, J. M. *et al.* Task-dependent modulation of 15–30 Hz coherence between rectified EMGs from human hand and forearm muscles. *J. Physiol. (Lond.)* **516**, 559–570 (1999).
58. Parkis, M. A., Feldman, J. L., Robinson, D. M. & Funk, G. D. Oscillations in endogenous inputs to neurons affect excitability and signal processing. *J. Neurosci.* **23**, 8152–8158 (2003).
59. Lee, D. Coherent oscillations in neuronal activity of the supplementary motor area during a visuomotor task. *J. Neurosci.* **23**, 6798–6809 (2003).
60. Brovelli, A. *et al.* Beta oscillations in a large-scale sensorimotor cortical network: directional influences revealed by Granger causality. *Proc. Natl Acad. Sci. USA* **101**, 9849–9854 (2004).
61. Courtemanche, R., Fujii, N. & Graybiel, A. M. Synchronous, focally modulated beta-band oscillations characterize local field potential activity in the striatum of awake behaving monkeys. *J. Neurosci.* **23**, 11741–11752 (2003).
The authors observed that small areas of the monkey striatum decouple from global beta oscillations during task performance.
62. Levy, R., Hutchison, W. D., Lozano, A. M. & Dostrovsky, J. O. Synchronized neuronal discharge in the basal ganglia of parkinsonian patients is limited to oscillatory activity. *J. Neurosci.* **22**, 2855–2861 (2002).
63. Paradiso, G. *et al.* Involvement of human thalamus in the preparation of self-paced movement. *Brain* **127**, 2717–2731 (2004).
64. Marsden, J. *et al.* Intermuscular coherence in Parkinson's disease: effects of subthalamic nucleus stimulation. *Neuroreport* **12**, 1113–1117 (2001).
65. MacKay, W. A. Synchronized neuronal oscillations and their role in motor processes. *Trends Cogn. Sci.* **1**, 176–183 (1997).
66. Timofeev, I. & Steriade, M. Neocortical seizures: initiation, development and cessation. *Neuroscience* **123**, 299–336 (2004).
67. Traub, R. D. Fast oscillations and epilepsy. *Epilepsy Curr.* **3**, 77–79 (2003).
68. van der Stelt, O., Belger, A. & Lieberman, J. A. Macroscopic fast neuronal oscillations and synchrony in schizophrenia. *Proc. Natl Acad. Sci. USA* **101**, 17567–17568 (2004).
69. Jeong, J. EEG dynamics in patients with Alzheimer's disease. *Clin. Neurophysiol.* **115**, 1490–1505 (2004).
70. Hutchison, W. D. *et al.* Neuronal oscillations in the basal ganglia and movement disorders: evidence from whole animal and human recordings. *J. Neurosci.* **24**, 9240–9243 (2004).
71. Bevan, M. D., Magill, P. J., Terman, D., Bolam, J. P. & Wilson, C. J. Move to the rhythm: oscillations in the subthalamic nucleus-external globus pallidus network. *Trends Neurosci.* **25**, 525–531 (2002).
72. Wichmann, T. & DeLong, M. R. Functional and pathophysiological models of the basal ganglia. *Curr. Opin. Neurobiol.* **6**, 751–758 (1996).
73. Lozano, A. M., Dostrovsky, J., Chen, R. & Ashby, P. Deep brain stimulation for Parkinson's disease: disrupting the disruption. *Lancet Neurol.* **1**, 225–231 (2002).
74. Levy, R., Hutchison, W. D., Lozano, A. M. & Dostrovsky, J. O. High-frequency synchronization of neuronal activity in the subthalamic nucleus of parkinsonian patients with limb tremor. *J. Neurosci.* **20**, 7766–7775 (2000).
75. Raz, A., Vaadia, E. & Bergman, H. Firing patterns and correlations of spontaneous discharge of pallidal neurons in the normal and the tremulous 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine vervet model of parkinsonism. *J. Neurosci.* **20**, 8559–8571 (2000).
76. Plenz, D. & Kital, S. T. A basal ganglia pacemaker formed by the subthalamic nucleus and external globus pallidus. *Nature* **400**, 677–682 (1999).

77. Brown, P. *et al.* Dopamine dependency of oscillations between subthalamic nucleus and pallidum in Parkinson's disease. *J. Neurosci.* **21**, 1033–1038 (2001).
In patients with Parkinson's disease, synchronization of neural activity occurs between the STN and the pallidum and is crucially dependent on dopaminergic treatment.
78. Cassidy, M. *et al.* Movement-related changes in synchronization in the human basal ganglia. *Brain* **125**, 1235–1246 (2002).
79. Williams, D. *et al.* Dopamine-dependent changes in the functional connectivity between basal ganglia and cerebral cortex in humans. *Brain* **125**, 1558–1569 (2002).
80. Limousin, P. *et al.* Effect of parkinsonian signs and symptoms of bilateral subthalamic nucleus stimulation. *Lancet* **345**, 91–95 (1995).
81. Siegfried, J. & Lippitz, B. Bilateral chronic electrostimulation of ventroposterolateral pallidum: a new therapeutic approach for alleviating all parkinsonian symptoms. *Neurosurgery* **35**, 1126–1129; discussion 1129–1130 (1994).
82. Hassler, R. Brain mechanisms of intention and attention with introductory remarks on other volitional processes. *Prog. Brain Res.* **54**, 585–614 (1980).
83. Brown, P. & Marsden, C. D. What do the basal ganglia do? *Lancet* **351**, 1801–1804 (1998).
84. Wichmann, T., Bergman, H. & DeLong, M. R. The primate subthalamic nucleus. III. Changes in motor behavior and neuronal activity in the internal pallidum induced by subthalamic inactivation in the MPTP model of parkinsonism. *J. Neurophysiol.* **72**, 521–530 (1994).
85. Kuhn, A. A. *et al.* Event-related beta desynchronization in human subthalamic nucleus correlates with motor performance. *Brain* **127**, 735–746 (2004).
86. Marsden, J. F., Limousin-Dowsey, P., Ashby, P., Pollak, P. & Brown, P. Subthalamic nucleus, sensorimotor cortex and muscle interrelationships in Parkinson's disease. *Brain* **124**, 378–388 (2001).
87. Brown, P. *et al.* Effects of stimulation of the subthalamic area on oscillatory pallidal activity in Parkinson's disease. *Exp. Neurol.* **188**, 480–490 (2004).
88. Timmermann, L. *et al.* Ten-Hertz stimulation of subthalamic nucleus deteriorates motor symptoms in Parkinson's disease. *Mov. Disord.* **19**, 1328–1333 (2004).
89. Bergman, H. & Deuschl, G. Pathophysiology of Parkinson's disease: from clinical neurology to basic neuroscience and back. *Mov. Disord.* **17** (Suppl. 3), S28–S40 (2002).
90. Bergman, H. *et al.* Physiology of MPTP tremor. *Mov. Disord.* **13** (Suppl. 3), 29–34 (1998).
91. Hurtado, J. M., Gray, C. M., Tamas, L. B. & Sigvardt, K. A. Dynamics of tremor-related oscillations in the human globus pallidus: a single case study. *Proc. Natl Acad. Sci. USA* **96**, 1674–1679 (1999).
92. Nini, A., Feingold, A., Slovin, H. & Bergman, H. Neurons in the globus pallidus do not show correlated activity in the normal monkey, but phase-locked oscillations appear in the MPTP model of parkinsonism. *J. Neurophysiol.* **74**, 1800–1805 (1995).
93. Deuschl, G. *et al.* The pathophysiology of parkinsonian tremor: a review. *J. Neurol.* **247** (Suppl. 5), V33–V48 (2000).
94. Volkmann, J. *et al.* Central motor loop oscillations in parkinsonian resting tremor revealed by magnetoencephalography. *Neurology* **46**, 1359–1370 (1996).
95. Timmermann, L. *et al.* The cerebral oscillatory network of parkinsonian resting tremor. *Brain* **126**, 199–212 (2003).
96. Guehl, D. *et al.* Tremor-related activity of neurons in the 'motor' thalamus: changes in firing rate and pattern in the MPTP vervet model of parkinsonism. *Eur. J. Neurosci.* **17**, 2388–2400 (2003).
97. Pollok, B., Gross, J., Müller, K., Aschersleben, G. & Schnitzler, A. The cerebral oscillatory network associated with auditorily paced finger movements. *Neuroimage* **24**, 646–655 (2005).
98. Pollok, B., Gross, J., Dirks, M., Timmermann, L. & Schnitzler, A. The cerebral oscillatory network of voluntary tremor. *J. Physiol. (Lond.)* **554**, 871–878 (2004).
99. Goldberg, J. A. *et al.* Enhanced synchrony among primary motor cortex neurons in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine primate model of Parkinson's disease. *J. Neurosci.* **22**, 4639–4653 (2002).
This study indicates that abnormal firing patterns and synchronization in the primary motor cortex, rather than changes in firing rates, underlie motor deficits in primate models of Parkinson's disease.
100. Hellwig, B. *et al.* Tremor-correlated cortical activity detected by electroencephalography. *Clin. Neurophysiol.* **111**, 806–809 (2000).
101. Magill, P. J., Bolam, J. P. & Bevan, M. D. Relationship of activity in the subthalamic nucleus-globus pallidus network to cortical electroencephalogram. *J. Neurosci.* **20**, 820–833 (2000).
102. Drouot, X. *et al.* Functional recovery in a primate model of Parkinson's disease following motor cortex stimulation. *Neuron* **44**, 769–778 (2004).
High-frequency stimulation of primary motor cortex in MPTP-treated baboons effectively reduces the symptoms of Parkinson's disease.
103. Sudmeyer, M. *et al.* Postural tremor in Wilson's disease: a magnetoencephalographic study. *Mov. Disord.* **19**, 1476–1482 (2004).
104. Hellwig, B. *et al.* Tremor-correlated cortical activity in essential tremor. *Lancet* **357**, 519–523 (2001).
105. Schnitzler, A., Munks, C., Butz, M., Timmermann, L. & Gross, J. The oscillatory cortico-subcortical network of essential tremor. *Mov. Disorder.* **19** (Suppl. 9), S454 (2004).
106. Raethjen, J. *et al.* Corticomuscular coherence in the 6–15 Hz band: is the cortex involved in the generation of physiologic tremor? *Exp. Brain Res.* **142**, 32–40 (2002).
107. Raethjen, J. *et al.* Is the rhythm of physiological tremor involved in cortico-cortical interactions? *Mov. Disord.* **19**, 458–465 (2004).
108. Timmermann, L., Gross, J., Kircheis, G., Haussinger, D. & Schnitzler, A. Cortical origin of mini-asterixis in hepatic encephalopathy. *Neurology* **58**, 295–298 (2002).
109. Timmermann, L. *et al.* Mini-asterixis in hepatic encephalopathy induced by pathologic thalamo-motor-cortical coupling. *Neurology* **61**, 689–692 (2003).
110. Silberstein, P. *et al.* Patterning of globus pallidus local field potentials differs between Parkinson's disease and dystonia. *Brain* **126**, 2597–2608 (2003).
111. Vitek, J. L. Pathophysiology of dystonia: a neuronal model. *Mov. Disord.* **17** (Suppl. 3), S49–S62 (2002).
112. Foffani, G. *et al.* Altered subthalamo-pallidal synchronisation in parkinsonian dyskinesias. *J. Neurol. Neurosurg. Psychiatry* **76**, 426–428 (2005).
113. Serrien, D. J., Orth, M., Evans, A. H., Lees, A. J. & Brown, P. Motor inhibition in patients with Gilles de la Tourette syndrome: functional activation patterns as revealed by EEG coherence. *Brain* **128**, 116–125 (2005).
114. Tijssen, M. A., Marsden, J. F. & Brown, P. Frequency analysis of EMG activity in patients with idiopathic torticollis. *Brain* **123**, 677–686 (2000).
115. Tijssen, M. A. *et al.* Descending control of muscles in patients with cervical dystonia. *Mov. Disord.* **17**, 493–500 (2002).
116. Grosse, P. *et al.* Patterns of EMG-EMG coherence in limb dystonia. *Mov. Disord.* **19**, 758–769 (2004).
117. Temel, Y. & Visser-Vandewalle, V. Surgery in Tourette syndrome. *Mov. Disord.* **19**, 3–14 (2004).
118. Bressler, S. L. & Kelso, J. A. Cortical coordination dynamics and cognition. *Trends Cogn. Sci.* **5**, 26–36 (2001).
119. Llinas, R. R., Ribary, U., Jeanmonod, D., Kronberg, E. & Mitra, P. P. Thalamocortical dysrhythmia: a neurological and neuropsychiatric syndrome characterized by magnetoencephalography. *Proc. Natl Acad. Sci. USA* **96**, 15222–15227 (1999).
120. Stam, C. J. *et al.* Generalized synchronization of MEG recordings in Alzheimer's disease: evidence for involvement of the gamma band. *J. Clin. Neurophysiol.* **19**, 562–574 (2002).
121. Koenig, T. *et al.* Decreased EEG synchronization in Alzheimer's disease and mild cognitive impairment. *Neurobiol. Aging* **26**, 165–171 (2005).
122. Stam, C. J., van der Made, Y., Pijnenburg, Y. A. & Scheltens, P. EEG synchronization in mild cognitive impairment and Alzheimer's disease. *Acta Neurol. Scand.* **108**, 90–96 (2003).
123. Pogarell, O. *et al.* EEG coherence reflects regional corpus callosum area in Alzheimer's disease. *J. Neurol. Neurosurg. Psychiatry* **76**, 109–111 (2005).
124. Rodriguez, R., Kallenbach, U., Singer, W. & Munk, M. H. Short- and long-term effects of cholinergic modulation on gamma oscillations and response synchronization in the visual cortex. *J. Neurosci.* **24**, 10369–10378 (2004).
125. Spencer, K. M. *et al.* Abnormal neural synchrony in schizophrenia. *J. Neurosci.* **23**, 7407–7411 (2003).
126. Spencer, K. M. *et al.* Neural synchrony indexes disordered perception and cognition in schizophrenia. *Proc. Natl Acad. Sci. USA* **101**, 17288–17293 (2004).
127. Passingham, R. E., Stephan, K. E. & Kotter, R. The anatomical basis of functional localization in the cortex. *Nature Rev. Neurosci.* **3**, 606–616 (2002).
128. Logothetis, N. K., Pauls, J., Augath, M., Trinath, T. & Oeltermann, A. Neurophysiological investigation of the basis of the fMRI signal. *Nature* **412**, 150–157 (2001).
129. Bennett, M. V. & Zukin, R. S. Electrical coupling and neuronal synchronization in the mammalian brain. *Neuron* **41**, 495–511 (2004).
130. Crick, F. & Koch, C. Constraints on cortical and thalamic projections: the no-strong-loops hypothesis. *Nature* **391**, 245–250 (1998).
131. Baker, S. N., Kilner, J. M., Pinches, E. M. & Lemon, R. N. The role of synchrony and oscillations in the motor output. *Exp. Brain Res.* **128**, 109–117 (1999).
132. Gervasoni, D. *et al.* Global forebrain dynamics predict rat behavioral states and their transitions. *J. Neurosci.* **24**, 11137–11147 (2004).
Intracranial LFP measurements in rats revealed specific spectral trajectories that are associated with specific brain states and their transitions.
133. Salinas, E. & Sejnowski, T. J. Correlated neuronal activity and the flow of neural information. *Nature Rev. Neurosci.* **2**, 539–550 (2001).
134. Steriade, M. Impact of network activities on neuronal properties in corticothalamic systems. *J. Neurophysiol.* **86**, 1–39 (2001).
135. Tass, P. A. *et al.* Synchronization tomography: a method for three-dimensional localization of phase synchronized neuronal populations in the human brain using magnetoencephalography. *Phys. Rev. Lett.* **90**, 088101 (2003).
136. David, O., Cosmelli, D., Hasboun, D. & Garnero, L. A multitrial analysis for revealing significant corticocortical networks in magnetoencephalography and electroencephalography. *Neuroimage* **20**, 186–201 (2003).
137. Hoechstetter, K. *et al.* BESA source coherence: a new method to study cortical oscillatory coupling. *Brain Topogr.* **16**, 233–238 (2004).
138. Rosenblum, M. G., Pikovsky, A. S. & Kurths, J. Phase synchronization of chaotic oscillators. *Phys. Rev. Lett.* **76**, 1804–1807 (1996).
139. Lachaux, J. P., Rodriguez, E., Martinerie, J. & Varela, F. J. Measuring phase synchrony in brain signals. *Hum. Brain Mapp.* **8**, 194–208 (1999).
140. Tass, P. *et al.* Detection of *n:m* phase locking from noisy data: application to magnetoencephalography. *Phys. Rev. Lett.* **81**, 3291–3294 (1998).
141. Rosenblum, M. G. & Pikovsky, A. S. Detecting direction of coupling in interacting oscillators. *Phys. Rev. E Stat. Nonlin. Soft Matter Phys.* **64**, 045202 (2001).
142. Baccala, L. A. & Sameshima, K. Partial directed coherence: a new concept in neural structure determination. *Biol. Cybern.* **84**, 463–474 (2001).
143. Halliday, D. M. *et al.* A framework for the analysis of mixed time series/point process data — theory and application to the study of physiological tremor, single motor unit discharges and electromyograms. *Prog. Biophys. Mol. Biol.* **64**, 237–278 (1995).
144. Dahlhaus, R., Eichler, M. & Sandkuhler, J. Identification of synaptic connections in neural ensembles by graphical models. *J. Neurosci. Methods* **77**, 93–107 (1997).
145. Alexander, G. E., Crutcher, M. D. & DeLong, M. R. Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, 'prefrontal' and 'limbic' functions. *Prog. Brain Res.* **85**, 119–146 (1990).
146. Alexander, G. E. & Crutcher, M. D. Functional architecture of basal ganglia circuits: neural substrates of parallel processing. *Trends Neurosci.* **13**, 266–271 (1990).
147. Hoover, J. E. & Strick, P. L. The organization of cerebellar and basal ganglia outputs to primary motor cortex as revealed by retrograde transneuronal transport of herpes simplex virus type 1. *J. Neurosci.* **19**, 1446–1463 (1999).
148. Albin, R. L., Young, A. B. & Penney, J. B. The functional anatomy of basal ganglia disorders. *Trends Neurosci.* **12**, 366–375 (1989).
149. DeLong, M. R. Primate models of movement disorders of basal ganglia origin. *Trends Neurosci.* **13**, 281–285 (1990).

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Competing interests statement

The authors declare no competing financial interests.

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