THE BRAINWEB: PHASE SYNCHRONIZATION AND LARGE-SCALE INTEGRATION

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The emergence of a unified cognitive moment relies on the coordination of scattered mosaics of functionally specialized brain regions. Here we review the mechanisms of large-scale integration that counterbalance the distributed anatomical and functional organization of brain activity to enable the emergence of coherent behaviour and cognition. Although the mechanisms involved in large-scale integration are still largely unknown, we argue that the most plausible candidate is the formation of dynamic links mediated by synchrony over multiple frequency bands.

The functional and anatomical specializations of the brain that are evident from physiological, neuropsychological and neuroimaging studies present a unique problem. How does the brain orchestrate the symphony of emotions, perceptions, thoughts and actions that come together effortlessly from neural processes that are distributed across the brain? What are the neural mechanisms that select and coordinate this distributed brain activity to produce a flow of adapted and unified cognitive moments? This is the large-scale integration problem — the central topic of this review.

Neural assemblies: a framework for analysis

Neural assemblies provide a conceptual framework for the integration of distributed neural activity[1–3]. For our purposes, neural assemblies will be defined as distributed local networks of neurons transiently linked by reciprocal dynamic connections[4–10]. A useful analogy is found in Worldwide Web systems such as Napster, in which geographically distant computers briefly transfer data to each other within transient assemblies that are formed on a static network of hardwired connections. In the brain, the emergence of a specific neuronal assembly is thought to underlie the operation of every cognitive act. Neurons that belong to a given assembly are linked by selective interactions; that is, they interact preferentially with a sub-ensemble of other neurons that are interconnected (FIG. 1). These interactions are mediated through direct (monosynaptic) or indirect (poly-

synaptic) connections that are typically reciprocal[11,12]. In this context, as discussed by Phillips and Singer[13], it is useful to distinguish between two types of connection. On the one hand, there are reciprocal connections within the same cortical area or between areas situated at the same level of the network. On the other, there exist connections that link different levels of the network in different brain regions to the same assembly and embody the true Web-like architecture of the brain. Connections of this type have been traditionally described as feedforward and feedback (or as bottom-up and top-down) (BOX 1). These neural assemblies have a transient, dynamical existence that spans the time required to accomplish an elementary cognitive act (a fraction of a second). But, at the same time, their existence is long enough for neural activity to propagate through the assembly, a propagation that necessarily involves cycles of reciprocal spike exchanges with transmission delays that last tens of milliseconds. So, in both the brain and the Web analogy, the relevant variable required to describe these assemblies is not so much the individual activity of the components of the system but the dynamic nature of the links between them.

Phase synchrony as a mechanism for integration

Clearly, any mechanism for neural integration must involve interactions between the participating local networks, but the specific nature of such interactions remains a point of debate. For some authors, the

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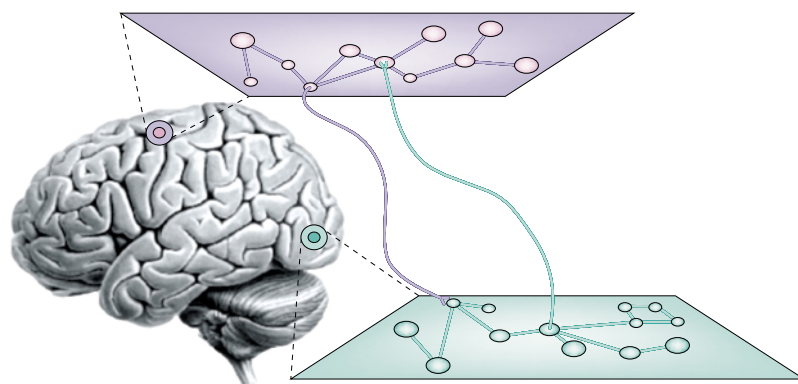
Figure 1 | **Schematic representation of transient distributed neural assemblies with dynamic long-range interactions.**

hierarchical organization of the brain suggests that the associative areas that mediate between sensory and motor areas provide the basis for integration (see REF. 14 for an example). By contrast, we and others have argued that networks of reciprocal interactions are the key for integration[4,10]. Among various modes of reciprocal interactions, we favour phase synchronization between the participating neuronal groups, which is certainly the most studied mechanism. Note that the terms synchrony and phase have been used in the literature with widely different connotations; here we adhere to the meaning derived from dynamic-systems analysis (BOX 2).

We describe here the experimental evidence that supports the above framework, as well as its limitations and the questions that remain unanswered. In order to study integration through synchronization, we need to focus on the temporal dynamics of neural networks in the millisecond range. We therefore concentrate on discussing results obtained with methods that have fast temporal resolution; that is, recordings of electrical and magnetic activity at various resolution levels. The possible contribution to, and links with, 'slow' imaging methods are discussed in BOX 3.

Box 1 | **Bottom-up and top-down activity**

With only few exceptions, the brain is organized on the basis of what we can call the principle of reciprocity: if area A connects to area B, then there are reciprocal connections from B to A[11,12]. Traditionally, the sensory end is taken as the starting point, so that perception is described as a feedforward or bottom-up hierarchy from 'lower' to 'higher' stages of processing. Vision has become a paradigmatic example of this approach, and the successive stages of elaboration of the visual stimuli from retina to the various visual areas have been extensively studied[98]. However, an alternative starting point can also be found in the endogenous activity that is provided by the states of preparation, expectation, emotional tone and attention (among others), which are necessarily active at the same time as the sensory inflow. Endogenous activity concerns activity typically from the frontal lobes or the limbic system, or in the middle of the whole network as temporal and associative cortices, but far removed from the sensors. This activity is referred to as top-down or feedback, and there is psychophysical and physiological evidence for their active participation even in early stages of sensory perception[1,33,68,99,100]. Bottom-up and top-down are heuristic terms for what is in reality a large-scale network that integrates both incoming and endogenous activity; it is precisely at this level where phase synchronization is crucial as a mechanism for large-scale integration.

Box 2 | **Phase and synchrony**

These terms have been used with widely different meanings, and some clarification is needed. In general, two signals $x(t)$ and $y(t)$ are correlated if we can predict the variations of one as a function of the other. This can be estimated by the widely used correlation coefficient (EQN 1):

$$C_{xy}(\tau) = \int_u \hat{x}(u)\hat{y}(u-\tau)du \qquad (1)$$

where $\hat{x}$ is the zero-mean, normalized transform of x (EQN 2):

$$\hat{x}(u) = \frac{(x(u) - \langle x \rangle_{time})}{\sqrt{\int\limits_{time}(x(u) - \langle x \rangle_{time})^2 dv}} \qquad (2)$$

High values of $C_{xy}(\tau)$ (that is, close to 1) indicate that x reproduces the variations of y, with a time lag t that can be different from zero, as observed in the visual system[101]. Similarly, if one is interested in the relation between the signals at a specific frequency f, one can band-pass x and y narrowly around f, and estimate their coherence, which is simply the correlation coefficient between the band-passed signals[102]. This classical measure has been extensively used in the studies reported in this review.

Synchrony measures the relation between the temporal structures of the signals regardless of signal amplitude. Two signals are said to be synchronous if their rhythms coincide. This idea can be made more precise in several ways. In its classical sense, the term synchrony has been applied to signals that had a dominant oscillatory mode, either originally or after filtration around a chosen frequency f. Such a signal $x(t)$ can be written in the frequency domain as EQN 3, a formulation in which the instantaneous amplitude $a(t)$ and phase $\phi(t)$ of $x(t)$ appear as clearly separated entities:

$$\tilde{x}(f,t) = a(t)\exp(i(ft + \phi_x(t))) \qquad (3)$$

Working with brain signals, this separation allows us to focus on phase as a measurement that contains all the information about the temporal structure of neural activity. Perfect synchrony between x and y means simply that $\phi_x(t) = \phi_y(t)$. Relationships between the temporal organization of x and y are best observed by their instantaneous phase difference (EQN 4):

$$\Phi_{xy}(t) = |n\phi_x(t) - m\phi_y(t)| \qquad (4)$$

where n and m are integers that indicate the ratios of possible frequency locking. Although most studies have focused on the case $n = m = 1$, evidence for 1:2 and 1:3 phase synchrony also exists.

In neuroscience, we are interested in the case when Φ is approximately constant over a limited time window T, which has a typical duration of hundreds of milliseconds. This is defined as a period of phase locking between two events, and can only be estimated in a statistical sense. Phase locking therefore becomes an indicator of the dynamic phase relationship between two local networks independently of their amplitude and is one the central concepts of this review.

Box 3 | **Synchrony and metabolic activity**

Large-scale integration through synchrony converges naturally with studies of large-scale interdependencies analysed through metabolic brain imaging. In fact, most functional brain imaging research during the last decade has focused on detecting the brain regions involved in various sensorimotor or cognitive tasks. However, as we argue here, brain organization cannot be understood if the coupling between brain regions is not analysed. Several works have already shown the importance of these ideas using positron-emission tomography (PET) or functional magnetic resonance imaging (fMRI) data[92,103,104].

Functional connectivity involves the identification of regions whose interaction during a cognitive task is reflected by a temporal correlation between the haemodynamic signals observed in these regions. To study these connections, several approaches have been developed[103,105–107]. Whereas functional connectivity concerns the correlation between cerebral signals and might have various origins, effective connectivity represents the strength of an effective connection established during a cognitive task; that is, the direct influence of a region on another. Two steps are necessary to form these maps of effective connectivity. First, a model must be defined: a group of cerebral regions is selected together with the connections that exist between these regions. This model of interacting regions is established from a priori anatomical knowledge and/or from maps of functional connectivity. The next step is to estimate the strength of the existing connections between these regions by, for example, solving the structural equations associated with the predefined model[104].

Connectivity maps are established for a given temporal range, typically a few minutes. So, one cannot investigate phase relations directly but several alternatives to these methods can be considered. One possibility is to estimate a coupling coefficient that varies across time through Kalman filtering[108], thereby proposing a measure of temporal integration. A complementary line of research is to use fMRI in monkeys to guide the implantation of microelectrodes[109]. This approach opens the possibility of, first, identifying effective connections in the whole brain during a task and, second, analysing these connections over time with electrodes selectively positioned in the interacting areas. An equally challenging approach is the use of metabolic imaging to estimate current sources by solving the INVERSE PROBLEM, while retaining the temporal relations of these sources[110,111].

Finally, it is now possible to modify directly the activity of selected cerebral areas while measuring the effect of this modification in the rest of the brain. This procedure has been performed in humans using transcranial magnetic stimulation (TMS) in combination with electroencephalography, fMRI and PET[112]. In a recent study using a combination of PET and TMS, a correlation was found between the number of TMS pulses in the frontal eye fields and the metabolic activity in the superior parietal and medial parieto-occipital regions[113]. These and other developments are central for bridging evidence from electrical and metabolic couplings concerning large-scale activity.

INVERSE PROBLEM
Mathematical analysis aimed at localizing the neural sources of the electromagnetic field measured at the scalp surface.

CORTICAL COLUMN
Cylinder of cortex with a diameter up to 1 mm that groups neurons with strong reciprocal connections.

BETA RHYTHM
Neural rhythmic activity (12–25 cycles per second).

GAMMA RHYTHM
Neural rhythmic activity (about 25–70 cycles per second).

Direct evidence supporting phase synchrony as a basic mechanism for brain integration has recently been provided by extensive studies of visual binding. The visual-binding problem can be stated as follows: how are the different attributes of an object brought together in a unified representation given that its various features — edges, colour, motion, texture, depth and so on — are treated separately in specific visual areas? One proposed solution is based on the idea that visual objects are coded by cell assemblies that fire synchronously[15]. So, visual binding refers to the 'local' integration of neuronal properties (that is, integration that takes place within neighbouring cortical areas, all specialized in the same modality), which allows the large-scale integration necessary for vision in the context of a complete cognitive moment. We argue that synchronization of neural assemblies is a process that spans multiple spatial and temporal scales in the nervous system (FIG. 2). In this sense, the large-scale integration and the well-known visual-binding problem address the same question but at opposite ends of the spatial continuum. It is parsimonious to assume that they share common mechanisms. However, this is an empirical issue, and the evidence is presented here.

Local and large-scale integration

What does 'local' mean? On a spatial scale of less than 2 mm, the cytoarchitectonic packing and the mixture of excitatory and inhibitory interneurons clustered together in (say) a CORTICAL COLUMN are prone to synchronize into a common resonance mode[16]. However, this tight interconnectivity is not just restricted to such a small area, as collaterals are known to extend over several millimeters, linking larger patches of neural tissue. For example, in columns of the primary visual cortex separated by 2–7 mm, which have non-overlapping receptive fields, neurons that share similar feature properties tend to synchronize[16]. A similar observation has been made in hippocampal slices over distances of several millimeters[17]. Destexhe *et al.*[18] recorded cortical activity from Brodmann areas 17 and 18 of the cat with electrodes separated by 1 mm during deep sleep, rapid-eye-movement (REM) sleep and wakefulness. During REM sleep and wakefulness, they observed oscillatory activities (BETA and GAMMA rhythms) that correlated between electrodes separated by as much as 5 mm; the strength of the correlation decreased with electrode separation. These correlations and the synchronization of activity are related to one type of connection mentioned before: reciprocal connections between areas situated at the same level of the network[13]. So, local integration occurs over a local network distributed over an area of ~1 cm through monosynaptic connections with conduction delays of typically 4–6 ms (REF. 19).

Large-scale synchronization concerns neural assemblies which are farther apart in the brain (> 1 cm; transmission delays > 8–10 ms over polysynaptic pathways)[19] such as, for example, assemblies between occipital and frontal lobes or across hemispheres, which are separated by dozens of milliseconds in transmission time. In this case, phase-locking synchrony (BOX 2) cannot be based on the local cytoarchitecture but must instead reside in distant connections, either cortico-cortical fibres or thalamocortical reciprocal pathways[5,20]. These pathways correspond to the second type of connection discussed above; that is, feedforward and feedback connections that link different levels of the network in different brain regions[13] (BOX 1).

Although the distinction between local and large-scale synchronization is fairly clear, it should not be taken rigidly. Neural synchrony can be established between regions whose separation falls in an intermediate spatial scale, such as between parietal and visual areas[21,22]. However, there is no simple continuum from strictly local, to regional to long-range networks. Our intention is to highlight the contrasts between local and large-scale binding, not to oppose them but rather to bring out the specific role of each one.
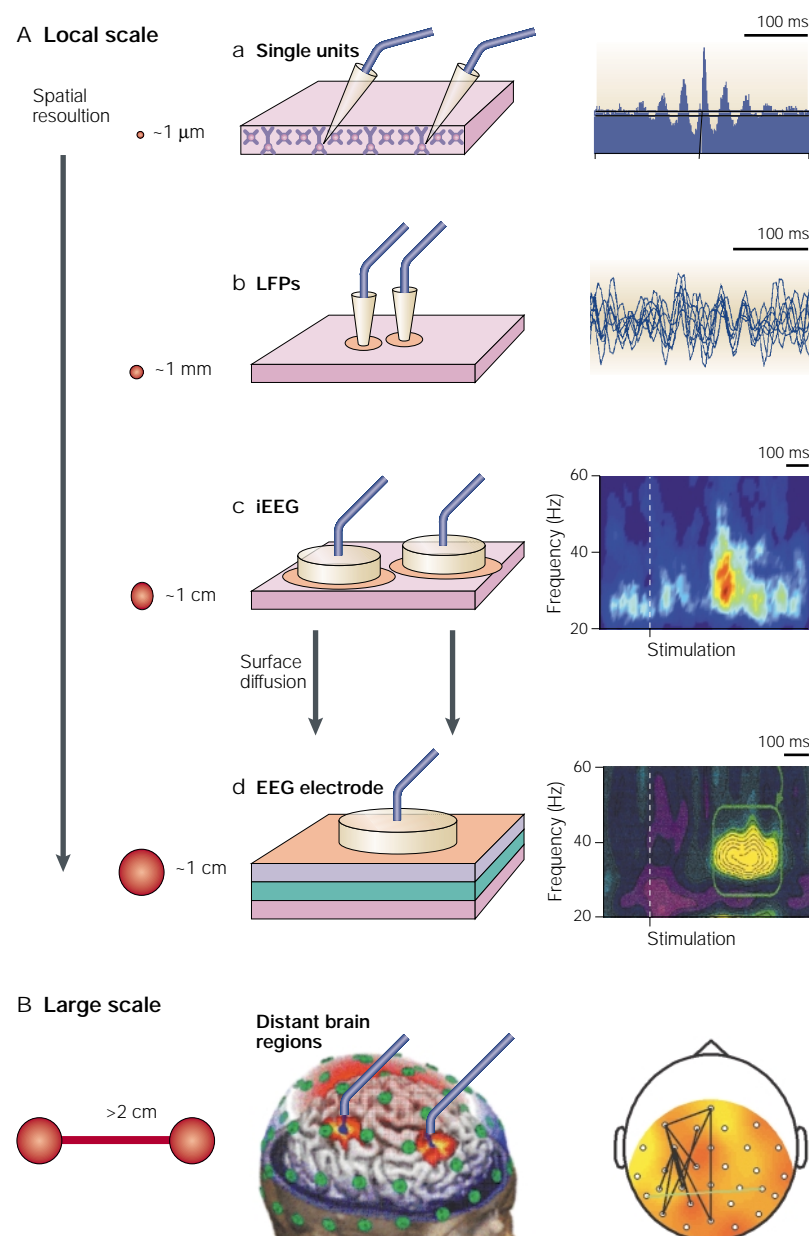
A Local scale

Spatial resolution

~1 μm

a Single units

100 ms

~1 mm

b LFPs

100 ms

~1 cm

c iEEG

100 ms

Frequency (Hz)

Stimulation

Surface diffusion

~1 cm

d EEG electrode

100 ms

Frequency (Hz)

Stimulation

B Large scale

>2 cm

Distant brain regions

Figure 2 | **Neural synchrony as a multiscale phenomenon. A** | Local scale: within a small brain region or local network, at least three levels of analysis can be distinguished. **a** | Synchrony between single units in monkey area V1 stimulated by a drifting grating, as measured by a cross-correlogram. **b** | Local field potentials (LFPs) from eight recording electrodes in the suprasylvian gyrus of an awake cat. Maximum separation between electrodes was 7 mm. The overlapping traces show a brief episode of synchronization between the fast oscillations. **c** | Transient episodes of synchrony within a population of neurons recorded intracranially over the occipito-temporal junction in an epileptic patient performing a visual discrimination task. TIME–FREQUENCY ANALYSIS revealed an enhancement of the local energy in the gamma band around 300 ms following the visual stimulation. This enhancement corresponds to the transient synchronization of underlying populations. **d** | When recorded from a surface electrode, such synchronous patches appear as spatial summation of cortical responses that give rise to transient increases in the gamma band. **B** | Large scale: patches of local synchrony in distant brain sites can enter into synchrony during cognitive tasks. Synchronous patterns between distant scalp electrodes were recorded in normal subjects engaged in a face recognition task. Black lines link electrodes that are synchronous during the perception of the face. (iEEG, intracortical electroencephalographic electrode; EEG, electroencephalography.) (Panel **Aa** is adapted from REF. 123; Panel **Ab** is adapted with permission from REF. 18 © (1999) Society for Neuroscience; panel **Ac** is adapted with permission from REF. 54 © (2000) Blackwell Sciences Ltd and from REF. 124 © (1999) Elsevier Science ; panel **B** is adapted with permission from REF. 55 © (1999) Macmillan Magazines Ltd.)

Mesoscale

The previous considerations bring to the fore the most adequate level of analysis for large-scale integration — the mesoscale[6,23–27]. In the timescale of many cognitive events (hundreds of milliseconds), a cortical neuron might fire only a few spikes, which is not sufficient to activate a target neuron unless these spikes coincide in time with many others from additional input neurons[2,27–30]. This indicates that the most relevant level of observation for integrative functions is the analysis of the coordinated behaviour of local neural groups through synaptic interactions. Observation at this level requires us to record activity either as multi-unit spike density or as summated dendritic current, which is measured as local field potentials (LFPs). LFPs blur the individual contribution of participating neurons but highlight their common action because of the topographic arrangement of neurons. One clear example is found in the hippocampus, where the alignment of pyramidal cells allows for the addition of their individual contribution to the measured electric field. The LFP therefore reflects the modulation of the temporal pattern of spikes that act on another local network. By this analysis, large-scale integration is optimally examined at the mesoscopic scale, which is naturally complemented by the analysis of single-neuron activity (microscale), as well as by the use of extracortical recordings (macrolevel) that represent a synthetic measure of multiple local circuits (FIG. 1). The mesoscale approach to synchronous assemblies has required the development of methods adapted to that level of resolution, beyond those traditionally used for single-neuron recordings (BOX 4).

Evidence for large-scale synchronization

Results from LFPs and multi-unit recordings. Large-scale synchronization is best illustrated by a series of studies by Roelfsema *et al.*[31–33], who recorded LFPs from several electrodes implanted in the cortex of cats. Cats were presented with a grating that signalled the onset of a trial. When the orientation of this grating changed (2–4 s later), the animal had to press a response key to obtain food reward. The dynamic changes in the correlation between the electrodes placed in visual, association, somatosensory and motor areas were then analysed over time (FIG. 3A). There was a selective increase in the correlation between the respective LFPs during the execution of the task. A coherent pattern appeared as soon as the animal focused its attention on the stimulus. This pattern was further increased until the task was completed, particularly between areas of the visual and parietal cortex, and areas of the parietal and motor cortex (FIG. 3A). Interestingly, this coherent pattern disappeared during the reward period, and neural activity shifted to low frequencies with no correlation between areas. This is direct evidence that large-scale synchrony (at least as inferred through correlation) emerges as the underlying basis for an active, attentive behaviour.

Convergent results have been reported by Bressler *et al.*[34–36], who recorded from the cortex of monkeys that were trained in a GO–NO-GO paradigm consisting of a preparation and discrimination task (FIG. 3B). The strength of coupling between widely spaced cortical

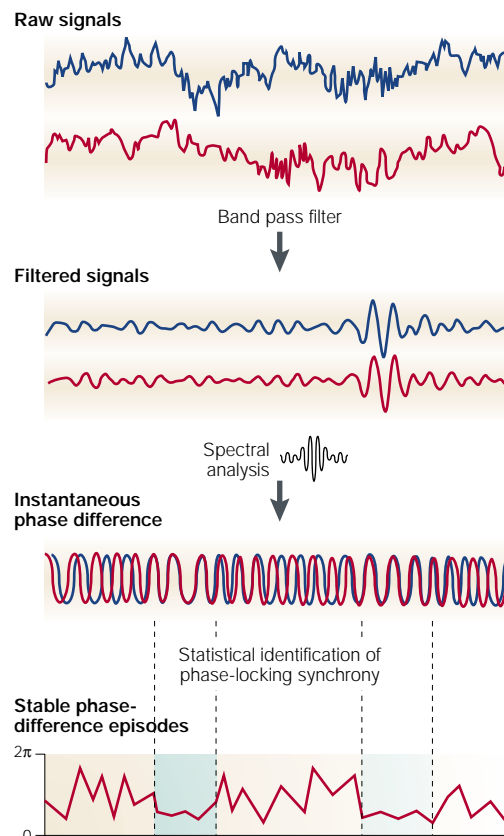Box 4 | **Methods for the study of phase synchrony**

Measuring phase synchrony in various experimental conditions is not straightforward; new dynamic imaging methods had to be developed, and some problems still remain. For the study of phase locking (see BOX 2), two steps are needed. First, to estimate the instantaneous phase of each signal and, second, to quantify the degree of phase locking during a period of time using statistical criteria (see figure). In practice, detecting phase locking between two microelectrodes that record single units can be reduced to the straightforward estimation of the CROSS-CORRELATION between spike occurrences. In fact, this is what neurobiologists who carry out single-cell studies have done for many years[114]. By contrast, for brain recordings at the meso- and macroscale levels of analysis, this estimation is not so straightforward, as one cannot rely on the intrinsic timing of spikes and the recorded signals include many frequencies. The challenge is to provide a measure of synchrony adapted to the transient nature of cell assemblies, despite the theoretical limitations of temporal resolution of any spectral analysis.

Two methods for instantaneous phase estimation have been introduced recently[53,77]. They are equivalent[115], and have adequate time and frequency resolution. Others have used an adaptive modelling of the signals to estimate the phase[61,116]. One limitation of these methods, however, is that they require the observation of multiple repetitions of the same cognitive procedure. To overcome this caveat, two methods have recently been proposed; they allow the estimation of synchrony on single-trials ('one-shot synchrony estimation') and its detection online while the subject is performing the task[117,118].

Whatever the method used, the estimated phases are buried in considerable background or intrinsic noise. As a consequence, phase differences between electrodes fluctuate around a constant value and the question of whether there is synchrony or not can only be treated in a statistical sense by means of several indicators, such as surrogate data or mutual entropy.

Several problems remain to be solved before phase locking can become a robust method for brain imaging. First, typical brain signals have broad bands and it is therefore difficult to interpret an instantaneous phase clearly. Consequently, the studies reviewed here have been carried out on filtered signals within a frequency band of a few Hertz. A generalized idea of synchrony applicable to a broader class of signals is a much-needed development[119]. Second, a troublesome difficulty comes from the lack of spatial resolution of electroencephalography (EEG) and magnetoencephalography (MEG), used in all studies of normal human subjects. In fact, two separate sensors can actually record from overlapping neural populations, opening the possibility for spurious synchrony between sensors not due to a coupling between brain structures but to volume conduction. One way to solve this problem is to use special techniques that enhance the spatial resolution of the data[120,121]. A more radical solution is to reconstruct the neural sources at the origin of EEG and MEG signals[122], and to measure synchrony directly between them[110,111]. This problem has been bypassed in studies on people suffering from epilepsy or Parkinson's disease by recording directly from intracranial electrodes implanted for therapeutic purposes[53].

Last, it is important to distinguish between phase synchrony and frequency coherence (BOX 2), which has been extensively used in most of the papers reviewed here (for example, see REFS 34,59,61). In principle, coherence mixes the effects of amplitude and phase in the interrelations between two signals. As we are interested in exploring the hypothesis that phase locking is the relevant biological mechanism of brain integration, we favour methods that focus exclusively on phase information.

Raw signals

Band pass filter

Filtered signals

Spectral analysis

Instantaneous phase difference

Statistical identification of phase-locking synchrony

Stable phase-difference episodes

2π

0

TIME–FREQUENCY ANALYSIS
Mathematical techniques used to estimate the spectral components (amplitude, frequency and phase) of short non-stationary signals (for example, Wavelets, ARMA, Hilbert).

CROSS-CORRELATION
Probability for a neuron to spike as a function of the latency of the last spike of a second neuron.

GO–NO-GO PARADIGM
Task in which the subject must produce a motor response for one class of stimulus while ignoring others.

areas measured by frequency coherence (BOX 2) changed dynamically during task performance and as a function of the structures considered. Importantly, these coherence changes corresponded broadly to beta and gamma bands, and appeared in coherence episodes that lasted 50–200 ms. This timescale has been consistently observed in most studies, at all levels of spatial resolution, and might be related to the time required for transient conjunctions between distributed areas that participate in attention. Subsequent analysis of the same data set[36] showed that pre-stimulus coherence showed a dynamic topography, organized in two large-scale oscillatory networks — dorsal and ventral. The coherence in these two networks was characterized by two different frequencies in the beta range. After the transition from preparation to recognition, the two networks reorganized into a new network that had peak coherence at yet another frequency (FIG. 3B). These observations are representative of several other studies showing that multiple areas coordinate their activities during normal perceptuomotor behaviour. This coordination occurs

through functional interdependency that is subserved by large-scale coherence of LFP oscillations[37–42]. So, large-scale integration seems to operate in networks with dynamic topography and multiple frequencies.

Evidence from medium-range recordings. In addition to these studies (which are exemplary for the analysis of large-scale integration), several other works have provided indirect information on this issue. These studies have focused on the strength and coupling at shorter distances within an area or between close connected brain areas. Spike synchrony has been observed between neurons (up to 2 cm apart) with heightened responses during expectancy in motor areas[43], in areas 17 and 18 of the visual cortex of cat[22,44] and monkey[45], between the two hemispheres[46], and between hippocampi[47]. Coherence has also been observed between LFPs from somatosensory and primary motor cortex separated by an estimated cortical distance of 2 cm (REF. 48), and between primary and premotor areas[49] during visuomotor behaviour in monkeys[50].

Studying single units in the frontal lobe of a behaving monkey during a go–no-go task, Vaadia *et al.*[51,52] found changes in spike synchronous patterns that could not be predicted from the firing rates of individual neurons. Interestingly, the phase organization changed from locking to dispersion during the duration of a trial. In the perspective of large-scale integration, this indicates that a single neuron might change its coupling to other neurons in its local vicinity and in distant regions, and thus participate intermittently in different ensembles.

Results from LFPs and surface recordings in humans. We have studied patients implanted with multiple electrodes in preparation for surgical resection for epilepsy[53,54]. In these people, we observed reliable power emission in narrow frequency bands in the gamma range when the subjects performed a simple visual-discrimination task. These intracortical oscillations showed large-scale synchrony between temporal and frontal lobes that appeared only during the execution of the discrimination task. Similarly, Aoki *et al.*[42] have provided converging evidence obtained from cortical grids
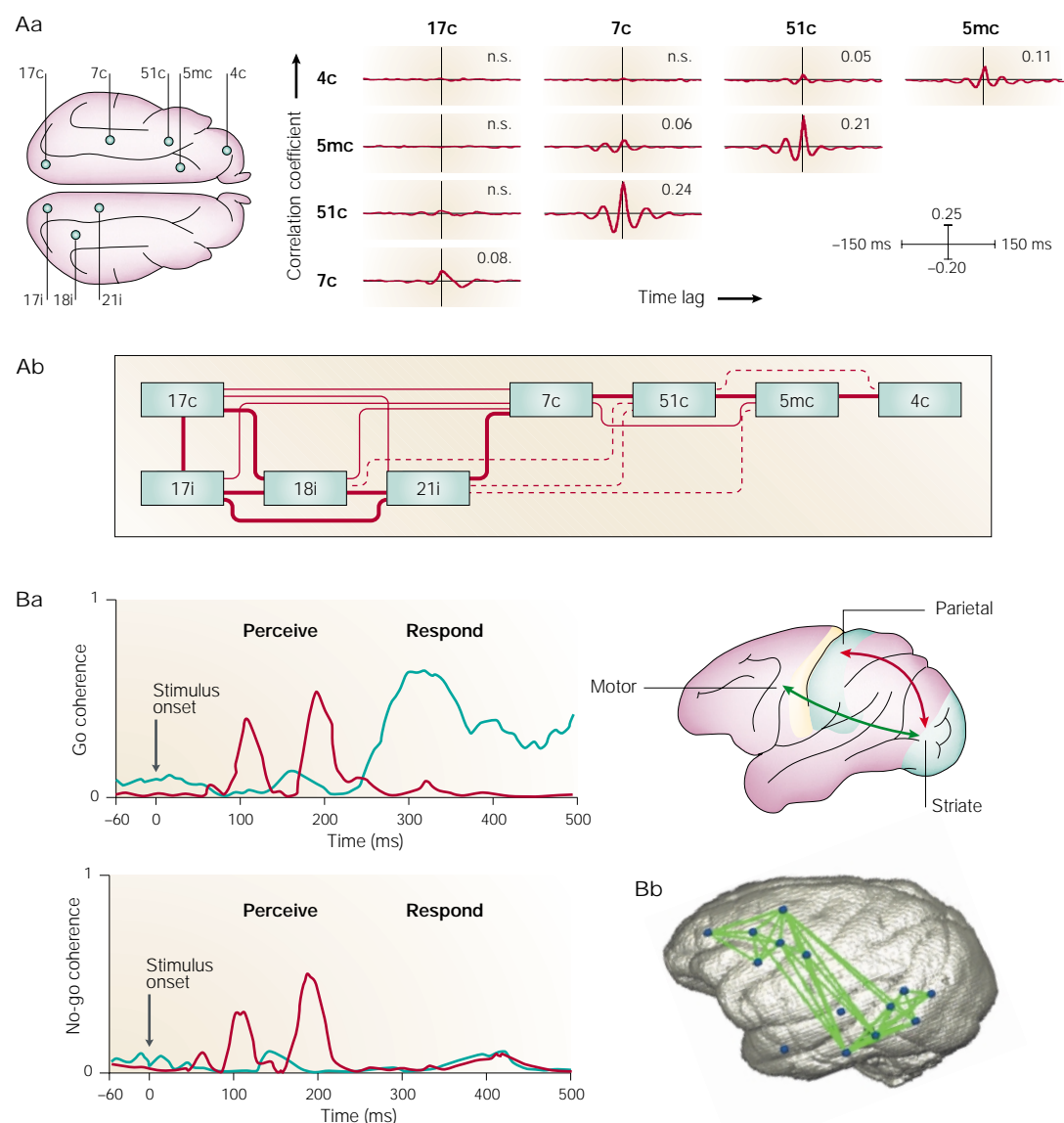

Figure 3 | **Long-range integration studies I. A** | Studies of a behaving cat during a sensorimotor task. **a** | Cross-correlation pattern between local field potentials (LFPs) from areas of the visual, parietal and motor cortex, while the animal waited for rotation of a visual pattern. Recordings from somatosensory and motor areas taken from the contralateral hemisphere (c) relative to the paw used in the task (i, ipsilateral; m, medial; n.s., not significant). **b** | Strength of the correlation functions among the areas recorded during the task period. Thick lines indicate a coefficient >10%, thin lines between 5 and 10%, dotted lines <5%. **B** | Studies of a behaving monkey during a go–no-go motor task. **a** | Coherence values for the gamma band between two electrode pairs over the course of a motor task. During the response onset, the striate–motor pattern changes (green lines) sharply, whereas it remains stable for the striate–parietal pair (red lines). **b** | Maps of significant coherence values after the stimulation, expressed as lines between recording sites, mapped onto the brain of one of the monkeys. Note the appreciable extent of large-scale interdependencies. (Panel **A** is adapted with permission from REF. 31 © (1997) Macmillan Magazines Ltd; panel **Ba** is adapted with permission from REF. 34 © (1993) Macmillan Magazines Ltd; panel **Bb** was provided by S. Bressler, and is adapted from REF. 36.)
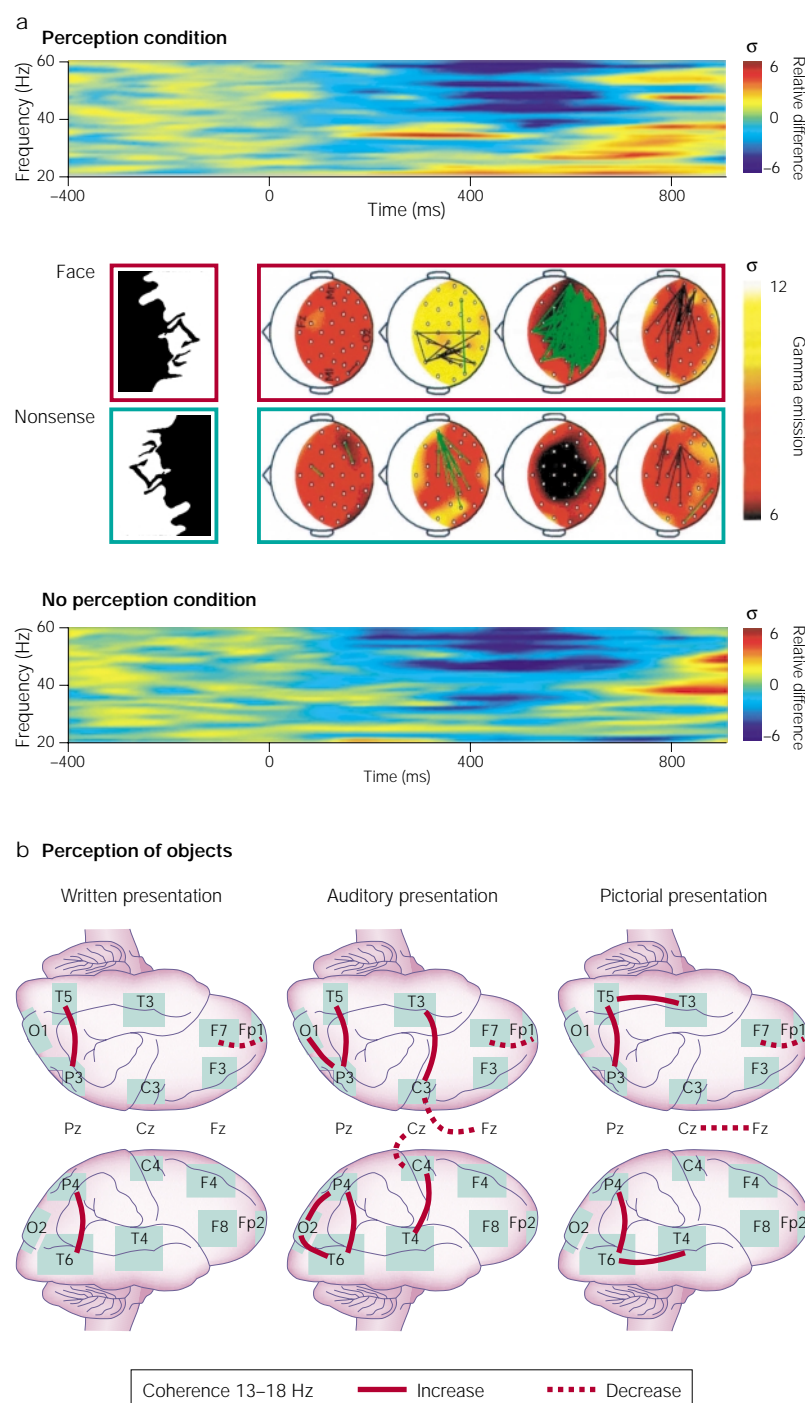
Figure 4 | Long-range integration studies II. a | Long-distance synchronization of the electroencephalographic signal during a face-recognition task. The recognition of a high-contrast face leads to a highly selective increase in phase-locking values in the 40 Hz range 200 ms after stimulus presentation (at *t* = 0) (upper time–frequency chart), which is absent when no face is recognized (lower time–frequency chart). The colour code indicates the degree of deviation from a reference period before stimulation. A second period of synchrony increase occurs after the motor response. In the middle panel, the perception condition is mapped onto surface electrodes. Here the colour code corresponds to the gamma emission over the scalp. Black lines indicate a significant level of synchrony over successive moments of time. Green lines indicate a marked phase scattering between electrodes; that is, the likelihood of being synchronous has decreased below reference values (also seen in blue code in the upper and lower charts). **b |** Coherence (red lines) in the beta band between temporal (T) and parietal (P) cortex during multimodal object identification; Pz, Cz, Fz are electrodes on the cortical midline. (Panel **a** is adapted with permission from REF. 55 © (1999) Macmillan Magazines Ltd.)

implanted over the motor cortex of patients performing three visuomotor tasks. All subjects showed a decrease of low frequency power emissions and an increase in gamma oscillations. In most cases, the active sites entered into frequency coherence during task performance over distant regions.

Significant evidence for large-scale synchronization has been provided recently from macropotentials recorded as electroencephalographic (EEG) or magneto-encephalographic (MEG) signals. Direct support for long-range synchrony has been found by Rodríguez *et al.*[55], who studied the perception of high-contrast human faces in healthy humans. A consistent pattern of synchrony between occipital, parietal and frontal areas was established during face recognition (around 250 ms after stimulus presentation). This synchrony was absent when the faces were presented upside down and not easily recognized (FIG. 4a). In both cases, a new pattern of synchrony in the gamma range emerged during the motor response given by the subject to indicate perception of the stimuli (720 ms). Interestingly, this study also showed that the two emerging synchronous patterns were punctuated in time by a transient but active process of phase scattering in which the probability of finding synchrony between two electrodes fell below the level observed before stimulation (FIG. 4a). This alternation or balance between phase synchronization and phase scattering has also been observed within and across hemispheres during arm movements[56] and has also been found between single units in behaving monkeys[57,58].

Srinivasan *et al.*[59] studied MEG responses during a BINOCULAR RIVALRY TASK, in which two different gratings were presented monocularly, flickering continuously at a distinct frequency. Depending on which stimulus was perceived, there was a marked increase in both interhemispheric and intrahemispheric coherence at the flashing rate of stimulus presentation. In another study, von Stein *et al.*[60] have reported EEG coherence related to the appearance of a supramodal object. They presented stimuli such as pictures, spoken or written words and studied coherence patterns between auditory and visual regions, searching for multimodal integration. A common pattern appeared in the beta band between temporal and parietal electrodes, although the low frequencies were enhanced in this study by the use of a large analysis window of 2 s.

Learning and attention. Miltner *et al.*[61] showed that the establishment of a visuotactile association was accompanied by gamma coherence between visual and somatosensory cortices. This learned coherence vanishes after a period of extinction. By contrast, Sarnthein *et al.*[62] observed a consistent increase in coherence between prefrontal and posterior association areas in the THETA band (4–8 Hz) during a working memory task. This increase in coherence was possibly linked to hippocampal pacemakers, although other frequency bands (including gamma) were also involved. In fact, phase-locked hippocampal–cortical loops have been proposed to correlate with the acquisition and retrieval of memories[63].
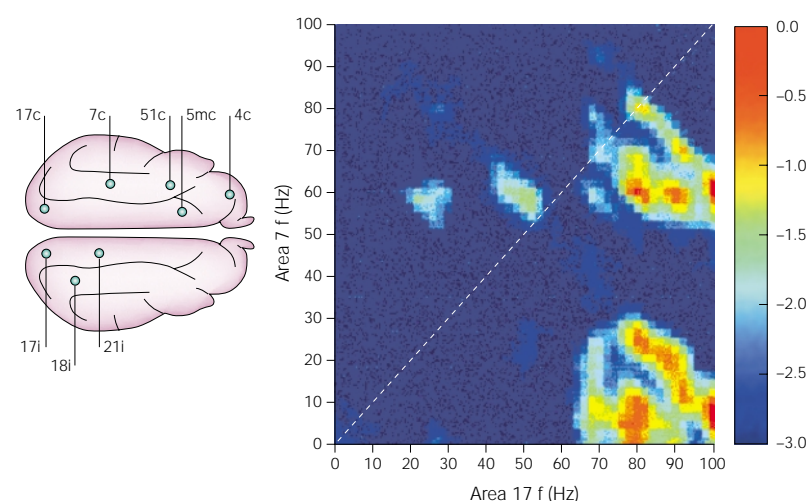
Figure 5 | **Interdependence between different frequency components from local field potentials recorded from the cortex of a behaving cat.** The dual cross-coherence is shown between two electrodes in area 17 and 7 in logarithmic values. The peak in the lower right, for instance, indicates a phase relation between gamma activity in area 17 and beta activity in area 7. (Adapted with permission from REF. 33 © (2000) National Academy of Sciences of the USA.)

Consistent with the putative functional role of synchronization, arousal and attention have repeatedly been found to modulate distributed patterns of synchronization fairly strongly[64]. Gamma coherence disappears during deep sleep induced by anaesthesia[65], but it is enhanced during return to wakefulness or following stimulation of the reticular formation[66,67]. More precisely, Steinmetz et al.[68] trained monkeys to switch their attention between visual and tactile stimuli and showed that pairs of synchronous cells in the somatosensory cortex followed the direction of attention. Synchrony increased by 80% and decreased by 20% in neuron pairs that corresponded to the modality towards which attention was re-directed.

If large-scale synchrony is the basis for normal brain functioning, then synchrony disruption should cause functional abnormalities[69,70]. In epilepsy, the local intrinsic frequencies become enslaved to a pacemaker and give rise to slow, uniform oscillations that arise over minutes[71,72]. In Parkinson's disease, TREMOR has been proposed to arise from the spread of abnormal coupling patterns between the representations of the limb muscles in basal ganglia[73]. It has also been proposed that a disruption of synchrony is related to the fragmented cognitive experience of patients with schizophrenia[74,75].

The studies that we have reviewed support the idea that phase synchrony is essential for large-scale integration. The evidence is well grounded in single-cell recordings and LFPs studies in animals, and also in evidence from humans using more global measurements such as EEG and MEG. Similar characteristics seem to emerge at all levels of resolution. We seem to be scratching the tip of a large new area of brain understanding that could become a dominant area of research in neuroscience.

BINOCULAR RIVALRY TASK
Task in which each eye of the subject is shown a different image. This results in a bistable visual experience.

THETA RHYTHM
Neural rhythmic activity (4–8 cycles per second).

PARKINSONIAN TREMOR
Abnormal rhythmic muscular activity (4–8 Hz) observed in Parkinsonian patients.

Themes for future research

Direct proof for the role of synchrony. The evidence available so far regarding the function of synchronization is only correlative. There is no direct proof that synchrony leads to changes in behaviour when it is selectively altered. Such direct evidence has only been obtained in the olfactory system of insects. Stopfer et al.[76] showed that odour discrimination deteriorates if synchronization patterns among olfactory bulb cells are disturbed. The search for similar evidence in the vertebrate brain is a daunting challenge, but future studies in this direction are a priority.

Long-range synchrony over several frequencies. Parallel phase synchrony over different frequency bands has been reported in several contexts, most prominently as an interplay between low and high frequencies[33,34,77–80]. This observation raises the possibility that different bands might carry different dimensions of the integration process. As these frequency bands are repeatedly found in different individuals during the same behaviour, they constitute a characteristic frequency (or 'eigenfrequency'), a signature of the specific spatiotemporal distribution of a resonant assembly. Friston[81] proposed a method for studying modulations across frequencies and found that, during a hand motion, gamma frequencies in the frontal cortex correlated with beta (20 Hz) activity in the parietal cortex. In a study of the behaving cat, von Stein et al.[33] found a strong cross-coherence between gamma activity in area 17 and beta activity in area 7 (FIG. 5). If multi-frequency synchrony proves to be a pervasive process during brain integration, then the basic synchrony mechanism will have to be extended into the study of cross-talk between frequencies and will probably require novel methods of analysis.

Phase synchrony and phase scattering. There is some evidence that phase synchronization is accompanied by phase scattering in other bands[55,57,79] or between different neuron pairs[58]. We suggest that this novel observation is crucial for the understanding of large-scale integration, which must implicate not only the establishment of dynamic links, but also their active uncoupling to give way to the next cognitive moment. Strictly speaking, the process of integration seems to be based on the interplay between phase locking and phase scattering across different bands and at different moments in time. The cellular mechanisms responsible for such active phase scattering are unknown at present but most probably involve inhibitory modulations of the neural rhythms, which lead to phase resetting of a local ensemble.

Cellular mechanisms of synchronization. Recent studies[82,83] have emphasized the different roles of the beta and gamma bands, on the basis of an analysis of the ion channels that give rise to the various rhythms. One important conclusion from this analysis is that the beta band is robust for the establishment of long-distance synchrony; that is, over transmission delays of 10–50 ms. By contrast, gamma rhythms tend to be more labile for

ALPHA RHYTHM
Neural rhythmic activity (8–12 cycles per second).

long-distance links and more probably serve to build local patches of synchrony[60]. Electrical stimulation of brain slices at different frequencies under optical imaging provides support to these ideas[5]. In fact, the interplay between beta and gamma bands has been found in some of the studies mentioned above. Further research is needed to refine our understanding of the cellular basis of the synchronization phenomena.

Relation between fast and slow brain rhythms. Although the fast gamma and beta frequencies are most clearly involved in the establishment of synchrony, they have to be understood in the context of the slower ALPHA and theta bands. The mutual influence between specific nuclei of the thalamus and the cortex is pervasive. The same is true for nonspecific nuclei such as the pulvinar, which projects to multiple cortical areas. These reciprocal relations can deploy across different frequencies (including the alpha range around 10 Hz (REFS 84,85)), which are involved in setting and resetting the cycles of excitatory postsynaptic potentials on pyramidal cells. A slower pacing occurs in the theta band below 7 Hz in limbic structures during memory consolidation[86,87]. These slower rhythms could provide the slower temporal framing for successive cognitive moments of synchronous assemblies, a slower beat within which beta and gamma rhythms operate. Research in this direction is much needed.

Beyond synchrony

The experimental evidence consistently shows that synchronous networks emerge and disappear in waves that last 100–300 ms; these transients represent a meaningful temporal scale of brain operation[7,88]. The transient nature of coherence is central to the entire idea of large-scale synchrony, as it underscores the fact that the system does not behave dynamically as having stable attractors, but rather metastable patterns — a succession of self-limiting recurrent patterns[25,26,52,89–91]. In the brain, there is no 'settling down' but an ongoing change marked only by transient coordination among populations, as the attractor itself changes owing to activity-dependent changes and modulations of synaptic connections.

The various aspects of large-scale integration through synchrony constitute the basis for several broader considerations about brain dynamics as coordinated spatiotemporal patterns[23,25,26,81,92,93]. A central issue is the solution to the apparently opposing needs of local specificity of activity versus the constraints imposed by other areas, which has been highlighted as the hallmark of brain complexity[94]. Under this vision, the brain appears as a resourceful complex system that satisfies simultaneously the exogenous and endogenous constraints that arise at each moment by transiently settling in a globally consistent state. These novel views on the brain might throw light on the emergent principles that link neuron and mind, as the large-scale integration of brain activity can be considered as the basis for the unity of mind familiar to us in everyday experience[95–97].

Links

ENCYCLOPEDIA OF LIFE SCIENCES **Brain imaging: localization of brain functions | Brain imaging: observing ongoing neural activity**

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