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Consciousness and the structure of neuronal representations

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The hypothesis is defended that brains expressing phenomenal awareness are capable of generating metarepresentations of their cognitive processes, these metarepresentations resulting from an iteration of self-similar cortical operations. Search for the neuronal substrate of awareness therefore converges with the search for the nature of neuronal representations. It is proposed that evolved brains use two complementary representational strategies. One consists of the generation of neurons responding selectively to a particular constellation of features and is based on selective recombination of inputs in hierarchically structured feedforward architectures. The other relies on the dynamic association of feature-specific cells into functionally coherent cell assemblies that, as a whole, represent the constellation of features defining a particular perceptual object. Arguments are presented that favour the notion that the metarepresentations supporting awareness are established in accordance with the second strategy. Experimental data are reviewed that are compatible with the hypothesis that evolved brains use assembly codes for the representation of contents and that these assemblies become organized through transient synchronization of the discharges of associated neurons. It is argued that central states favouring the formation of assembly-based representations are similar to those favouring awareness.

Keywords: consciousness; phenomenal awareness; cognitive neuroscience; synchronization; oscillations

1. INTRODUCTION

The term ‘consciousness’ has a number of different connotations ranging from phenomenal awareness of one’s perceptions and sensations to self-awareness, the perception of oneself as an agent that is endowed with intentionality and free will. Here I take the position that the first connotation of consciousness, phenomenal awareness, should in principle be tractable within neurobiological description systems because the problem can be reduced to the question of how neuronal representations are organized. However, before discussing concepts concerning the putative structure of neuronal representations in evolved brains I shall attempt a few qualifications of the explanandum.

Brains capable of processing signals at a conscious level seem to have the ability to represent the outcome of their distributed computational operations in a common format. These metarepresentations comprise protocols not only of sensory and motor processes but also of the state of value-assigning systems. Thus, brains that have consciousness possess a representational metalevel at which internal states are explicitly represented: they have what one might call an ‘inner eye’ function. They can compare protocols of their own performance with incoming signals and derive from the outcome of these ‘internal deliberations’ decisions for future acts. This allows them to respond with more flexibility to changing conditions than brains that lack consciousness and are confined to reacting to stimuli without the option of further reflection and internal deliberation. The intercalation of a further processing step between primary

sensory computations and the programming of motor responses has obvious adaptive functions and this might have contributed to the evolution of brains capable of being conscious of their own performance.

To run protocols of processes occurring within the brain, additional cognitive structures are required that analyse these processes and generate neuronal representations of them. Thus the implementation of monitoring functions requires second-order processing levels that generate metarepresentations of the computational results provided by first-order processes. The most likely substrate for such operations are cortical areas that have been added in the course of evolution and that treat the output of lower-order cortical areas in the same way that these treat input from the sensory periphery. The inner-eye function could thus be realized by a reflexive iteration of self-similar cortical functions. This interpretation is compatible with the neuroanatomical evidence that the phylogenetically more recent cortical areas are remote from primary sensory input and interact mainly, either through the thalamus or directly through corticocortical connections, with areas of lower order.

If these more recent monitoring structures have in turn access to the motor system—and available evidence indicates that this is so—brains endowed with such monitoring functions would in addition have the possibility to signal to other organisms the result of the internal monitoring. Through mimics, gestures, vocalizations and in humans also language, such brains could signal to others what their perceptions, intentions, value assignments and action plans are. As such information markedly increases the predictability of future actions of

the respective other, it is likely to have an important function in the consolidation of social systems. This could be another adaptive function of consciousness that could have favoured its evolution.

Two arguments, one based on evolution and the other on ontogeny, suggest that consciousness is a graded phenomenon whereby the gradations are correlated with the phylogenetic and ontogenetic differentiation of the cerebral cortex. The evolutionary argument is derived from the evidence that brains have evolved gradually, the most recent evolutionary changes being confined to an expansion of cerebral cortex and the apposition of new cortical areas. This suggests that consciousness evolved as a consequence of cortical expansion and therefore is probably not an all-or-none phenomenon. The ontogenetic argument is based on the observation that the various manifestations of consciousness from rudimentary awareness of sensations to the fully expressed self-consciousness of the adult go in parallel with the gradual maturation of cerebral structures, in particular of the phylogenetically more recent cortical areas.

If consciousness is indeed a graded phenomenon and if the expression of its various facets is related to the increasing differentiation of the cerebral cortex, certain aspects of consciousness such as phenomenal awareness and the ability to retain memories consciously should also be present in animals. This possibility is supported by the evidence that functions intimately related to consciousness are present in both humans and higher animals. In humans, only signals selected by attentional mechanisms reach the level of phenomenal awareness and only these selected signals can be integrated in episodic memories. This suggests that the processing capacity of the internal monitoring system is limited, requiring preselection of the contents to be monitored. Thus, the ability to establish metarepresentations seems to be associated with the implementation of attentional mechanisms. Both functions, in turn, are likely prerequisites of the ability to generate episodic memories. Higher mammals, and in particular primates, possess attentional mechanisms and episodic memory functions that closely resemble those of humans. It follows that these animals, too, have the option to generate metarepresentations of primary sensory processes and motor processes and hence should be granted some form of consciousness.

If one accepts the scenario that the aspect of consciousness that we address as phenomenal awareness results from an iteration of the same cognitive operations that support primary sensory processing, the explanatory gap reduces itself to the question of how the cerebral cortex processes signals and generates representations. If this question is answered with respect to primary sensory functions, the discovered strategies should be generalizable to the formation of metarepresentations, the representation of the brain's own computational operations that assume the postulated inner-eye function.

However, there are other aspects of consciousness such as self-awareness and the experience of individuality, that seem to require explanations that transcend purely neurobiological reductionism. It is my perception that the ontological status of these phenomena differs from that of the qualia of phenomenal awareness, and that it is these

aspects of consciousness that give rise to the hard problems in the philosophy of mind and provide the incentive for adopting dualistic positions. The most challenging phenomenon in this context is that we perceive ourselves as agents endowed with intentionality and the freedom to decide, implying that the self is actually capable of controlling by will processes in the brain. We experience these aspects of consciousness as mental phenomena that govern in some sense the neuronal processes in the brain and hence we tend to assign them to an ontological category that differs from that of phenomenal awareness that we also grant animals.

I propose that these latter connotations of consciousness are perceived as different because they require, for their development, interactions among brains that are sufficiently differentiated to signal to one another that they are endowed with phenomenal awareness. Such brains are able to enter dialogues of the kind 'I know that you know how I feel' or 'I know that you know what my intentions are', etc. My proposal is that the experience of the 'self' with all its mental attributes originates from such a dialogue between brains, and hence has the ontological status of a social reality. If true, it is only the interaction with other human beings, above all the interaction between care-givers and babies that instils the experience of individuality and responsibility, and as a consequence leads to the intuition that one is endowed with intentionality and free will. These aspects of consciousness would then have to be considered as a product of cultural evolution. They would have a historical dimension and therefore would transcend pure neurobiological description systems that focus on individual brains.

The mechanisms that enable us to experience ourselves as endowed with mental capacities do, of course, reside in individual brains, but the contents of this experience would have to be assigned the status of cultural constructs. The reason why the experience of the self is so obviously different from other experiences that we derive from social interactions, is probably that the dialogue that leads to this experience is initiated during an early developmental stage, and long before episodic memory matures and begins to keep track of what the brain experiences. There is therefore no conscious record of the processes that led to the experience of the self and the associated subjective connotations of consciousness. Because of this amnesia these experiences lack causation, and I propose that this is the reason why these subjective connotations of consciousness are perceived as having transcendental qualities that resist reductionistic explanations.

2. THE ORGANIZATION OF NEURONAL REPRESENTATIONS

If the argument is valid that the internal monitoring functions that lead to metarepresentations rest on the same cognitive operations as the sensory processes that deal with signals conveyed by the sense organs, the search for the neuronal substrate of phenomenal awareness converges with the search for the structure of neuronal representations in general. In the following paragraphs I

shall therefore expose hypotheses on the putative structure of neuronal representations.

The working hypothesis proposed here is that evolved brains use two complementary strategies to represent contents (see also Singer 1995). The first strategy is thought to rely on individual neurons that are tuned to particular constellations of input activity. Through their selective responses, these neurons establish explicit representations of particular constellations of features. It is commonly held that the specificity of these neurons is brought about by the selective convergence of input connections in hierarchically structured feedforward architectures. This representational strategy allows rapid processing and is ideally suited for the representation of frequently occurring stereotyped combinations of features; however, the strategy is expensive in terms of the number of required neurons and is not suited to cope with the virtually infinite diversity of possible feature constellations encountered in real-world objects. The second strategy in the proposal consists of the temporary association of neurons into functionally coherent assemblies that as a whole represent a particular content whereby each of the participating neurons is tuned to one of the elementary features of composite perceptual objects. This representational strategy is more economical with respect to neuron numbers because a particular neuron can, at different times, participate in different assemblies, just as a particular feature can be part of many different perceptual objects. Moreover, this representational strategy is more flexible. It allows the rapid *de novo* representation of constellations that have never been experienced before because there are virtually no limits to the dynamic association of neurons in ever-changing constellations, provided that the participating neurons are interconnected. Thus, for the representation of highly complex and permanently changing contents this second, implicit, strategy seems to be better suited than the first explicit strategy.

The mechanism that generates the metarepresentations required for phenomenal awareness has to cope with contents that are particularly unpredictable and rich in combinatorial complexity. Such metarepresentations are necessarily polymodal and need to reconfigure themselves at the same pace as the contents of phenomenal awareness change. It therefore seems as though the second representational strategy, based on the formation of dynamic assemblies, would be more suitable than the explicit strategy for the implementation of metarepresentations. Further support for this view can be derived from the argument that conditions required for the formation of metarepresentations ought to be the same as those required for awareness to occur. Neuronal codes that are readily observable in deep anaesthesia, or during slow-wave sleep, or in the absence of attention, should not be accepted as correlates of awareness or consciousness. As the receptive fields of individual neurons tend to differ only little in awake and anaesthetized brains, it is unlikely that the explicit representations encoded by individual neurons are the substrate of the metarepresentations that support consciousness. As detailed below, brain states that are compatible with the manifestation of consciousness also favour the emergence of ordered spatio-temporal activity patterns that could serve as substrates for the formation of assemblies.

The following sections will therefore focus on the question of whether there is any evidence that contents are represented not only explicitly by tuned neurons but also by dynamically associated assemblies, and, if so, what the electrophysiological manifestations of such assemblies might be. The hypothesis will be put forward that one signature of assemblies is the synchronization of responses of participating neurons, and data will be reviewed that suggest a correlation between the occurrence of response synchronization on the one hand and brain states favourable for the occurrence of awareness on the other.

3. THE SIGNATURE OF ASSEMBLIES

In assembly coding, two important constraints need to be met. First, a selection mechanism is required that permits the dynamic yet consistent association of neurons into distinct, functionally coherent assemblies. Second, responses of neurons that have been identified as groupable must be labelled so that they can be recognized by subsequent processing stages as belonging together. This is necessary to ensure that responses, once they are bound together, are evaluated jointly as constituents of a coherent code and do not get confounded with responses of cells belonging to other, simultaneously formed, assemblies that represent different contents. Numerous theoretical studies have addressed the question of how assemblies can self-organize on the basis of cooperative interactions within associative neuronal networks (Braitenberg 1978; Edelman 1987; Palm 1990; Gerstein & Gochin 1992). Here I shall focus on the second problem of assembly coding: the question of how responses of cells that have been grouped into an assembly can be tagged as related. An unambiguous signature of relatedness is absolutely crucial for assembly codes because, unlike in explicit single-cell codes, the meaning of responses changes with the context in which they are interpreted. Hence, in assembly coding, false conjunctions are deleterious. Tagging responses as related is equivalent to raising their saliency jointly and selectively, because this ensures that they are processed and evaluated together at the subsequent processing stage. This can be achieved in three ways. First, non-grouped responses can be inhibited; second, the amplitude of the selected responses can be enhanced; and third, the selected cells can be made to discharge in precise temporal synchrony. All three mechanisms enhance the relative impact of the grouped responses at the next higher processing level. Selecting responses by modulating discharge rates is common in labelled-line coding where a particular cell always signals the same content. However, this strategy might not always be suited to the distinction of assemblies because it introduces ambiguities (von der Malsburg 1985) and reduces processing speed (Singer *et al.* 1997). Ambiguities could arise because the discharge rates of feature selective cells vary over a wide range as a function of the match between stimulus and receptive field properties; these modulations of response amplitude would not be distinguishable from those signalling the relatedness of responses. Processing speed would be reduced because rate-coded assemblies need to be maintained for some time to be distinguishable, but they cannot overlap in time within

the same processing stage; if they did, it would be impossible to distinguish which responses belonged to which assembly. This limits the rate at which different assemblies can follow one another within the same processing stage.

The ambiguities resulting from both stimulus-related rate fluctuations and the temporal constraints can be overcome if the selection and labelling of responses is achieved through the synchronization of individual discharges (von der Malsburg 1985; Gray *et al.* 1989; Singer & Gray 1995). Expressing the relatedness of responses by synchronization resolves the ambiguities resulting from stimulus-dependent rate fluctuations because synchronization can be modulated independently of rates. Response amplitudes could thus be reserved to signal how well particular features match the preferences of neurons, and synchronicity could be used in parallel to signal how these features are related. Defining assemblies by synchronization also accelerates the rate at which different assemblies can follow one another because the selected event is the individual spike or a brief burst of spikes; saliency is enhanced only for those discharges that are precisely synchronized and generate coincident synaptic potentials in target cells at the subsequent processing stage. The rate at which different assemblies can follow one another without getting confounded is then limited only by the duration of the interval over which synaptic potentials sum effectively.

Another advantage of selecting responses by synchronization is that the timing of input events is preserved with high precision in the output activity of cells because synchronized input is transmitted with minimal latency jitter (Abeles 1982; Softky 1994; König *et al.* 1996). This, in turn, can be exploited to preserve the signature of relatedness across processing stages, thus reducing further the risk of obtaining false conjunctions. Finally, synchronization enhances processing speed also by accelerating synaptic transmission *per se* because synchronized excitatory postsynaptic potentials (EPSPs) trigger action potentials with minimal delay.

4. CELLULAR PREREQUISITES FOR SELECTION BY SYNCHRONIZATION

At the level of cellular mechanisms, two prerequisites need to be fulfilled to exploit synchronization as a coding mechanism: first, neurons must be able to act as coincidence detectors, i.e. they must be particularly sensitive to coincident synaptic inputs; second, mechanisms must exist that permit the rapid and context-dependent temporal coordination of distributed discharge patterns.

The question of whether neurons in the central nervous system are capable of performing coincidence detection with the required precision is controversial because both theoretical arguments and simulation studies have led to opposite conclusions (Softky 1994; König *et al.* 1996; Shadlen & Newsome 1994). However, experimental evidence clearly indicates that neurons can evaluate temporal relations between incoming activities with sometimes surprising precision. In the auditory system, coincidence detection is used to locate sound sources. Neurons in auditory nuclei of the brainstem evaluate the delays between incoming signals from the two ears with a

precision in the submillisecond range (reviewed by Carr (1993)). Another example is the oscillatory responses of retinal ganglion cells that can be synchronized over large distances with a phase-lag of close to zero (Neuenschwander & Singer 1996). Because of the high frequency of these oscillations (up to 100 Hz) the neuronal mechanism responsible for synchronization must operate with time constants in the millisecond range. This time-modulated activity is reliably transmitted up to cortical neurons as indicated by cross-correlation analysis between retinal ganglion cells and cortical neurons. The implication is that neurons along the transmission chain must have operated with integration time constants not longer than a half cycle of the oscillation, and hence no more than 5 ms. The ability of cortical networks to handle temporally structured activity with high precision can also be inferred from the abundant evidence on the oscillatory patterning and synchronization of neuronal responses in the neocortex (reviewed by Singer & Gray (1995)). Such temporally coordinated discharge patterns can emerge and stabilize only if the temporal structure of activity is preserved during synaptic transmission and is not dispersed and smeared too much by temporal integration. In the awake performing brain, the oscillatory patterning of cortical responses is typically in the γ -frequency range (30–60 Hz) and synchronization peaks often have a width at base in the range 10–15 ms, indicating that temporal integration intervals should be on average no longer than 10 ms.

5. RAPID SYNCHRONIZATION

If synchronization is to have a role as a signature of assemblies, it must be possible to synchronize discharges rapidly because of the constraints set by processing speed.

Early simulation studies that used harmonic oscillators, rather than single spiking neurons, showed that it might indeed take a few cycles before synchronicity is established through phase locking (König & Schillen 1991). However, later simulations with spiking neurons revealed that networks of appropriately coupled units can undergo sudden state changes in which the synchronization of discharges and their oscillatory patterning occur promptly and virtually simultaneously (reviewed by Singer *et al.* (1997)).

Very rapid synchronization has been observed recently in the visual cortex of awake cats for neurons with similar orientation preferences. When these neurons were activated by the onset of an appropriately orientated grating, their initial responses were already better synchronized than expected from mere stimulus locking (Fries *et al.* 1997a). Comparison between actual response latencies and immediately preceding fluctuations of the local field potential revealed that the response latency shifted as a function of the polarity of the preceding field potential fluctuation. Because these fluctuations were not independent between the different recording sites, response latencies became synchronized. Thus coordinated fluctuations of excitability act as a dynamic filter and cause a virtually instantaneous synchronization of the very first discharges of responses (Fries *et al.* 1997a). Because the spatio-temporal patterns of these fluctuations reflect the architecture of intracortical association

connections, grouping by synchronization can be extremely fast and still occur as a function of the prewired associational dispositions of the cortical network.

Evidence suggests that an oscillatory patterning of responses might be instrumental for the internal synchronization of neurons, in particular when interactions comprise substantial conduction delays or occur across polysynaptic pathways (König *et al.* 1995). Experiments *in vitro* support this conjecture, showing that subthreshold oscillatory modulation of the membrane potential is ideally suited to establish synchronization because it permits the shifting of response latencies rapidly, and over long intervals (Volgushev *et al.* 1998). For slowly decaying EPSPs that contain late components caused by the activation of the *N*-methyl-d-aspartate (NMDA) type of glutamate receptors or by polysynaptic inputs, the timing of the output can become decoupled from the timing of the input. Irrespective of when the EPSP is generated relative to the phase of the oscillation cycle, the first discharge is most likely to occur shortly after the peak of the respective next depolarizing cycle. The reasons are twofold: first, the depolarization removes the Mg^{2+} ion that blocks the NMDA receptor at resting potential, so that receptors still occupied by glutamate are reactivated; second, subthreshold oscillatory modulation of the membrane potential activates a transient (1–2 ms) conductance for Na^+ ions that makes oscillating cells highly susceptible to synaptic inward currents shortly after the depolarizing peak. Thus, in cells with oscillating membrane potential, responses can become considerably delayed; the maximal possible delay interval depends on oscillation frequency and can amount to nearly the duration of one cycle. With such a mechanism, responses to temporally dispersed EPSPs can become synchronized within less than an oscillation cycle in cells exhibiting coherent fluctuations of their membrane potential.

6. FUNCTIONAL CORRELATES OF RESPONSE SYNCHRONIZATION

(a) *Perceptual grouping*

After the discovery of stimulus-related response synchronization between neurons in the cat visual cortex (Gray & Singer 1987, 1989) numerous experiments have been performed in the search for a correlation between the occurrence of response synchronization and particular stimulus configurations. The prediction to be tested was that synchronization probability should reflect some of the Gestalt criteria according to which the visual system groups related features during scene segmentation. Among the grouping criteria examined so far have been continuity, vicinity and similarity in the orientation domain, and collinearity and common fate in the motion domain (for the cat, see Gray *et al.* (1989), Engel *et al.* (1991*b,c*) and Freiwald *et al.* (1995); for the monkey, see Kreiter & Singer (1996)). So far the results of these investigations are compatible with the hypothesis that the probability of response synchronization reflects the Gestalt criteria applied for perceptual grouping (see figure 1). Stimulus-specific response synchronization has been found within and across different areas, and even between hemispheres (reviewed by Singer & Gray (1995)); most importantly, none of these synchronization

phenomena were detectable by correlating successively recorded responses. This indicates that they were not due to stimulus locking but to internal dynamic coordination of spike timing. Thus the observed temporal coherence between responses is much greater than expected from mere covariation of event-related rate changes. Studies involving lesions (Engel *et al.* 1991*a*; Nowak *et al.* 1995) and developmental manipulations (Löwel & Singer 1992; König *et al.* 1993) indicate that the interactions responsible for these dynamic synchronization phenomena are mediated to a substantial extent by corticocortical connections. The criteria for perceptual grouping should then be reflected in the architecture of these connections and this postulate agrees with the evidence that corticocortical connections preferentially link neurons with related feature preferences (reviewed by Schmidt *et al.* (1997)).

(b) *Response synchronization and behavioural states*

Most of the early experiments in search of synchronization phenomena were performed in lightly anaesthetized animals; it was therefore important to investigate whether response synchronization occurs also during states in which the electroencephalogram (EEG) is actually desynchronized as is characteristic for the awake, attentive brain. Evidence from cats and monkeys indicates that high-precision internally generated synchrony is considerably more pronounced in the awake brain than in the anaesthetized brain. Whenever tested, and data are available from the primary visual cortex of cats and monkeys, the motion-sensitive areas MT and MST in monkeys, and the infero-temporal cortex of monkeys, the synchronization phenomena were readily demonstrable and showed a similar dependence on stimulus configuration to the synchronization measured under anaesthesia (reviewed by Singer *et al.* (1997)).

Of particular interest in this context is the recent finding that response synchronization is especially pronounced when the global EEG desynchronizes and when the animals are attentive. Stimulating the mesencephalic reticular formation in anaesthetized animals leads to a transient desynchronization of the EEG, resembling the transition from slow-wave sleep to rapid-eye-movement sleep. Munk *et al.* (1996) have recently shown that stimulus-specific synchronization of neuronal responses is drastically facilitated when the EEG is in a desynchronized rather than in a synchronized state.

Direct evidence for an attention-related facilitation of synchronization has been obtained from cats that had been trained to perform a visually triggered motor response (Roelfsema *et al.* 1997). Simultaneous recordings from visual, association, somatosensory and motor areas revealed that the cortical areas involved in the execution of the task synchronized their activity, predominantly with zero phase-lag, as soon as the animals prepared themselves for the task and focused their attention on the relevant stimulus. Immediately after the appearance of the visual stimulus, synchronization increased further over the visual areas, and these coordinated activation patterns were maintained until the task was completed. However, once the reward was available and the animals were engaged in eating, these coherent patterns collapsed and gave way to low-frequency oscillatory activity that

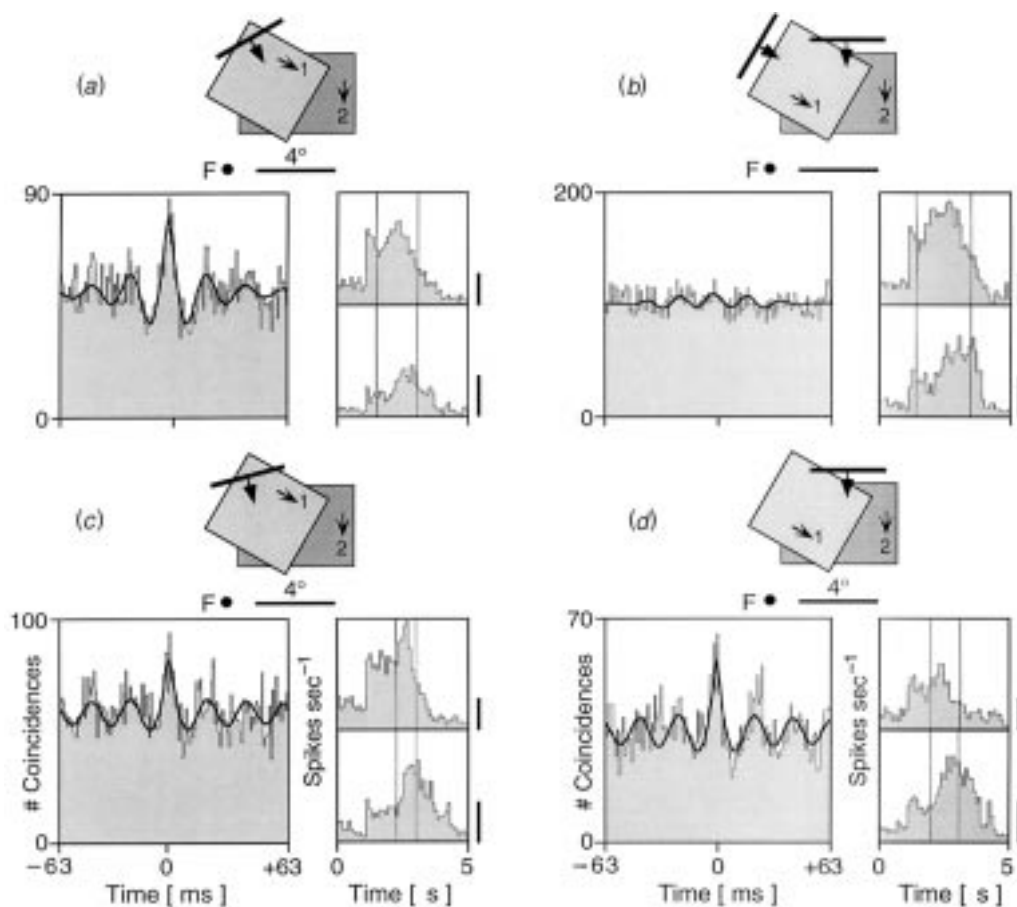


Figure 1. Stimulus dependence of neuronal synchronization in area MT of the visual cortex of a macaque monkey performing a fixation task. Neuronal responses were obtained from two cell groups with different directional preferences. The figure shows cross-correlograms and peri-stimulus-time histograms for four different stimulation conditions. The small insets indicate the receptive field locations (1,2) with respect to the fixation point, F, and the directional preference of the neurons (small arrows). (a) A single moving stimulus bar, whose direction of motion was intermediate between the neurons' preferences, led to a pronounced synchronization of the two cell groups, as indicated by the central maximum in the cross-correlogram. (b) Presentation of two stimuli moving in the respective preferred directions of cell group 1 and 2 abolishes synchronization. (c, d) The synchronization observed with a single stimulus does not depend on its particular orientation. (c) Changing orientation and direction of motion by 15° or (d) using one of the bars from the configuration in (b) had little influence on synchronization. Scale bars for the peri-stimulus-time histograms correspond to 40 spikes s^{-1} . The continuous line superimposed on the correlograms represents a damped cosine function that was fitted to the data to assess the significance of the correlogram modulation. (Modified from Kreiter & Singer (1996).)

did not exhibit any consistent phase relations. This close correspondence between the execution of an attention-demanding visuo-motor performance and the occurrence of zero phase-lag synchrony suggests a functional role of this temporal patterning. One possibility is that the synchronization observed during the preparatory period reflects an entrainment of activity into a temporal pattern that is common to selected cortical areas so as to facilitate the rapid temporal coordination of signals once the stimulus has become available. Attentional mechanisms could impose a coherent subthreshold modulation on neurons in cortical areas that need to participate in the execution of the anticipated task, thereby permitting the rapid synchronization of selected responses by using the synchronizing mechanisms described above. According to this scenario, the attentional mechanisms would induce what one might call a state of expectancy in the respective cortical areas by imposing on them a specific, task-related dynamic activation pattern that then, once

stimulus-driven input becomes available, acts like a dynamic filter causing the rapid synchronization of selected responses, thereby accomplishing the required grouping and binding of responses.

(c) Perception

In a series of visual experiments, attempts have been made to find correlations between perceptual disturbances and abnormalities in neuronal synchronization. Kittens were made strabismic shortly after eye opening, resulting in an inability to group the signals generated by the two eyes into a coherent percept.

This inability is reflected by the failure of neurons driven by the two eyes to synchronize their responses even if these are evoked by a single object (König *et al.* 1993). A likely reason for the disruption of response synchronization is that the tangential intracortical connections between neurons driven by different eyes are lost during early development owing to consistent

decorrelation of the responses evoked from the two eyes (Löwel & Singer 1992). In animals that had not developed amblyopia, hence normal monocular vision in both eyes, synchronization between neurons driven by the same eye was normal with respect to its frequency of occurrence, stimulus specificity and strength.

A subgroup of the strabismic animals developed in addition a syndrome called strabismic amblyopia. Subjects suffering from strabismic amblyopia, and this is true for both animals and humans, have reduced visual acuity in the amblyopic eye. Moreover, they have difficulties in identifying figures if these are embedded in a contour-rich background, suggesting problems with perceptual grouping. In these amblyopic animals there was a close correlation between perceptual deficits and abnormalities in response synchronization but there was no evidence for abnormalities in the response properties of individual cells. Quite unexpectedly, neurons in the primary visual cortex responded equally well to visual stimuli, irrespective of whether these were shown to the normal or to the amblyopic eye. Thus neurons driven by the amblyopic eye continued to respond vigorously to gratings that the animals had not been able to resolve with this eye during previous behavioural testing. Responses mediated by the normal and the amblyopic eye showed no difference in their amplitude-specific or feature-specific tuning, irrespective of the spatial frequency of the applied test gratings. The only significant difference was the reduced ability of neurons driven by the amblyopic eye to synchronize their responses; this difference was particularly pronounced when the spatial frequency of the grating stimuli approached the range beyond which the animals had no longer been able to resolve gratings with the amblyopic eye (Roelfsema *et al.* 1994). In area 17, there is therefore a close correlation between a specific perceptual deficit and alterations in synchronization; this relationship could very well be causal. If synchronization is used to group responses together and to label them for further joint processing, one expects that disturbances in synchronization should lead to disturbances in perceptual grouping, such as occur for interocular binding operations in all strabismic animals and for monocular grouping operations in animals suffering from strabismic amblyopia. Because reduced synchronization is likely to reduce the saliency of responses conveyed by the amblyopic eye, it can also account for the fact that the amblyopic eye consistently loses in interocular competition when both eyes are open. Here, then, is a clear case in which the firing of neurons in a cortical area does not correspond to perception, suggesting that the firing of individual neurons is only a necessary, but not a sufficient, condition to support perception. Additional, and in this case indispensable, information seems to be conveyed by the precise temporal relations between the discharges of simultaneously active neurons.

Another close correlation between response synchronization and perception and a remarkable dissociation between individual responses and perception has been found in experiments on binocular rivalry. When the two eyes are presented with patterns that cannot be fused into a single coherent percept, the two patterns are perceived in alternation rather than as a superposition of their components. As demonstrated by Logothetis *et al.* (1996),

some of this rivalry might be due to competition between the figural representations of the different patterns rather than to competition between the inputs from the two eyes. However, a clear case of interocular competition that is not contaminated by additional figural rivalry is observed in strabismic subjects. Owing to experience-dependent modifications of processing circuitry (see above), perception always alternates between the two eyes, irrespective of the similarity of the patterns presented to the two eyes. This implies that there is a central gating mechanism that selects in alternation the signals arriving from the two eyes for further processing. Interocular rivalry is thus a suitable paradigm for investigating the neuronal correlates of dynamic response selection, a process closely related to the formation of assemblies.

This paradigm has been applied to investigate how neuronal responses that are selected and perceived differ from those that are suppressed and excluded from supporting perception. Multi-unit and field potential responses were recorded with chronically implanted electrodes from up to 30 sites in cat primary visual cortex while the animals were exposed to rivalrous stimulation conditions (Fries *et al.* 1997b). Because the animal performs tracking eye movements only for the pattern that is actually perceived, patterns moving in opposite directions were presented dichoptically to determine from the optokinetic tracking response which of the two eyes was selected. The outcome of these experiments was surprising: the discharge rate of neurons in areas 17 and 18 failed to reflect the suppression of input from the respective non-dominant eye. A close and highly significant correlation existed, however, between changes in the strength of response synchronization and the outcome of rivalry. Cells mediating responses of the eye that won in interocular competition increased the synchronicity of their responses on introduction of the rivalrous stimulus, whereas the reverse was true for cells driven by the eye that became suppressed. Thus, in this particular case of competition, selection of responses for further processing seems to be achieved by raising their saliency through synchronization rather than by enhancing discharge frequency. Likewise, suppression is not achieved by inhibiting responses but by desynchronization (figure 2).

As in the amblyopic animals there is thus a remarkable dissociation, at least in primary visual areas, between perception and the discharge rate of individual neurons. Cells whose responses are not perceived and are excluded from controlling behaviour respond as vigorously as cells whose responses are perceived and support behaviour. This dissociation is particularly stringent in rivalry because here responses to physically unchanged stimuli were recorded from the same neurons before and after introducing the rivalrous stimulus. Responses could be followed continuously while they passed from a condition in which they were readily perceivable to a condition in which they either continued to support perception despite rivalry or became excluded from perception. Another puzzling result of the rivalry study is that responses that win the competition increase their synchronicity on presentation of the rivalrous stimulus. This suggests the action of a mechanism that enhances the saliency of the selected responses by improving their synchronicity so as

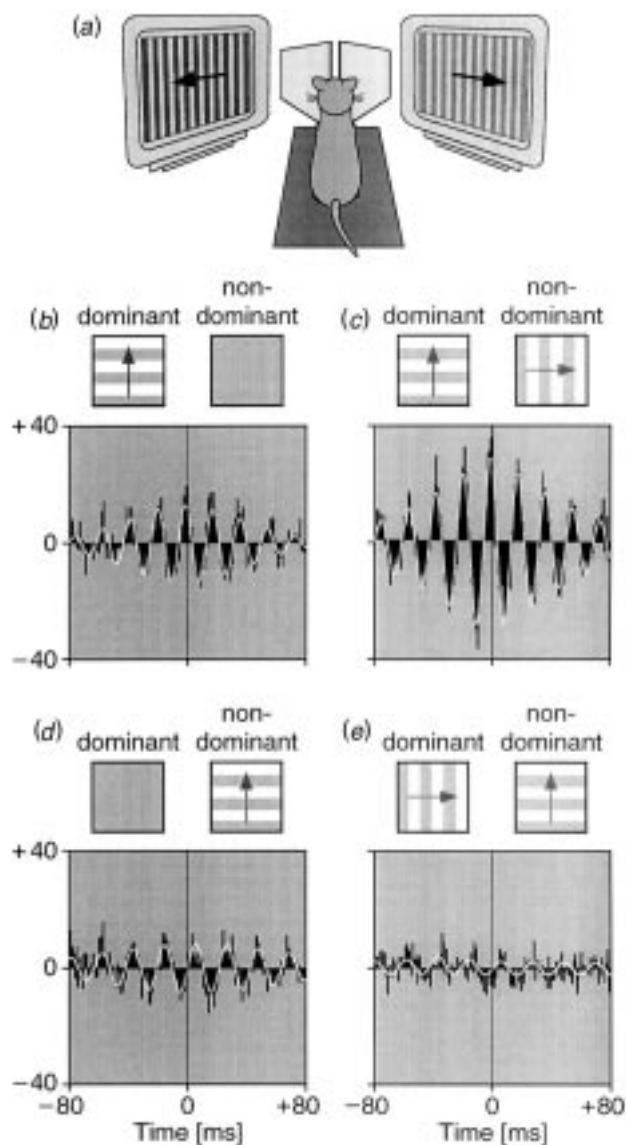


Figure 2. Neuronal synchronization under conditions of binocular rivalry. (a) Using two mirrors, different patterns were presented to the two eyes of strabismic cats. (b–e) Normalized cross-correlograms for two pairs of recording sites activated by the eye that won (b, c) or lost (d, e) in interocular competition, respectively. Insets above the correlograms indicate stimulation conditions. Under monocular stimulation (b), cells driven by the winning eye show a significant correlation that is enhanced after introduction of the rivalrous stimulus to the other eye (c). The reverse is true for cells driven by the losing eye (compare conditions (d) and (e)). The white continuous line superimposed on the correlograms represents a damped cosine function fitted to the data. RMA, relative modulation amplitude of the centre peak in the correlogram, computed as the ratio of peak amplitude over offset of correlogram modulation. This measure reflects the strength of synchrony. (Modified from Fries *et al.* (1997b).)

to protect them against the interference caused by the rivalrous stimulus.

These results provide direct support for the hypothesis that precise temporal relations between the discharges of spatially distributed neurons matter in cortical processing and that synchronization might be exploited to jointly raise the saliency of the responses selected for further

processing. The important point here is that this selection can obviously be achieved without inhibiting the non-selected responses. Thus, in principle, it should be possible to select a second group of responses by synchronizing them independently of the first. The result would be two coexisting, but functionally distinct, assemblies at the same processing level. The example of rivalry also illustrates how synchronization and rate modulation depend on each other. The signals from the suppressed eye failed to induce tracking eye movements, indicating that eventually the vigorous but poorly synchronized responses in primary visual areas failed to drive the neurons responsible for the execution of eye movements. Thus changes in synchronicity result in changes of response amplitudes at subsequent processing stages. This convertibility provides the option to use both coding strategies in parallel to encode complementary information (see above).

In conclusion, the data reviewed in this section indicate that the evaluation of internally generated correlation patterns between responses of simultaneously recorded neurons permits the extraction of information about stimulus configurations, behavioural states and perception that cannot be obtained by analysing the responses of individual neurons sequentially. The relevant variable containing this additional information is the rather precise synchronization of a fraction of the discharges constituting the respective responses. The data indicate further that responses containing synchronized epochs have a higher probability of being processed further and eventually to be perceived than responses lacking such synchronized epochs, supporting the hypothesis that synchronization is used as a mechanism for response selection. Because synchronization necessarily involves at least two neurons, it inevitably raises simultaneously the saliency of more than one response. It is thus well suited to select subsets of responses for further joint processing, thereby defining the group of selected responses as related. Thus synchronization fulfils the requirements postulated for a binding mechanism that selects from a larger number of simultaneously active neurons a subset and labels the responses of this subset in a way that favours joint processing at the subsequent processing stage. The evidence that synchronization probability reflects Gestalt criteria that guide perceptual grouping supports the hypothesis that synchronization serves as a binding mechanism in the context of assembly formation by jointly raising the saliency of selected subsets of responses.

7. THE GENERALITY OF SYNCHRONICITY

Studies in non-visual sensory modalities and in the motor system indicate that synchrony and oscillatory activity might be ubiquitous in the nervous system. Synchronization in the γ -frequency range occurs in the olfactory system of various vertebrate and invertebrate species, where it has been related to the processing of odour information (reviewed by Laurent (1996)). In the auditory cortex, synchronized γ -oscillations have been described both in humans (reviewed by Joliot *et al.* (1994)) and in animals (Eggermont 1992; de Charms & Merzenich 1996). In the somatosensory system, synchronized oscillatory activity in this frequency range has recently been described both in the cat (Steriade *et al.*

1996) and in the monkey (Murthy & Fetz 1996). Furthermore, synchronized oscillatory firing has been observed in other systems such as the hippocampus (Buzsáki & Chrobak 1995) and the frontal cortex (Vaadia *et al.* 1995).

Similar evidence is available for the motor system, where neural synchronization in the γ -frequency range has been discovered in cats (Steriade *et al.* 1996), monkeys (Murthy & Fetz 1996; Sanes & Donoghue 1993) and humans (Kristeva-Feige *et al.* 1993). The putative functional role of oscillatory activity and its temporal coordination is supported further by the dynamics of so-called central pattern generators. These consist of networks of coupled oscillators, in the brain stem and spinal cord of vertebrates and in the nervous system of invertebrates, that are involved in the execution of basic motor programs (Grillner *et al.* 1991). Although in these cases the frequency of rhythmic activity is far below the γ -range, the principles of pattern generation seem similar. The same sets of neurons can be used to generate a large diversity of different patterns by changing the coupling strength between oscillatory modules and by modulating oscillation frequencies.

Remarkably, there is evidence suggesting that synchrony might also have a role in sensorimotor integration. In awake behaving monkeys, task-dependent synchronization between units distributed across sensory and motor cortical areas and within motor cortex itself has been reported (Murthy & Fetz 1996; Sanes & Donoghue 1993; Hatsopoulos *et al.* 1997; Ojakangas *et al.* 1997; Riehle *et al.* 1997). Thus synchrony also seems to have a role in visuomotor coordination and in the programming of motor responses. As proposed previously, it might be instrumental for the flexible channelling (binding) of sensory signals to particular motor programs (Roelfsema *et al.* 1996).

Synchronization also seems to have a role in the linkage between cortical assemblies and subcortical target structures such as the superior colliculus. This possibility is suggested by the existence of precise temporal relationships between the discharges of neurons in areas of the visual cortex and the superior colliculus (Brecht *et al.* 1998). In these experiments it was shown that cortico-tectal interactions are strongly dependent on the temporal coherence of cortical activity. If cortical neurons engage in synchronous oscillatory activity either with partners within the same cortical area or with cells in other cortical areas, their impact on tectal cells is enhanced, indicating that tectal cells are driven more effectively by synchronous than by asynchronous cortical activity. This finding is consistent with the idea that the temporal organization of activity patterns has an important role in defining the output of the cortex.

Taken together, available evidence suggests that comparable synchronization phenomena are found in a large number of different functional systems. It therefore seems justified to generalize the results obtained in the visual cortex and to suggest that temporal coordination of discharges might be of general relevance for neural information processing. Importantly, there is increasing evidence that dynamic synchronization, in particular at frequencies in the γ -band, occurs also in the human brain. EEG studies have provided evidence for the precise

synchronization of activity in the γ -frequency range in human visual cortex that is related to perception and reflects the subjective coherence of stimulus arrangements (Tallon-Baudry *et al.* 1996).

8. SYNCHRONICITY AS A GENERAL CODE FOR RELATEDNESS

If synchronicity serves as the signature of relatedness, synchronized responses should be interpreted as being related, irrespective of the cause of synchronization. Psychophysical evidence supports this conjecture, indicating that synchronously presented stimuli are bound perceptually and interpreted as elements of the same figure with greater probability than texture elements appearing asynchronously (Leonards *et al.* 1996; Leonards & Singer 1997, 1998 (but also see Kiper *et al.* 1996)). Hence, the synchronicity of responses imposed by texture elements appearing simultaneously (stimulus-locked synchronization) seems to be exploited for perceptual grouping. It is unlikely that processing stages beyond primary visual cortex distinguish between externally induced and internally generated synchrony. Because the psychophysical results indicate that the former is interpreted as a signature of relatedness, it would be puzzling if this were not also true for internally generated synchrony. The most parsimonious assumption is that synchronization serves as a general tag of relatedness, irrespective of whether it results from the coincidence of external events or from internal grouping operations. Another example of a putative grouping by synchronization in simple feedforward processing is the intraretinal synchronization of responses to continuous stimuli (Neuenschwander & Singer 1996). By influencing the synchronization probability of cortical neurons (Castelo-Branco *et al.* 1996), this early, internally generated, signature of relatedness could bias the subsequent feature-dependent grouping operations in the visual cortex.

Thus synchronization could serve as a general tag of relatedness both in simple feedforward processing and assembly coding, and it is likely that this tagging occurs over quite different temporal and spatial scales at different levels of processing. Synchronization caused by internal interactions is usually associated with an oscillatory patterning of responses, in which the frequency of these oscillations tends to decrease as one proceeds from low to high processing levels. It ranges from up to 100 Hz in the retina to as low as 7 Hz in the infero-temporal cortex of the monkey (Freiwald *et al.* 1998). This indicates that grouping operations can occur at different rates and suggests the possibility of a temporal nesting of grouping results. Cell groups located at different levels of the processing hierarchy can have a fraction of their discharges synchronized, even if they oscillate at different, non-harmonically related, frequencies (Castelo-Branco *et al.* 1996). Moreover, synchronization across levels need not be transitive and can be graded; for instance, group A can be synchronized to group B and group B can be synchronized to group C without group B having to be synchronized to group A (Roelfsema *et al.* 1996, 1997). Because the time interval over which a particular relation is defined by synchronicity is longer when synchronization occurs on the basis of slow rather than fast oscillations,

it should, in principle, be possible to define graded and hierarchically structured relations between grouping operations that occur at different spatial and temporal scales at different levels of the processing hierarchy. Such nesting could contribute to solving the problem of representing the compositionality of perceptual objects (Roelfsema *et al.* 1997), a problem that arises from the fact that complex objects consist of parts that are all independently recognizable and at the same time are perceived as being specifically related components of a single object.

9. CONCLUSION

The hypothesis defended here made the following assumptions: (i) phenomenal awareness necessitates and emerges from the formation of metarepresentations; (ii) these are realized by the addition of cortical areas of higher order that process the output of lower-order areas in the same way as these process their respective input; (iii) to account for the required combinatorial flexibility these metarepresentations are implemented by the dynamic association of distributed neurons into functionally coherent assemblies rather than by individual specialized cells; (iv) the binding mechanism that groups neurons into assemblies and labels their responses as related is the transient synchronization of discharges with a precision in the millisecond range; and (v) the formation of such dynamically associated, synchronized cell assemblies requires activated brain states characterized by a 'desynchronized' EEG and is facilitated by attentional mechanisms. The first assumption differs from the others because it is a conceptual premise that by itself does not provide any experimentally testable predictions; however, each of the following subordinate assumptions leads to predictions about structural and functional features of brains capable of generating metarepresentations. The data reviewed above illustrate that there is supportive experimental evidence for many of these features. However, we are lacking the proof that the observed features actually serve the function that our theories assign to them. This is true not only for the more recently discovered functional properties such as the transient synchronization of distributed neuronal responses, but also for the rate-modulated discharges of individual neurons. As long as we have no complete theory on the structure of neuronal representations, it cannot be decided whether a sequence of discharges of a particular unit signifies that this unit participates in an assembly that lasts as long as the sequence of discharges, whether the unit participates in several different, successively organized, assemblies, or whether it represents a content on its own. This uncertainty is due to the difficulty in identifying assemblies. Assemblies can be identified only if one succeeds in recording simultaneously from a sufficiently large fraction of neurons actually participating in a particular assembly. For reasons detailed elsewhere (Singer *et al.* 1997) this is technically very demanding; attempts at identifying assemblies are therefore still at the very beginning. Thus, if it is true that the generation of the metarepresentations required for consciousness involves the organization of highly distributed assemblies, we are a long way from the direct identification of the

neuronal correlates of even the simplest forms of consciousness.

As long as analysis remains confined to the activity of individual neurons it will remain difficult to decide whether a recorded response is only a necessary condition for consciousness or whether it is sufficient. Obviously, neurons need to discharge to convey information; if a group of neurons in a particular transmission chain stops responding, the content conveyed by that group of neurons cannot be perceived. Hence, correlations between perceptual awareness and cellular responses indicate only that the discharges of cells at a particular processing stage are necessary for a particular content to reach the level of awareness. To find out whether additional conditions have to be fulfilled, e.g. the binding of these responses into widely distributed assemblies, variables need to be determined that permit the assessment of order parameters beyond the level of single units. This can only be achieved with recording techniques that disclose the spatio-temporal activation profile of large numbers of neurons. The fact that the most global of these methods, the EEG, differentiates quite reliably between brain states in which consciousness is or is not possible favours the hypothesis that the generation of consciousness-supporting metarepresentations requires the coordination of activity well beyond the level of single-cell firing. Consciousness manifests itself only during brain states characterized by 'desynchronized' EEG. These states, in turn, favour the occurrence of γ -oscillations and long-distance synchronization of neuronal responses with a precision in the millisecond range. It therefore seems not unreasonable to pursue the hypothesis that the metarepresentations required for phenomenal awareness to manifest itself consist of large assemblies of distributed neurons whose signature of relatedness is the internally generated synchronicity of discharges.

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