Dynamic Formation of Functional Networks by Synchronization

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The cerebral cortex consists of numerous, densely interconnected, functionally specialized areas that need to cooperate in ever-changing constellations depending on the actual cognitive or executive task. One way to achieve this dynamic coordination could be phase-locking of synchronized oscillatory activity. In this issue of *Neuron*, Hipp et al. provide supportive evidence by analyzing EEG signals associated with an ambiguous audiovisual discrimination task.

The cerebral cortex of mammals and in particular of primates is organized into a large number of functionally specialized areas that need to cooperate in a context- and goal-directed way in order to support cognitive and executive functions. Meta-analyses of anatomically identified cortico-cortical connections as well as investigations of effective connectivity with multisite recordings of electrical activity or functional magnetic resonance imaging (fMRI) indicate that the cortical connectome has small-world properties. Small-world network architectures assure that all nodes in the network can communicate with each other via pathways with minimal length and minimal number of intervening nodes (for review see Sporns and Koetter, 2004).

Nothing, however, comes without price. In such a highly connected system, the flow of signals has to be constrained and coordinated in a task-dependent way. Thus, from instance to instance communication among the nodes of the network needs to be gated in order to allow for the selection of relevant sensory information and the configuration of functional networks that are optimally adapted to the respective behavioral goal. This requires dynamic control of information flow on timescales of tens to a few hundreds of milliseconds within the dense network of fixed anatomical connections. As a consequence the efficiency of the connections needs to be continuously adjusted.

There are numerous options to dynamically modify the gain of neuronal connections: both the efficiency of synapses and the responsivity of postsynaptic neurons can be changed by multiple mechanisms that operate at various timescales and in a use-dependent manner. In addition, there are computational strategies to effectively gate communication among neurons. A connection can be rendered more effective if its discharges occur at higher frequencies (temporal summation) or coincide with those of other connections converging onto the same target cell (spatial summation). Likewise, the excitatory input can be made ineffective if it coincides with simultaneously arriving inhibitory events that shunt or hyperpolarize the postsynaptic neuron.

More recently, a complementary mechanism has been proposed that combines saliency enhancement with synchronization (spatial summation) and vetoing of transmission by synaptic inhibition. This proposal has evolved from the evidence that cortical neurons, when engaged in processing, get entrained into oscillatory activity in the beta and gamma frequency range (Gray et al., 1989). Distinct networks of inhibitory interneurons serve as pacemakers for these oscillations. These networks tend to oscillate in characteristic frequency ranges due to mutual interactions via chemical and electrical synapses. Because these interneurons are reciprocally coupled to excitatory principal cells in their vicinity, both groups of neurons engage in synchronized oscillatory discharges (for review see Kopell et al., 2000 and Buzsáki and Draguhn, 2004). Furthermore, the local oscillators can synchronize with other oscillating cell groups via reciprocal cortico-cortial connections (Engel et al., 1991). Because the inward and outward currents caused by the regular alternation of synchronized EPSPs and IPSPs summate effectively, they give rise to an oscillating local field potential (LFP) (Gray and Singer, 1989). Thus, when engaged in oscillatory activity, neuronal responsiveness to excitatory input varies periodically, being maximal around the depolarizing peak and minimal when the membrane is subsequently shunted by the massive synchronized inhibitory volley. As a consequence, oscillating cells are able to listen to the messages sent by other cells only during a narrow window of opportunity (Fries, 2005; Fries et al., 2007). The duration of this window is inversely proportional to the oscillation frequency and at high gamma frequencies may be as short as a few milliseconds. Hence, the information flow between cell groups oscillating at the same frequency can be gated very effectively by shifting the phase relations (Womelsdorf et al., 2007).

This gating mechanism is attractive for several reasons: investigations of networks consisting of coupled oscillators indicate that phase shifts can be accomplished very rapidly and with minimal investment of energy. Moreover, if oscillations occur at different frequencies—which is the case in cerebral cortex—coupling can be gated differentially and in parallel between a large number of different nodes of the network, thus allowing for the coexistence of several subnetworks that can remain functionally isolated from each other and still share the same anatomical backbone. Finally, by concatenating different rhythms, nested relations can be established among simultaneously

active subnetworks (Roopun et al., 2008). Despite the fact that dynamic coordination of neuronal interactions by phase adjustment exploits well-established mechanisms of spatial summation and inhibitory gating, direct evidence for its involvement in cortical functions has so far been sparse.

In this issue of *Neuron*, a study by Hipp et al. (2011) based on high-density EEG recordings from human subjects provides supportive evidence for the dynamic configuration of networks through phase-locking of synchronized oscillations. The authors developed a new analysis method based on a combination of beam forming procedures and cluster permutation statistics that allows an unbiased search for synchronized networks across the entire human brain. The subjects' task was to judge the configuration of an ambiguous audiovisual stimulus consisting of two approaching bars that crossed over and then continued to move apart from each other. At the moment of contact a click sound was played. Perception of this stimulus spontaneously alternates between two bars bouncing off each other or passing one another, the addition of the click increasing the relative frequency of the bouncing percept, which indicates polymodal integration.

In accordance with previous MEG studies, the authors find that the stimulus induces a tonic increase of high gamma band activity (64–128 hz) over most of the visual cortex, suggesting that their methods of source analysis greatly improved the spatial resolution of the EEG signals. Comparing cortico-cortical coherence at the source level between stimulation and baseline periods revealed a highly structured cortical network that showed enhanced beta band coherence (15–23 hz) during stimulation. This network comprised extra striate visual areas, frontal regions covering the frontal eye fields, and posterior parietal and temporal cortices. Most importantly, the authors found that beta synchrony was not only enhanced during stimulus processing, but also predicted the subjects' percept of the stimulus. When bouncing and passing trials were contrasted, it was found that bounce trials were associated with enhanced beta coherence, and receiver operating characteristic (ROC) analysis revealed that this relation held at a single-trial level and that the enhanced beta synchrony preceded the actual crossing of the bars. Interestingly, this perception predicting modulation of synchrony was inversely related to beta power. This is compatible with the frequent observation that synchronization of spike trains is often associated with either no change or even a decrease in discharge frequency (Gray et al., 1989).

While the network defined by beta coherence was determined relative to baseline, the direct comparison of bounce and pass percepts revealed another left hemispheric network consisting of central and temporal regions that showed significantly stronger high gamma band coherence for bounce trials. Interestingly, these percept-dependent changes in gamma synchronization were negatively correlated with the effect that the click had on biasing the percept. Subjects that were strongly influenced by the click showed less gamma modulation than subjects for which the additional click had little influence on the percept. The authors interpret this as suggesting that subjects who constitutively attribute less significance to the auditory stimulus have to invest more in dynamic binding operations.

In conclusion, this study provides a novel methodological framework for the characterization of interactions in a full pairwise cortico-cortical space that can be applied to any bivariate parameter field. Moreover, the results provide further evidence for the functional relevance of phase-locking across large-scale cortical networks in that they establish direct relations between the magnitude of synchronization and the outcome of a bistable perceptual task. As perceiving the bounce requires more cross-modal integration than perceiving the pass, the increase in phase-locking both in the beta and in the gamma network is compatible with the hypothesis that synchronization serves dynamic coordination of interactions.

While the present results establish compelling relations between network synchronization and perception and even show that measures of the former predict the latter, much of the presented evidence is still correlative in nature. However, in this respect studies on oscillations and synchrony are not that different from those on relations between spiking activity and behavior, where, here too, with the notable exception of a few studies (see i.e. Salzman et al., 1992), most of the evidence is correlative. Badly needed are methods that allow one to selectively modulate oscillation frequencies and/or phase relations without affecting other response variables and to demonstrate that these manipulations influence behavior in a predicted way. While there is no shortage of methods for modulating oscillation dynamics, with a few exceptions their ability to influence the relevant variables has not been examined systematically. Weak electrical stimuli as well as transcranial magnetic stimulation can be used to reset oscillations and thereby induce phase shifts. Oscillatory networks can also be slaved to a particular frequency by applying weak alternating electrical fields. These procedures have been validated in vitro and in vivo (Fröhlich and McCormick, 2010; Ozen et al., 2010), but they have not yet been applied in a behavioral context. Finally, there have been successful attempts using optogenetic stimulation methods to induce gamma oscillations in vivo, and these experiments have shown that enhanced gamma oscillations increase the precision of the timing of neuronal discharges in the whisker system (Cardin et al., 2009). It is mandatory now to examine how such manipulations affect behavioral performance. However, this should not detract from the necessity to further investigate correlations between oscillations, synchrony, phase relations, and behavior, as we also have come a long way by contenting ourselves with correlative evidence on the relation between single-unit activity and cognitive and executive functions.

Another intriguing question related to the present study of Hipp et al. concerns the supraordinate mechanisms that orchestrate the dynamic coordination of functional networks. This question is usually answered by referring to attentional mechanisms. In the case of bottom-up modulation of attention, we have a handle on some of the mechanisms, but when it comes to top-down causation, we by and large ignore how the effects observed along sensory processing streams are initiated and mediated. At the present stage we are

left with the unsatisfactory notion that functional networks obviously self-organize in a context- and goal-dependent way and that the driving forces for these self-organizing processes must somehow be the result of an interplay between the functional architecture of the system, the ongoing activity patterns, the actually impinging stimuli, and some set-defining instructions kept in working memory. Thus, much is left to be done, and it seems obvious that advances at this high-systems level will require massive parallel recording of distributed neuronal activity and the application of sophisticated mathematical procedures for the interpretation of the obtained data—along the lines followed in the paper by Hipp et al. (2011).

REFERENCES

Buzsáki, G., and Draguhn, A. (2004). Science *304*, 1926–1929.

Cardin, J.A., Carlén, M., Meletis, K., Knoblich, U., Zhang, F., Deisseroth, K., Tsai, L.-H., and Moore, C.I. (2009). Nature *459*, 663–667.

Engel, A.K., Koenig, P., Kreiter, A.K., and Singer, W. (1991). Science *252*, 1177–1179.

Fries, P. (2005). Trends Cogn. Sci. *9*, 474–480.

Fries, P., Nikolic, D., and Singer, W. (2007). Trends Neurosci. *30*, 309–316.

Fröhlich, F., and McCormick, D.A. (2010). Neuron *67*, 129–143.

Gray, C.M., and Singer, W. (1989). Proc. Natl. Acad. Sci. USA *86*, 1698–1702.

Gray, C.M., Koenig, P., Engel, A.K., and Singer, W. (1989). Nature *338*, 334–337.

Hipp, J.F., Engel, A.K., and Siegel, M. (2011). Neuron *69*, this issue, 387–396.

Kopell, N., Ermentrout, G.B., Whittington, M.A., and Traub, R.D. (2000). Proc. Natl. Acad. Sci. USA *97*, 1867–1872.

Ozen, S., Sirota, A., Belluscio, M.A., Anastassiou, C.A., Stark, E., Koch, C., and Buzsáki, G. (2010). J. Neurosci. *30*, 11476–11485.

Roopun, A.K., Kramer, M.A., Carracedo, L.M., Kaiser, M., Davies, C.H., Traub, R.D., Kopell, N.J., and Whittington, M.A. (2008). Frontiers Neurosci. *2*, 145–154.

Salzman, C.D., Murasugi, C.M., Britten, K.H., and Newsome, W.T. (1992). J. Neurosci. *12*, 2331–2355.

Sporns, O., and Koetter, R. (2004). PLOS Biol. *2*, e369.

Womelsdorf, T., Schoffelen, J.-M., Oostenveld, R., Singer, W., Desimone, R., Engel, A.K., and Fries, P. (2007). Science *316*, 1609–1612.