

Dynamic Network Communication as a Unifying Neural Basis for Cognition, Development, Aging, and Disease

Bradley Voytek and Robert T. Knight

ABSTRACT

Perception, cognition, and social interaction depend upon coordinated neural activity. This coordination operates within noisy, overlapping, and distributed neural networks operating at multiple timescales. These networks are built upon a structural scaffolding with intrinsic neuroplasticity that changes with development, aging, disease, and personal experience. In this article, we begin from the perspective that successful interregional communication relies upon the transient synchronization between distinct low-frequency (<80 Hz) oscillations, allowing for brief windows of communication via phase-coordinated local neuronal spiking. From this, we construct a theoretical framework for dynamic network communication, arguing that these networks reflect a balance between oscillatory coupling and local population spiking activity and that these two levels of activity interact. We theorize that when oscillatory coupling is too strong, spike timing within the local neuronal population becomes too synchronous; when oscillatory coupling is too weak, spike timing is too disorganized. Each results in specific disruptions to neural communication. These alterations in communication dynamics may underlie cognitive changes associated with healthy development and aging, in addition to neurological and psychiatric disorders. A number of neurological and psychiatric disorders—including Parkinson's disease, autism, depression, schizophrenia, and anxiety—are associated with abnormalities in oscillatory activity. Although aging, psychiatric and neurological disease, and experience differ in the biological changes to structural gray or white matter, neurotransmission, and gene expression, our framework suggests that any resultant cognitive and behavioral changes in normal or disordered states or their treatment are a product of how these physical processes affect dynamic network communication.

Keywords: Anxiety, Autism, Coherence, Coupling, Depression, Gamma, Network dynamics, Neural oscillations, Parkinson's disease, Schizophrenia, Theta

<http://dx.doi.org/10.1016/j.biopsycho.2015.04.016>

A complete model of cognitive function and dysfunction must account for a diversity of factors including, but not limited to, brain structure and genetics, rapid neuronal temporal dynamics and neuroplasticity, and developmental and sociological considerations (1,2). Cognition is critically reliant upon the dynamic, parallel coordination of large groups of neurons separated by substantial neural distances. This coordination is surprisingly flexible but remarkably precise (3), especially considering behavior emerges in an inherently noisy electrochemical neuronal environment (4).

We propose a theory for how disruptions to dynamic network communication can lead to the neurocognitive changes observed during development and aging, as well as in neurological and psychiatric disorders. Our theory is predicated on evidence that neuronal oscillations bias the probability of spiking such that action potentials are more likely to occur during periods of interregional oscillatory coherence. We extend this by arguing that such oscillatory-mediated spike synchrony would feed back onto the local field potential (LFP), increasing LFP coherence. In the pathologic case, we theorize that this mechanism results in an

exaggerated state of overcoupling. To break cycles of LFP-induced spike synchrony causing reinforced LFP coherence causing even stronger spike synchrony, some controlling or interfering mechanism needs to be introduced. We posit that one mechanism may be neural noise, defined as temporally decorrelated spikes occurring during nonpreferred LFP oscillatory phases.

This dynamic network communication framework differs from purely structural or neurochemical accounts in that, although neural architecture and neurochemistry play a critical role in cognitive functioning by providing the scaffolding upon which the dynamic communication system is built, structure and chemistry alone are insufficient for understanding neuronal dynamics (2,5); ultimately, cognition reduces to the dynamics of neural communication.

In this article, we begin by reviewing the evidence for the causal role of oscillatory interregional communication in support of healthy cognition and present an accounting for the possible neurophysiological basis for such a communication mechanism. We then explore the consequences of alterations to network communication dynamics, including both failures

to establish and failures to break an oscillatory communication network. We then argue that these changes might be observable in mesoscale or even macroscale electrophysiological recordings, reflected in specific components of the power spectral density (PSD). We conclude by presenting a theoretical framework for how these disruptions to network communication dynamics provide a unifying framework for understanding a variety of neurological and psychiatric disorders in terms of neuronal activity, using Parkinson's disease, depression, anxiety, schizophrenia, and autism as exemplar cases. Thus, we argue that the resultant behavioral syndrome of any structural or neurochemical changes associated with development, aging, experience, and disease are manifested by their effect on dynamic network communication.

OSCILLATORY COMMUNICATION

Oscillations Bias Spiking Activity

Neural oscillations are (usually) lower frequency (< 80–100 Hz) and play a causal role in neural communication, cognition, and behavior (6,7) (though there exists rhythmic activity at higher frequencies, such as hippocampal ripples). Research into the functional role of scalp electroencephalography (EEG) and magnetoencephalography oscillations shows that ongoing visual cortical oscillatory phase (8–10) and power (11,12) predict performance on a variety of tasks (13–16). For example, people are more likely to correctly respond to target visual stimuli when those stimuli appear during the preferred phase or power of ongoing oscillatory activity, perhaps due to ongoing oscillatory phase biasing neuronal excitability (9).

In more causal direct tests on spiking activity, experiments have shown that applying relatively weak, low-amplitude oscillatory electric fields bias neuronal firing. This finding, known as ephaptic coupling (6,17), shows that subthreshold changes in extracellular electric fields affect the transmembrane voltage of nearby neurons. Experimental manipulations using exogenous oscillatory electric fields have found that low-frequency oscillatory stimulation (< 2 Hz) can entrain cortical—or even hippocampal—neurons in proportion to the

stimulation intensity and behavioral state of the animal (18). Similarly, oscillatory gamma (~30 Hz) hippocampal stimulation affects cornu ammonis 1 pyramidal spike timing, locking spikes to the phase of the stimulation oscillation (19). The authors of that report argue that a decoherent extracellular field could lead to less temporally correlated spiking, which could act as a “safety mechanism to prevent hypersynchronization.” This interaction between the coherence of the oscillatory field and spiking activity is a critical element in our framework, and we will refer to it throughout this article.

Synchronization and Neural Communication

There are a variety of methods for assessing interregional neural communication depending on the measurement scale and signal source. The LFP, which is the extracellular electrical potential recorded invasively using penetrating electrodes, is influenced by a number of factors including neuronal geometry and laminar depth. Electrical activity recorded either on the cortical surface, such as with electrocorticography (ECoG), or from noninvasive scalp EEG is dominated by postsynaptic potentials. Increases in local population firing rate are reflected by elevated broadband activity in the LFP and ECoG (20–23). This broadband shift is particularly evident in the high-gamma (70–200 Hz) range and less in the low-frequency range, possibly because the lower frequency portion of the PSD is masked by a simultaneous reduction in the oscillatory components of the LFP, which are less directly linked to neural firing rates and may reflect local excitatory-inhibitory circuit motifs (24) (Figure 1).

Interregional communication can be inferred, at the level of the LFP, from the interregional oscillatory phase coherence between two regions (25,26). In functional magnetic resonance imaging (fMRI), the temporal profile of activity in a seed region may be correlated with the activity in other regions (27). Such methods can be generalized as a statistical assessment of how much information the activity in one region provides about the activity in a second region. These methods are used to index neural communication; interestingly, fMRI blood oxygen level-dependent (BOLD) signal correlations may be driven

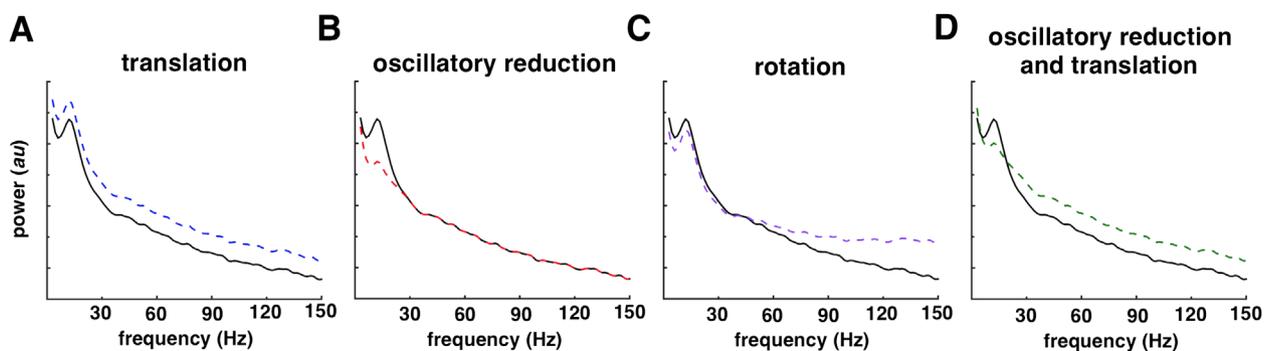


Figure 1. Example power spectral changes. All four plots contain an exemplar power spectral density (PSD) consisting of a $1/f$ process plus an oscillation centered around 12 Hz (solid black lines). This PSD is then modified in four different ways (dashed colored lines). **(A)** In this example, the PSD in black has been modified by simple translation, adding power at all frequencies (blue line). **(B)** Here, the background $1/f$ process remains unaffected; all that has changed is that the 12-Hz oscillation has been reduced in power (red line). **(C)** A single manipulation—rotation of the PSD about a pivot frequency (40 Hz)—results in a simultaneous decrease in low-frequency power and an increase in high-frequency power (purple line). **(D)** Here two separate effects—translation of the PSD and reduction of 12-Hz oscillatory power—have a similar effect as the single rotation process described in **(C)** in that low-frequency power is reduced and high-frequency power is increased [c.f. Miller *et al.* (21)].

by low-frequency LFP oscillatory coupling, which, in turn, affects high gamma activity in the coupling regions (28).

A mechanism for neuronal communication through oscillatory coherence has been proposed (29–31). This theory, dubbed communication through coherence, is predicated on the fact that synaptic input arriving at a postsynaptic neuron is most likely to cause an action potential if the presynaptic activity arrives during the peak of the neuron's excitability relative to an oscillatory membrane potential. In other words, the local oscillatory field biases the probability of neuronal firing, enhancing action potential precision (32) and/or computation (24). This means that the complex interrelationship between oscillatory coupling and local spiking may be necessary for coordinating brain dynamics (33,34).

Phase/Amplitude Coupling

Although the communication through coherence theory is strictly referring to spike/field coupling, given that broadband high gamma likely reflects local population activity and is modulated with the phase of oscillatory LFP, it is plausible that this phase/amplitude coupling (PAC) may be a mesoscale analog of spike/field coupling and ephaptic coupling [when appropriate analytical considerations are accounted for (35)]. We propose that PAC provides a bridge between local microscale (36,37) and systems-level macroscale neuronal ensembles (29,31,38,39) allowing for dynamic network communication (40–43). This assertion is supported by the fact that PAC tracks behavior, including learning (44,45), working memory performance (46), attention (39), and reward processing (47,48) across species (49) [see Johnson and Knight (50) for a review]. Recent evidence suggests that PAC might operate over short (< 500 msec) timescales, providing a mechanism for interregional coordination between the oscillatory local field and broadband gamma (51).

Low-frequency oscillations may be nested within other frequency bands (38,52–55) that themselves interact with one another. The carrier oscillation to which broadband high-gamma activity is coupled depends on brain region and task (56,57). Such complex multiplexing may allow for multiple parallel communication streams, providing a mechanistic basis for neural communication (7,31,58–61). Computational models suggest that this neural communication mechanism is susceptible to noise (62), and with relatively small changes in spiking statistics, such as the temporal autocorrelation of a single unit or synchronization across a local population, could lead to large, nonlinear effects on PAC.

NEURAL COMMUNICATION DISRUPTIONS

Within the proposed dynamic network communication framework, disruptions to communication may arise in three ways: 1) failures to establish communication; 2) inaccuracies and/or noise in the communicated information; and 3) failures to terminate communication. Substantial neuroscientific research has focused on the presence of communication, using a variety of analytical methods such as functional connectivity, coupling/synchronization/coherence, mutual information, and other metrics. We hypothesize that to communicate with fidelity, neuronal ensembles must enter a stage of oscillatory coherence, during which there is a brief window of facilitated spiking (31). Although

the origin of LFP oscillations remains unclear, evidence suggests that LFP oscillations are not epiphenomena arising from neuronal synchrony but may also reflect glial activity, which itself relates to the LFP (63). Given that the extracellular electric field alters neuronal membrane potential (ephaptic coupling), it is reasonable to assert that there is a complex interplay between spiking and LFP oscillatory coupling.

The LFP-mediated alignment of spiking probability itself feeds back onto the local field, increasing LFP coherence. In the pathologic case, we argue that this mechanism results in a state of overcoupling detrimental to effective interregional communication. There is accumulating evidence that neurological and psychological disorders are associated with such pathologic overcoupling (64), wherein two regions that are too strongly coupled are thought to also result in diminished information transfer. We posit that to break this pathologic overcoupling cycle, a controlling or interfering mechanism is needed. One such mechanism may be neural noise, defined as decreased spike/field coupling, or increased spiking during nonpreferred phases of the carrier oscillation, which has been argued to be a plausible mechanism to prevent hypersynchronization (19). This temporal decorrelation feeds back onto the oscillatory activity, weakening LFP coherence, in turn disrupting neural synchrony and so on. We argue that this controlling mechanism can also take a pathologic form, resulting in a runaway state of undercoupling. In the nonpathologic case, this push/pull relationship is a self-correcting mechanism that prevents pathologic coupling on one end and temporally decorrelated spiking noise undercoupling on the other.

MEASURING OSCILLATIONS AND SPIKING

Power Spectral Density

Given the importance that the distinction between oscillatory and spiking portions of the LFP plays in our conceptualization, we will outline the current understanding of the relationship between the LFP and spiking activity. First, the LFP power spectrum contains a mixture of signals, including a background, broadband $1/f^\alpha$ (65–68) process that can be described by two parameters: its slope and offset (69), as well as narrowband peaks that rise above this background $1/f$ activity (70). This means that the oscillatory components must be measured not absolutely but relative to this background $1/f$ activity, the offset and slope of which, we argue, contain meaningful information about the neural activity.

This broadband $1/f$ is different from an oscillation (71), which are narrowband spectral processes within the PSD (70) and which may have a separate neurophysiological mechanism from spiking activity. Low-frequency oscillations have high power and can be recorded at the level of scalp EEG (72). In contrast, high-gamma activity has significantly lower amplitude and is more difficult to detect due to the lower relative signal-to-noise (72). The frequency of a narrowband oscillation can be different from the spike rate of individual neurons within that network (73,74). Example PSDs are shown in Figures 1 and 2.

Inferring Spiking from the Power Spectrum

Power in the low frequencies (< 20 Hz) is negatively correlated with both population spiking activity and fMRI BOLD signal,

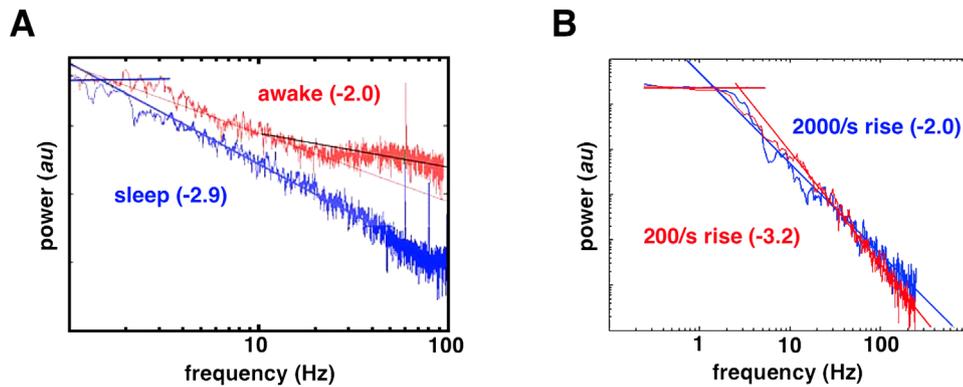


Figure 2. Evidence for spectral slope changes. **(A)** During sleep, the human subdural electrocorticography power spectral density (PSD) has a steep negative slope that flattens (whitens) during wakefulness. **(B)** Simulations of human electrocorticography PSD suggest that PSD slope changes arise as a function of the dendritic response to an input. As the strength of the input increases, more neurons fire simultaneously, forcing a greater local population to become refractory within a shorter time window, increasing the rise time. Thus, for weaker inputs with greater rise times, the slope of the PSD is flatter (blue), whereas for stronger

inputs with smaller rise times, the slope of the PSD is steeper (red). Thus, within our framework, if the dendritic response is driven by ephaptic coupling, the stronger the coupling, the steeper the slope; with weaker ephaptic coupling, spike times are less temporally correlated and the slope is flatter. [Reproduced with permission from Freeman and Zhai (67).]

whereas increases in broadband high-gamma activity are positively correlated with spiking and BOLD (75). Often, event-related decreases in low-frequency power are often observed simultaneously with increases in broadband high gamma (21,42,51,72,76–79). While high-gamma activity is difficult to detect at the level of noninvasive scalp EEG, task-related decreases in low-frequency power are readily observed (72).

To give an example of how the $1/f$ and oscillatory components might interact, note that with increased cortical excitation there is often a concomitant decrease in low-frequency power. This suggests that there is either: 1) a push/pull relationship between broadband gamma and oscillatory power if these metrics are separable, or 2) a direct inverse relationship if they reflect a core underlying phenomenon. The difference between these two theories is critical for understanding the physiology generating this phenomenon. By way of illustration, an apparent decrease in low-frequency power can be caused by a drop in the amplitude of the underlying oscillation (Figure 1B, red line) or by a rotation of the entire PSD about a point (Figure 1C, purple line). In the former, the low-frequency oscillatory power has dropped while the background $1/f$ remains the same, whereas in the latter, the entire PSD shape has changed, with the rotation leading to a high-gamma power increase and a low-frequency power decrease. In the latter scenario, the magnitude of the narrowband oscillation remains unchanged relative to the background $1/f$ (21,22,80). This exemplifies the importance and need for measuring and modeling each of these electrophysiological processes independently: $1/f$ slope and offset, as well as narrowband oscillatory activity relative to the $1/f$ background. This is because the $1/f$ background will affect estimates of the oscillatory amplitude, and the oscillatory components will affect estimates of the $1/f$ slope and offset.

Oscillations and Spiking Noise

The fact that population spiking and the oscillatory frequency of a neuronal population can be different from the spiking frequency of individual neurons in the neural region generating the oscillation (73,74) and that some oscillatory processes may have nonneuronal (glial) origins that affect behavior and neural

communication (81,82) suggests that spiking and oscillations are distinct. However, as noted above, oscillations and spiking interact with externally applied electric fields to modulate network activity in humans (83), nonhuman primates (84), and rats (7).

While the $1/f$ offset likely reflects population spiking activity, there is little research on the neural origin of the spectral slope. However, computational models provide evidence that the spectral slope reflects temporal correlations in the population spiking activity (85,86) and that the slope changes with behavioral state (87). More specifically, Freeman and Zhai (67) simulated the ECoG signal to identify plausible physiological mechanisms that lead to changes in power spectral slope and offset. As noted by Freeman and Zhai (67), EEG and ECoG signals are not simply a summation of action potentials but rather the output of the dendrites that are synaptically driven by action potentials. This response can be characterized by an impulse function that has a rapid rise and prolonged return to background levels due to, they argue, “the reverberation of firing among the thousands of neurons transmitting and re-transmitting to each other,” in the local population. This is reflected by slowed rise rate and quickened decay rate. In their words, “when the strength of the driving impulse input is increased, [this] forces more neurons to fire and then become refractory.” They found that the PSD slope flattens with increasing rise rate but is unaffected by decay rate. Thus, we argue that the flattened power spectral slope is related to higher background rates of firing decoupled from an oscillatory carrier frequency—noise—driven by greater local positive excitatory feedback possibly caused by increased excitation/inhibition ratio [neural noise as defined by, e.g., Rubenstein and Merzenich (88)].

This result shows that stronger inputs cause more neurons to fire within a shorter time window, putting a greater proportion of the population into a refractory period. This means that relatively weak inputs result in more temporal variability in the input response, resulting in a flatter spectrum (Figure 2B, blue). For stronger inputs, the PSD is steeper (Figure 2B, red). Therefore, within our framework, if the dendritic response is being modulated by ephaptic coupling,

stronger ephaptic coupling would lead to a stronger dendritic response and thus a steeper PSD; the weaker the ephaptic coupling, the flatter the PSD. That is, local population spiking can be inferred from the PSD offset, while spiking statistics and noise may be inferred from the PSD slope (66,89,90).

NEURAL COMMUNICATION PATHOLOGY

Pathologic Overcoupling

In our theoretical framework, overcoupling, or hypersynchronization, is caused by an enhanced spike/field coupling process where the oscillatory local field causes the population spike timing to lock to the oscillation, which would feed back onto the local field. Recent research has demonstrated that patients with Parkinson's disease, off medication, show pathologically strong motor cortical beta/high-gamma PAC (91–93) [though the relationship between oscillatory beta and broadband high-gamma activity through the frontal cortex, thalamus, and basal ganglia is more complex (94)]. This pathologic PAC is reduced when a subthalamic deep brain stimulator (DBS) is turned on, resulting in prompt motor improvement in the patient (93). DBS stimulation shuts off the subthalamic nucleus altering basal ganglia firing patterns. Here, we would argue that the loss of dopaminergic modulation of the basal ganglia-thalamocortical network causes a state of pathologic network overcoupling (95). Thus, a possible mechanism of DBS is to induce enhanced high-frequency neural activity of the basal ganglia-thalamocortical network to disrupt abnormal excessive coupling (96) and regularize neuronal firing (97), a phenomenon that has been called an informational lesion (98). We should also note that there is emerging evidence of the involvement of thalamic structures in control of cortical oscillations in both attention via the pulvinar (99) and memory via the anterior thalamic nucleus (45). These findings suggest that thalamic modulation might provide a venue for treatment of deficits outside the motor domain.

Of particular interest is promising new evidence for the use of DBS in treating psychiatric disorders, such as depression, anxiety, or obsessive-compulsive disorder (100,101). In the case of depression and anxiety, patients have a tendency to ruminate, a metacognitive process wherein patients overly attend to negative or distressing emotions (102). From a dynamic network communication perspective, we argue that life events strengthen or weaken connections between brain regions, and via normal Hebbian learning mechanisms (103), networks that are more commonly activated are strengthened. In this framework, depression and anxiety might be conceived of as an overcoupling of the default mode network (104,105), perhaps caused by reinforcement via experience and rumination.

From this perspective, we hypothesize that the underlying mechanism of DBS efficacy in these psychiatric diseases—which are quite different in etiology from Parkinson's disease—is to some degree similar as to Parkinson's disease: the introduction of noisy neural activity into the pathologically overcoupled network via DBS permits normal network communication by decoupling a pathologically overcoupled network (106). This DBS mechanism may short-circuit normal, e.g., serotonergic modulation of network activity, which acts

within the cortex to decrease functional network connectivity (107). Importantly, in Parkinson's disease the anatomical target for DBS, the subthalamic nucleus, is clearly identifiable. In contrast, the key anatomical target for DBS in depression is the subgenual anterior cingulate cortex, which is not as well defined based on magnetic resonance imaging alone. Thus, one could argue that presurgical mapping of the anterior cingulate to identify regions of pathologic coupling could be used to guide DBS implantation for depression.

Pathological Undercoupling

On the opposite end of the network communication disorder spectrum from pathologic overcoupling is pathologic undercoupling. In our framework, the precise spike timing relative to network oscillatory activity is degraded with noisy temporally decorrelated spikes that occur during nonfacilitatory oscillatory phases. Here, one prominent example might be the neural noise hypothesis for age-related cognitive decline (108), wherein noise in this interpretation is operationalized as extraneous spikes not involved in encoding or communication. Viewed again from a dynamic network communication perspective, these noisy spikes serve to decouple the synchronization mechanism between brain regions, leading to communication and/or representational errors that, in turn, result in age-related cognitive deficits.

From a neurobiological standpoint, excitatory/inhibitory balance helps control runaway excitation and may lead to errors in encoding and/or interregional communication (109). Similar to the pathologic overcoupling case, this hypothesis can be extended to account for the behavioral symptoms seen in psychiatric or neurological disorders. For example, both autism and schizophrenia have been shown to be associated with reduced neuronal signal-to-noise (110–112) or, more directly, increased neural noise possibly caused by disease-related alterations in the ratio of excitation to inhibition (88) or overall reduced inhibition (113). Given that the slope of the PSD may reflect the level of neural noise, we predict that schizophrenia and autism may show flattened LFP power spectra relative to control subjects.

A recent study showed that in an autism spectrum disorder group, alpha/gamma PAC was reduced compared with matched control subjects (114). Note that this is in contrast to Parkinson's disease patients who show increased beta/high gamma PAC before DBS (91). This PAC reduction in autism supports the pathologic noise hypothesis in that temporally decorrelated noise, by definition, means more spikes occurring during nonpreferred phases of the low-frequency oscillation. Importantly, within the dynamic network communication framework, increased neural noise (decreased PAC) should also result in decreased interregional oscillatory coherence, which is what was shown (114).

This noise-induced pathologic undercoupling model may also explain some of the neurophysiological findings in relation to schizophrenia. Behaviorally, the majority of patients with schizophrenia show cognitive deficits in several domains, ranging from attention and working memory to social cognition (115). One proposal for the underlying cause for this broad array of cognitive impairments is that patients with schizophrenia suffer from a core working memory deficit (116). This

has been referred to as a rate limiting deficit, in that a generalized inability to hold or maintain information in working memory results in a multitude of downstream cognitive effects. Within our proposed framework, such working memory deficits would result from an impairment of a prefrontal-dependent working memory network that may include sensory cortical and subcortical regions (117–119). This network dysfunction might arise from an inability to maintain oscillatory communication due to increased neural noise and decreased PAC.

Neurophysiologically, schizophrenia is associated with decreased frontal beta coherence (120,121), decreased dopamine-mediated frontal lobe signal-to-noise (112), and broadband oscillatory decreases in signal-to-noise (122). Pharmacologically reducing (excitatory) glutamate release using metabotropic glutamate 2/3 receptor agonists improves schizophrenia symptoms (both positive and negative) (123), suggesting that reducing spiking activity has antipsychotic effects. Within our proposed framework, spurious, noisy spiking disrupts the ability for oscillatory communication networks to form via destructive resonance. As noted above, schizophrenia is associated with decreased frontal coherence and decreased signal-to-noise. Thus, metabotropic glutamate 2/3 receptor agonists, which reduce excitatory glutamate release, result in a reduction of temporally decorrelated spiking, which improves the spike/field coupling, resulting in improved oscillatory coherence and communication by improving signal-to-noise. In computational models, random noisy spiking has been shown to destabilize network dynamics, which has been proposed to underlie the behavioral symptoms of schizophrenia (124). These results align with our dynamic network communication hypothesis in that a reduction of noisy spiking activity would re-normalize pathologic undercoupling and improve network communication and PAC.

SUMMARY

Neuropsychiatric disorders have a long history of being viewed predominantly from a pharmacologic perspective. We suggest that an electrophysiological perspective might provide a fuller understanding of the gamut of neuropsychiatric disorders and provide a path toward novel treatment interventions aimed at normalizing effective network communication. Recent advances in noninvasive stimulation methods, such as transcranial alternating current stimulation, transcranial random noise stimulation, and transcranial magnetic stimulation (125,126), as well as the introduction of smart, closed-loop invasive neurostimulators (127–129), may prove to be useful tools for dynamically modulating pathologic network activity in disabling neuropsychiatric conditions [though their utility in this domain remains uncertain (130)].

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by the University of California, San Diego, Qualcomm Institute, California Institute for Telecommunications and Information Technology, Strategic Research Opportunities program (BV) and a Sloan Research Fellowship (BV), as well as National Institute of Neurological Disorders and Stroke Grant R37 NS21135-27 (RTK) and Defense Advanced

Research Projects Agency Systems-Based Neurotechnology for Emerging Therapies (RTK).

We thank Roemer van der Meij, Erik Peterson, Amitai Shenhav, Avgusta Shestuyuk, and Timothy Verstynen for their comments and careful reading of earlier drafts.

All authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Department of Cognitive Science, Neurosciences Graduate Program, and the Institute for Neural Computation (BV), University of California, San Diego, La Jolla; and Department of Psychology and Helen Wills Neuroscience Institute (RTK), University of California, Berkeley, Berkeley, California.

Address correspondence to Bradley Voytek, Ph.D., University of California, San Diego, Department of Cognitive Science, 9500 Gilman Dr, La Jolla, CA 92093-0515; E-mail: bradley.voytek@gmail.com.

Received Sep 26, 2014; revised Apr 15, 2015; accepted Apr 23, 2015.

REFERENCES

1. Wang X-J, Krystal JH (2014): Computational psychiatry. *Neuron* 84: 638–654.
2. Kopell NJ, Gritton HJ, Whittington MA, Kramer MA (2014): Beyond the connectome: The dynamome. *Neuron* 83:1319–1328.
3. Sejnowski TJ, Paulsen O (2006): Network oscillations: Emerging computational principles. *J Neurosci* 26:1673–1676.
4. Faisal AA, Selen LPJ, Wolpert DM (2008): Noise in the nervous system. *Nat Rev Neurosci* 9:292–303.
5. McCarthy MM, Ching S, Whittington MA, Kopell N (2012): Dynamical changes in neurological diseases and anesthesia. *Curr Opin Neurobiol* 22:693–703.
6. Anastassiou CA, Perin R, Markram H, Koch C (2011): Ephaptic coupling of cortical neurons. *Nat Neurosci* 14:217–223.
7. Fröhlich F, McCormick DA (2010): Endogenous electric fields may guide neocortical network activity. *Neuron* 67:129–143.
8. Busch NA, Vanrullen R (2010): Spontaneous EEG oscillations reveal periodic sampling of visual attention. *Proc Natl Acad Sci U S A* 107: 16048–16053.
9. Mathewson KE, Gratton G, Fabiani M, Beck DM, Ro T (2009): To see or not to see: Prestimulus alpha phase predicts visual awareness. *J Neurosci* 29:2725–2732.
10. Yamagishi N, Callan DE, Anderson SJ, Kawato M (2008): Attentional changes in pre-stimulus oscillatory activity within early visual cortex are predictive of human visual performance. *Brain Res* 1197: 115–122.
11. Van Dijk H, Schoffelen J-M, Oostenveld R, Jensen O (2008): Prestimulus oscillatory activity in the alpha band predicts visual discrimination ability. *J Neurosci* 28:1816–1823.
12. Thut G, Nietzel A, Brandt SA, Pascual-Leone A (2006): Alpha-band electroencephalographic activity over occipital cortex indexes visuo-spatial attention bias and predicts visual target detection. *J Neurosci* 26:9494–9502.
13. Palva S, Palva JM (2007): New vistas for α -frequency band oscillations. *Trends Neurosci* 30:150–158.
14. Spaak E, de Lange FP, Jensen O (2014): Local entrainment of alpha oscillations by visual stimuli causes cyclic modulation of perception. *J Neurosci* 34:3536–3544.
15. Sokoliuk R, Vanrullen R (2013): The flickering wheel illusion: When α rhythms make a static wheel flicker. *J Neurosci* 33:13498–13504.
16. Landau AN, Fries P (2012): Attention samples stimuli rhythmically. *Curr Biol* 22:1000–1004.
17. Anastassiou CA, Koch C (2014): Ephaptic coupling to endogenous electric field activity: Why bother? *Curr Opin Neurobiol* 31C:95–103.
18. Ozen S, Sirota A, Belluscio MA, Anastassiou CA, Stark E, Koch C, Buzsaki G (2010): Transcranial electric stimulation entrains cortical neuronal populations in rats. *J Neurosci* 30:11476–11485.
19. Radman T, Su Y, An JH, Parra LC, Bikson M (2007): Spike timing amplifies the effect of electric fields on neurons: Implications for endogenous field effects. *J Neurosci* 27:3030–3036.

20. Manning JR, Jacobs J, Fried I, Kahana MJ (2009): Broadband shifts in local field potential power spectra are correlated with single-neuron spiking in humans. *J Neurosci* 29:13613–13620.
21. Miller KJ, Honey CJ, Hermes D, Rao RP, denNijs M, Ojemann JG (2014): Broadband changes in the cortical surface potential track activation of functionally diverse neuronal populations. *Neuroimage* 85:711–720.
22. Winawer J, Kay KN, Foster BL, Rauschecker AM, Parvizi J, Wandell BA (2013): Asynchronous broadband signals are the principal source of the bold response in human visual cortex. *Curr Biol* 23:1145–1153.
23. Ray S, Crone NE, Niebur E, Fransaszczuk PJ, Hsiao SS (2008): Neural correlates of high-gamma oscillations (60–200 Hz) in macaque local field potentials and their potential implications in electrocorticography. *J Neurosci* 28:11526–11536.
24. Womelsdorf T, Valiante TA, Sahin NT, Miller KJ, Tiesinga P (2014): Dynamic circuit motifs underlying rhythmic gain control, gating and integration. *Nat Neurosci* 17:1031–1039.
25. Lachaux JP, Rodriguez E, Martinerie J, Varela FJ (1999): Measuring phase synchrony in brain signals. *Hum Brain Mapp* 8:194–208.
26. Engel AK, Fries P, Singer W (2001): Dynamic predictions: Oscillations and synchrony in top-down processing. *Nat Rev Neurosci* 2:704–716.
27. Rissman J, Gazzaley A, D'Esposito M (2004): Measuring functional connectivity during distinct stages of a cognitive task. *Neuroimage* 23:752–763.
28. Wang L, Saalman YB, Pinsk MA, Arcaro MJ, Kastner S (2012): Electrophysiological low-frequency coherence and cross-frequency coupling contribute to BOLD connectivity. *Neuron* 76:1010–1020.
29. Lisman JE, Idiart MA (1995): Storage of 7 +/- 2 short-term memories in oscillatory subcycles. *Science* 267:1512–1515.
30. Buzsáki G, Draguhn A (2004): Neuronal oscillations in cortical networks. *Science* 304:1926–1929.
31. Fries P (2005): A mechanism for cognitive dynamics: Neuronal communication through neuronal coherence. *Trends Cogn Sci* 9:474–480.
32. Schaefer AT, Angelo K, Spors H, Margrie TW (2006): Neuronal oscillations enhance stimulus discrimination by ensuring action potential precision. *PLoS Biol* 4:163.
33. Tognoli E, Kelso JAS (2014): The metastable brain. *Neuron* 81:35–48.
34. Canolty RT, Edwards E, Dalal SS, Soltani M, Nagarajan SS, Kirsch HE, *et al.* (2006): High gamma power is phase-locked to theta oscillations in human neocortex. *Science* 313:1626–1628.
35. Aru J, Aru J, Priesemann V, Wibral M, Lana L, Pipa G, *et al.* (2015): Untangling cross-frequency coupling in neuroscience. *Curr Opin Neurobiol* 31:51–61.
36. Colgin LL, Denninger T, Fyhn M, Hafting T, Bonnevie T, Jensen O, *et al.* (2009): Frequency of gamma oscillations routes flow of information in the hippocampus. *Nature* 462:353–357.
37. Quilichini P, Sirota A, Buzsáki G (2010): Intrinsic circuit organization and theta-gamma oscillation dynamics in the entorhinal cortex of the rat. *J Neurosci* 30:11128–11142.
38. Canolty RT, Knight RT (2010): The functional role of cross-frequency coupling. *Trends Cogn Sci* 14:506–515.
39. Szczepanski SM, Crone NE, Kuperman RA, Auguste KI, Parvizi J, Knight RT (2014): Dynamic changes in phase-amplitude coupling facilitate spatial attention control in fronto-parietal cortex. *PLoS Biol* 12:e1001936.
40. Vanhatalo S, Palva JM, Holmes MD, Miller JW, Voipio J, Kaila K (2004): Infralow oscillations modulate excitability and interictal epileptic activity in the human cortex during sleep. *Proc Natl Acad Sci U S A* 101:5053–5057.
41. Lakatos P, Karmos G, Mehta AD, Ulbert I, Schroeder CE (2008): Entrainment of neuronal oscillations as a mechanism of attentional selection. *Science* 320:110–113.
42. Miller KJ, Hermes D, Honey CJ, Hebb AO, Ramsey NF, Knight RT, *et al.* (2012): Human motor cortical activity is selectively phase-entrained on underlying rhythms. *PLoS Comput Biol* 8:e1002655.
43. Miller KJ, Hermes D, Honey CJ, Sharma M, Rao RPN, Nijs den M, *et al.* (2010): Dynamic modulation of local population activity by rhythm phase in human occipital cortex during a visual search task. *Front Hum Neurosci* 4:197.
44. Tort ABL, Komorowski RW, Manns JR, Kopell NJ, Eichenbaum H (2009): Theta-gamma coupling increases during the learning of item-context associations. *Proc Natl Acad Sci U S A* 106:20942–20947.
45. Sweeney-Reed CM, Zaehle T, Voges J, Schmitt FC, Buentjen L, Kopitzki K, *et al.* (2014): Corticothalamic phase synchrony and cross-frequency coupling predict human memory formation. *Elife* 3:e05352.
46. Axmacher N, Henseler MM, Jensen O, Weinreich I, Elger CE, Fell J (2010): Cross-frequency coupling supports multi-item working memory in the human hippocampus. *Proc Natl Acad Sci U S A* 107:3228–3233.
47. Cohen MX, Axmacher N, Lenartz D, Elger CE, Sturm V, Schlaepfer TE (2009): Good vibrations: Cross-frequency coupling in the human nucleus accumbens during reward processing. *J Cogn Neurosci* 21:875–889.
48. Cohen MX, Axmacher N, Lenartz D, Elger CE, Sturm V, Schlaepfer TE (2009): Nuclei accumbens phase synchrony predicts decision-making reversals following negative feedback. *J Neurosci* 29:7591–7598.
49. Canolty RT, Ganguly K, Kennerley SW, Cadieu CF, Koepsell K, Wallis JD, Carmena JM (2010): Oscillatory phase coupling coordinates anatomically dispersed functional cell assemblies. *Proc Natl Acad Sci U S A* 107:17356–17361.
50. Johnson EL, Knight RT (2015): Intracranial recordings and human memory. *Curr Opin Neurobiol* 31:18–25.
51. Voytek B, D'Esposito M, Crone N, Knight RT (2013): A method for event-related phase/amplitude coupling. *Neuroimage* 64:416–424.
52. Schanze T, Eckhorn R (1997): Phase correlation among rhythms present at different frequencies: Spectral methods, application to microelectrode recordings from visual cortex and functional implications. *Int J Psychophysiol* 26:171–189.
53. Tort ABL, Kramer MA, Thorn C, Gibson DJ, Kubota Y, Graybiel AM, Kopell NJ (2008): Dynamic cross-frequency couplings of local field potential oscillations in rat striatum and hippocampus during performance of a T-maze task. *Proc Natl Acad Sci U S A* 105:20517–20522.
54. Roopun AK, Kramer MA, Carracedo LM, Kaiser M, Davies CH, Traub RD, *et al.* (2008): Period concatenation underlies interactions between gamma and beta rhythms in neocortex. *Front Cell Neurosci* 2:1.
55. Roopun AK, Kramer MA, Carracedo LM, Kaiser M, Davies CH, Traub RD, *et al.* (2008): Temporal interactions between cortical rhythms. *Front Neurosci* 2:145–154.
56. Voytek B, Canolty RT, Shestyuk A, Crone N, Parvizi J, Knight RT (2010): Shifts in gamma phase–amplitude coupling frequency from theta to alpha over posterior cortex during visual tasks. *Front Hum Neurosci* 4:191.
57. Foster BL, Parvizi J (2012): Resting oscillations and cross-frequency coupling in the human posteromedial cortex. *Neuroimage* 60:384–391.
58. Watrous AJ, Tandon N, Conner CR, Pieters T, Ekstrom AD (2013): Frequency-specific network connectivity increases underlie accurate spatiotemporal memory retrieval. *Nat Neurosci* 16:349–356.
59. Panzeri S, Brunel N, Logothetis NK, Kayser C (2010): Sensory neural codes using multiplexed temporal scales. *Trends Neurosci* 33:111–120.
60. Koepsell K, Wang X, Hirsch JA, Sommer FT (2010): Exploring the function of neural oscillations in early sensory systems. *Front Neurosci* 4:53.
61. Fujisawa S, Buzsáki G (2011): A 4 Hz oscillation adaptively synchronizes prefrontal, VTA, and hippocampal activities. *Neuron* 72:153–165.
62. Deco G, Jirsa V, McIntosh AR, Sporns O, Kottler R (2009): Key role of coupling, delay, and noise in resting brain fluctuations. *Proc Natl Acad Sci U S A* 106:10302–10307.

63. Mishima T, Hirase H (2010): In vivo intracellular recording suggests that gray matter astrocytes in mature cerebral cortex and hippocampus are electrophysiologically homogeneous. *J Neurosci* 30: 3093–3100.
64. Menon V (2011): Large-scale brain networks and psychopathology: A unifying triple network model. *Trends Cogn Sci* 15:483–506.
65. Pritchard WS (1992): The brain in fractal time: 1/f-like power spectrum scaling of the human electroencephalogram. *Int J Neurosci* 66:119–129.
66. Bédard C, Kröger H, Destexhe A (2006): Does the 1/f frequency scaling of brain signals reflect self-organized critical states? *Phys Rev Lett* 97:118102.
67. Freeman WJ, Zhai J (2009): Simulated power spectral density (PSD) of background electrocorticogram (ECoG). *Cogn Neurodyn* 3: 97–103.
68. He BJ (2014): Scale-free brain activity: Past, present, and future. *Trends Cogn Sci* 18:480–487.
69. He BJ, Zempel JM, Snyder AZ, Raichle ME (2010): The Temporal Structures and Functional Significance of Scale-free Brain Activity. *Neuron* 66:353–369.
70. Lopes da Silva F (2013): EEG and MEG: Relevance to neuroscience. *Neuron* 80:1112–1128.
71. He BJ (2014): Scale-free brain activity: past, present, and future. *Trends in Cognitive Sciences* 18:480–487.
72. Voytek B, Secundo L, Bidet-Caulet A, Scabini D, Stiver SI, Gean AD, et al. (2010): Hemicraniectomy: A new model for human electrophysiology with high spatio-temporal resolution. *J Cogn Neurosci* 22:2491–2502.
73. Whittington MA, Cunningham MO, LeBeau FEN, Racca C, Traub RD (2010): Multiple origins of the cortical gamma rhythm. *Dev Neurobiol* 71:92–106.
74. Brunel N, Wang X-J (2003): What determines the frequency of fast network oscillations with irregular neural discharges? I. Synaptic dynamics and excitation-inhibition balance. *J Neurophysiol* 90: 415–430.
75. Mukamel R, Gelbard H, Arieli A, Hasson U, Fried I, Malach R (2005): Coupling between neuronal firing, field potentials, and fMRI in human auditory cortex. *Science* 309:951–954.
76. Crone NE, Miglioretti DL, Gordon B, Sieracki JM, Wilson MT, Uematsu S, Lesser RP (1998): Functional mapping of human sensorimotor cortex with electrocorticographic spectral analysis. I. Alpha and beta event-related desynchronization. *Brain* 121: 2271–2299.
77. Crone NE, Miglioretti DL, Gordon B, Lesser RP (1998): Functional mapping of human sensorimotor cortex with electrocorticographic spectral analysis. II. Event-related synchronization in the gamma band. *Brain* 121:2301–2315.
78. Edwards E (2005): High gamma activity in response to deviant auditory stimuli recorded directly from human cortex. *J Neurophysiol* 94:4269–4280.
79. Jacobs J, Kahana MJ (2009): Neural representations of individual stimuli in humans revealed by gamma-band electrocorticographic activity. *J Neurosci* 29:10203–10214.
80. Hermes D, Miller KJ, Wandell BA, Winawer J (2014): Stimulus dependence of gamma oscillations in human visual cortex [published online ahead of print May 22]. *Cereb Cortex*.
81. Lee HS, Ghetti A, Pinto-Duarte A, Wang X, Dziewczapolski G, Galimi F, et al. (2014): Astrocytes contribute to gamma oscillations and recognition memory. *Proc Natl Acad Sci U S A* 111:E3343–E3352.
82. Fellin T, Pascual O, Gobbo S, Pozzan T, Haydon PG, Carmignoto G (2004): Neuronal synchrony mediated by astrocytic glutamate through activation of extrasynaptic NMDA receptors. *Neuron* 43: 729–743.
83. Ali MM, Sellers KK, Frohlich F (2013): Transcranial alternating current stimulation modulates large-scale cortical network activity by network resonance. *J Neurosci* 33:11262–11275.
84. Haegens S, Nacher V, Luna R, Romo R, Jensen O (2011): α -Oscillations in the monkey sensorimotor network influence discrimination performance by rhythmical inhibition of neuronal spiking. *Proc Natl Acad Sci U S A* 108:19377–19382.
85. Usher M, Stemmler M, Olami Z (1995): Dynamic pattern formation leads to 1/f noise in neural populations. *Phys Rev Lett* 74:326–329.
86. Pozzorini C, Naud R, Mensi S, Gerstner W (2013): Temporal whitening by power-law adaptation in neocortical neurons. *Nat Neurosci* 16:942–948.
87. Podvalny E, Noy N, Harel M, Bickel S, Chechik G, Schroeder CE, et al. (2015): A unifying principle underlying the extracellular field potential spectral responses in the human cortex [published online ahead of print April 8]. *J Neurophysiol*.
88. Rubenstein JLR, Merzenich MM (2003): Model of autism: Increased ratio of excitation/inhibition in key neural systems. *Genes Brain Behav* 2:255–267.
89. Hanggi P, Jung P (1995): Colored noise in dynamical systems. *Adv Chem Phys* 89:239–326.
90. Sosnoff JJ, Newell KM (2011): Aging and motor variability: A test of the neural noise hypothesis. *Exp Aging Res* 37:377–397.
91. de Hemptinne C, Ryapolova-Webb ES, Air EL, Garcia PA, Miller KJ, Ojemann JG, et al. (2013): Exaggerated phase-amplitude coupling in the primary motor cortex in Parkinson disease. *Proc Natl Acad Sci U S A* 110:4780–4785.
92. Yang AI, Vanegas N, Lungu C, Zaghoul KA (2014): Beta-coupled high-frequency activity and beta-locked neuronal spiking in the subthalamic nucleus of Parkinson's disease. *J Neurosci* 34:12816–12827.
93. de Hemptinne C, Swann N, Ostrem JL, Ryapolova-Webb ES, Luciano M, Galifianakis NB, Starr PA (2015): Therapeutic deep brain stimulation reduces cortical phase-amplitude coupling in Parkinson's disease. *Nat Neurosci* 18:779–786.
94. Cannon J, McCarthy MM, Lee S, Lee J, Börgers C, Whittington MA, Kopell N (2013): Neurosystems: Brain rhythms and cognitive processing. *Eur J Neurosci* 39:705–719.
95. Sharott A, Magill PJ, Harnack D, Kupsch A, Meissner W, Brown P (2005): Dopamine depletion increases the power and coherence of β -oscillations in the cerebral cortex and subthalamic nucleus of the awake rat. *Eur J Neurosci* 21:1413–1422.
96. McIntyre CC, Savasta M, Kerkerian-Le Goff L, Vitek JL (2004): Uncovering the mechanism(s) of action of deep brain stimulation: Activation, inhibition, or both. *Clin Neurophysiol* 115:1239–1248.
97. McConnell GC, So RQ, Hilliard JD, Lopomo P, Grill WM (2012): Effective deep brain stimulation suppresses low-frequency network oscillations in the basal ganglia by regularizing neural firing patterns. *J Neurosci* 32:15657–15668.
98. Grill WM, Snyder AN, Miocinovic S (2004): Deep brain stimulation creates an informational lesion of the stimulated nucleus. *Neuroreport* 15:1137–1140.
99. Saalman YB, Pinski MA, Wang L, Li X, Kastner S (2012): The pulvinar regulates information transmission between cortical areas based on attention demands. *Science* 337:753–756.
100. Holtzheimer PE, Mayberg HS (2011): Deep brain stimulation for psychiatric disorders. *Annu Rev Neurosci* 34:289–307.
101. Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, et al. (2005): Deep brain stimulation for treatment-resistant depression. *Neuron* 45:651–660.
102. Holtzheimer PE, Mayberg HS (2011): Stuck in a rut: Rethinking depression and its treatment. *Trends Neurosci* 34:1–9.
103. Hebb DO (1949): *The Organization of Behavior*. New York: John Wiley & Sons.
104. Berman MG, Peltier S, Nee DE, Kross E, Deldin PJ, Jonides J (2011): Depression, rumination and the default network. *Soc Cogn Affect Neurosci* 6:548–555.
105. Bar M (2009): A cognitive neuroscience hypothesis of mood and depression. *Trends Cogn Sci* 13:456–463.
106. Brittain J-S, Sharott A, Brown P (2014): The highs and lows of beta activity in cortico-basal ganglia loops. *Eur J Neurosci* 39:1951–1959.
107. Schaefer A, Burmann I, Regenthal R, Arélin K, Barth C, Pampel A, et al. (2014): Serotonergic modulation of intrinsic functional connectivity. *Curr Biol* 24:2314–2318.

108. Cremer R, Zeef EJ (1987): What kind of noise increases with age? *J Gerontol* 42:515–518.
109. Haider B, McCormick DA (2009): Rapid neocortical dynamics: Cellular and network mechanisms. *Neuron* 62:171–189.
110. Dinstein I, Heeger DJ, Lorenzi L, Minshew NJ, Malach R, Behrmann M (2012): Unreliable evoked responses in autism. *Neuron* 75:981–991.
111. Weinger PM, Zemon V, Soorya L, Gordon J (2014): Low-contrast response deficits and increased neural noise in children with autism spectrum disorder. *Neuropsychologia* 63:10–18.
112. Winterer G, Weinberger DR (2004): Genes, dopamine and cortical signal-to-noise ratio in schizophrenia. *Trends Neurosci* 27:683–690.
113. Vogels TP, Abbott LF (2009): Gating multiple signals through detailed balance of excitation and inhibition in spiking networks. *Nat Neurosci* 12:483–491.
114. Khan S, Gramfort A, Shetty NR (2013): Local and long-range functional connectivity is reduced in concert in autism spectrum disorders. *Proc Natl Acad Sci U S A* 110:3107–3112.
115. Keefe RSE, Harvey PD (2012): Cognitive impairment in schizophrenia. *Handb Exp Pharmacol* 213:11–37.
116. Silver H, Feldman P, Bilker W, Gur RC (2003): Working memory deficit as a core neuropsychological dysfunction in schizophrenia. *Am J Psychiatry* 160:1809–1816.
117. Barcelo F, Suwazono S, Knight RT (2000): Prefrontal modulation of visual processing in humans. *Nat Neurosci* 3:399–403.
118. Szczepanski SM, Knight RT (2014): Insights into human behavior from lesions to the prefrontal cortex. *Neuron* 83:1002–1018.
119. Voytek B, Knight RT (2010): Prefrontal cortex and basal ganglia contributions to visual working memory. *Proc Natl Acad Sci U S A* 107:18167–18172.
120. Uhlhaas PJ, Linden DEJ, Singer W, Haenschel C, Lindner M, Maurer K, Rodriguez E (2006): Dysfunctional long-range coordination of neural activity during Gestalt perception in schizophrenia. *J Neurosci* 26:8168–8175.
121. Uhlhaas PJ, Singer W (2010): Abnormal neural oscillations and synchrony in schizophrenia. *Nat Rev Neurosci* 11:100–113.
122. Winterer G, Coppola R, Goldberg TE, Egan MF, Jones DW, Sanchez CE, Weinberger DR (2004): Prefrontal broadband noise, working memory, and genetic risk for schizophrenia. *Am J Psychiatry* 161:490–500.
123. Patil ST, Zhang L, Martenyi F, Lowe SL, Jackson KA, Andreev BV, *et al.* (2007): Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: A randomized Phase 2 clinical trial. *Nat Med* 13:1102–1107.
124. Rolls ET, Loh M, Deco G, Winterer G (2008): Computational models of schizophrenia and dopamine modulation in the prefrontal cortex. *Nat Rev Neurosci* 9:696–709.
125. Paulus W (2011): Transcranial electrical stimulation (tES – tDCS; tRNS, tACS) methods. *Neuropsychol Rehabil* 21:602–617.
126. Antal A, Paulus W, Nitsche MA (2011): Electrical stimulation and visual network plasticity. *Restor Neurol Neurosci* 29:365–374.
127. Sun FT, Morrell MJ (2014): Closed-loop neurostimulation: The clinical experience. *Neurotherapeutics* 11:553–563.
128. Azodi-Avval R, Gharabaghi A (2015): Phase-dependent modulation as a novel approach for therapeutic brain stimulation. *Front Comput Neurosci* 9:26.
129. Chang EF (2015): Towards large-scale, human-based, mesoscopic neurotechnologies. *Neuron* 86:68–78.
130. Horvath JC, Forte JD, Carter O (2015): Evidence that transcranial direct current stimulation (tDCS) generates little-to-no reliable neurophysiologic effect beyond MEP amplitude modulation in healthy human subjects: A systematic review. *Neuropsychologia* 66:213–236.