

Cognitive neurophysiology of the prefrontal cortex

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Abstract

The prefrontal cortex (PFC) provides the structural basis for complex rule-guided goal-directed behavior. However, the functional mechanisms that underlie cognitive control and flexibility are not as well understood. Over the last decade, novel electrophysiological methods and analysis techniques have begun to elucidate the neural mechanisms underlying higher cognitive functions. Here we review how electrophysiology and, in particular, intracranial recordings in humans and primates enable imaging of cognitive processing with an unprecedented spatiotemporal resolution. Convergent evidence from multiple species and across several spatial scales suggests that cell assemblies and transient synchronized network activity constitute the functional units of PFC implementation of organized behavior. These observations indicate that the functional architecture of cognition is inherently rhythmic and not static. We highlight that prefrontal neurons exhibit a mixed selectivity to various task-relevant aspects and code information in a time-varying dynamic population code and not at the level of individual neurons or in stable coding schemes. We argue that network neuroscience and network neurology are emergent paradigms to understand complex behavior and mental diseases.

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THE NEURAL BASIS OF GOAL-DIRECTED BEHAVIOR AND COGNITIVE CONTROL

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Numerous lesion and imaging studies have documented that the prefrontal cortex constitutes the structural basis for goal-directed behavior and a variety of higher cognitive functions (Miller and Cohen, 2001; Sakai, 2008; Stuss and Knight, 2013). However, the prefrontal cortex is anatomically not as clearly organized as primary sensory areas. Therefore, it remains unclear which functional mechanisms give rise to cognitive flexibility and abstract, rule-guided and contextually adequate behavior (Rainer et al., 1998; Wallis et al., 2001; Mante et al., 2013; Voytek et al., 2015). In this chapter, we discuss how electrophysiology in humans and primates begins to elucidate the functional architecture of flexible cognitive control.

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First, we will review a variety of common electrophysiological methods that are routinely being used in clinical and preclinical settings to study behavior and cortical

functions. Then, we discuss analytical approaches, with a particular focus on metrics that capture complex spatiotemporal dynamics of prefrontal cognitive operations. Notably, we will focus on how intracranial electrophysiology has advanced our understanding of prefrontal-dependent cortical processing. Hence, we will first illustrate three recent examples where groundbreaking and unexpected results from intracranial studies have significantly contributed to our understanding of the prefrontal functional organization.

Following this, we discuss emerging concepts in cognitive neurophysiology and systems neuroscience in more detail. We revisit the neuron doctrine and review evidence that supports the notion that neuronal assemblies are the functional unit of the central nervous system (CNS) and not solely individual neurons. Importantly, we consider how information might be encoded at the population level and how rhythmic activity in large-scale networks might determine the timescale of cognition.

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To this end, we review PFC-dependent, large-scale cortical and subcortical networks that support cognitive flexibility and behavior, as well as emerging technologies, which allow modulating oscillatory brain activity *in vivo*. We then highlight how impaired network synchrony might be implicated in various neuropsychiatric diseases.

In the last section, we provide an outlook on how multimodal analytic approaches enable updating of current models of prefrontal physiology. Specifically, we focus on nonlinear population-based methods, which might capture complex prefrontal interactions better than strictly linear metrics. Finally, we argue that challenging established concepts of prefrontal-dependent processing would provide valuable insights into the underlying computations giving rise to flexible cognitive control. We posit that intracranial electrophysiology combined with causal interventions will illuminate the underlying processes that support fluid prefrontal-dependent behavior.

IMAGING COGNITION WITH HIGH SPATIOTEMPORAL RESOLUTION

Cognitive control stems from the flexible integration of endogenous priors with task-relevant rules according to the current context and constitutes a hallmark of human goal-directed behavior (Miller and Cohen, 2001). Numerous behavioral lesion and fMRI studies have suggested that the prefrontal cortex constitutes a core area for flexible cognitive control (Stuss and Knight, 2013). However, both approaches lack the temporal resolution to clarify the neurophysiological mechanisms that give rise to human behavior and the ability to adapt to a new context or rule in a few hundred milliseconds (Miller and Cohen, 2001). This section focuses on methods that allow imaging human cognitive processing with a high temporal resolution. Noninvasive approaches, such as EEG (electroencephalography) or MEG (magnetoencephalography), are ideally suited to test larger study populations (Buzsáki et al., 2012; Lopes da Silva, 2013; Baillet, 2017; Cohen, 2017). While it has been argued that MEG has a superior spatial resolution due to the number of available sensors (normally 151 or 306 for MEG instead of 32, 64, or 128 for EEG), one requires an additional structural MRI scan to coregister MEG recordings to the individual anatomy to take full advantage of the increased spatial precision (Gross et al., 2013; Baillet, 2017). Recently, several methodological advances, such as high density electrode arrays, as well as advanced signal-processing techniques such as independent component analysis (ICA; Hyvärinen and Oja, 2000) and source projection methods (e.g., linear beamforming (Van Veen et al., 1997; Gross et al., 2001) or low-resolution brain

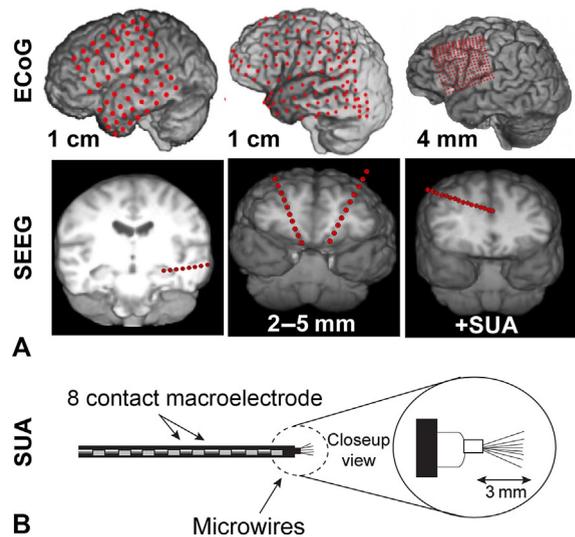


Fig. 3.1. Intracranial EEG electrodes. (A) Various examples of intracranial EEG electrode placement: Red dots depict individual electrode contacts. The first row highlights three examples of the commonly utilized ECoG grid electrodes with either 64 (left and center; 8×8 electrodes; 1-cm interelectrode spacing) or 256 electrodes (right; 16×16 electrodes; 4-mm spacing). The second row illustrates stereotactically placed depth electrodes in the hippocampus (left), OFC (center), and cingulate cortex (right). Interelectrode spacing and number of contacts is variable. Note that electrode contacts are present all throughout the shaft, allowing simultaneous recordings from subcortical and cortical regions, such as the temporal cortex (left) or DLPFC (center and right). (B) Depth electrodes might house additional wire bundles in their lumen, which allow recording of single and multiunit activity at the tip of the depth electrode. Panel (B): Modified from Ad-Tech Medical Product Catalog Volume VII.

electromagnetic tomography (Pascual-Marqui et al., 1994; Lantz et al., 1997), LORETA) have significantly improved the spatial resolution of EEG. Several comparative studies indicated that the information that can be extracted from EEG and MEG is comparable for frequencies below 30 Hz, while MEG has a superior signal-to-noise ratio for higher frequencies (Siems et al., 2016).

Currently, the best spatiotemporal resolution in human electrophysiological recordings can be obtained from invasive recordings (intracranial EEG) in patients who suffer from pharmaco-resistant epilepsy and who undergo presurgical evaluation for seizure localization. These patients are implanted with either grid electrodes (electrocorticography, ECoG), depth electrodes that are being placed stereotactically (sEEG), or a combination of both types (Fig. 3.1A).

Typically, only a subpopulation of electrodes is deemed epileptic after multiple days of monitoring, while the majority cover intact brain tissue and may be used for further analysis to address human cognition

with an unprecedented spatiotemporal resolution. More recently, several groups began to record activity from single neurons in awake patients, while they perform various tasks (Engel et al., 2005; Fried et al., 2014). The most common approach is associated with minimal risk for the patient and limited to sEEG (Fig. 3.1B): Depth electrodes have an open lumen, where an additional wire bundle with eight contacts (+1 reference wire) can be advanced up to 5 mm below the most distant electrode contact to record unit activity and local field potentials (LFPs) with a high sampling rate necessary for spike sorting (>32 kHz). Hence, unit recordings are only possible at the tip of the electrode, which are routinely inserted into medial temporal lobe structures, anterior cingulate, medial PFC, or orbitofrontal cortex (Fried et al., 2014; Kamiński et al., 2017; Mormann et al., 2017). This unique setup prevents recordings from regions such as the dorsolateral prefrontal cortex (DLPFC) since the single-unit activity (SUA) wires are only at the tip of the sEEG electrode shaft. In a different approach, a few groups have used multielectrode arrays (MEAs; Utah array), which are inserted into healthy cortical tissue that was part of the assumed resection zone. Hence, recording unit activity is not always limited to deeper brain structures. However, in several cases the tissue where the MEA was inserted was not resected and patients were left with permanent cortical scarring. Given that single-unit recordings do not contribute to the clinical assessment, this approach should be limited to selective usage such as brain-machine interface applications to ensure patient safety and minimize surgical risks.

In contrast, acute or semichronic recordings are routinely used in primate research to simultaneously record unit activity and LFPs (Buzsáki et al., 2012). Previously, simultaneous recordings were often limited to one or two ROIs and units were grouped into pseudopopulations by pooling data from multiple recording sessions and treating them as one simultaneous population recording (Meyers et al., 2008; Quian Quiroga and Panzeri, 2009; Stokes et al., 2013). Recently it has become possible to record from several distant regions simultaneously. For example, Siegel et al. (2015) recorded from a total of six regions, including parietal (LIP), temporal (MT, V4, and IT) and frontal cortex (DLPFC and FEF).

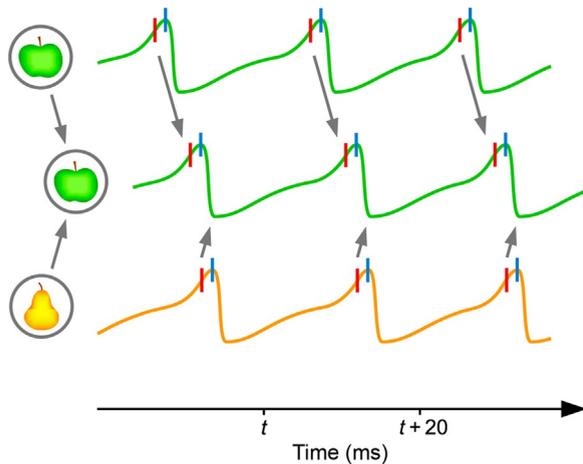
One inherent shortcoming of all electrophysiological methods is that they are often correlative in nature (Herrmann et al., 2016). Establishing a causal relationship between observed electrophysiological signatures, such as neuronal oscillations, would imply modulating brain activity and studying the impact on behavior (Thut et al., 2012, 2017). Over the last few years several methods have been introduced that allow the targeted modulation of ongoing brain dynamics. For example, rhythmic transcranial magnetic stimulation (rTMS) and

transcranial alternating current stimulation (tACS) offer the opportunity to noninvasively drive cortical activity and endogenous electric fields (Thut et al., 2011a; Fröhlich et al., 2015; Herrmann et al., 2016), while the use of direct cortical electric stimulation (DES) is limited to the clinical setting. While previous stimulation studies attempted to activate or deactivate a certain cortical area to ascertain its causal contribution, novel protocols aim to modulate ongoing patterns to establish functional relationships (Alagapan et al., 2016).

In most studies, behavior is assessed by mean accuracies or reaction times. Recently, several groups have explored methods inspired by electrophysiological analyses to probe the timescale of cognition (Landau and Fries, 2012; Fiebelkorn et al., 2013; Song et al., 2014). These approaches probe behavior on a fine-grained temporal scale to obtain multiple estimates of behavior. For instance, target detection can be probed at different offset latencies after a train of noninformative sensory events, thus providing time-resolved behavioral estimates. The resulting time course can then be analyzed by means of spectral analyses to highlight the fact that perception and cognition are not constant over time; rather, they exhibit intrinsic temporal profiles that wax and wane as a result of the underlying rhythmicity of intrinsic brain activity.

SPATIOTEMPORAL COORDINATION IN CORTICAL NETWORKS

Over the last 25 years cognitive neuroscience has benefited from methodological advances to analyze neuronal time series data (Buzsáki and Draguhn, 2004; Buzsáki, 2006; Buzsáki et al., 2013). While early noninvasive scalp EEG and invasive single-unit recordings were limited to a few recording sites, which were sampled several hundred times per second, novel recording setups permit simultaneous recordings from hundreds of electrodes at high sampling rates (Fukushima et al., 2015; Panzeri et al., 2015). These advances in recording of neuronal activity triggered a surge of new analytic approaches, which have had a tremendous effect on our current understanding of how the prefrontal cortex supports cognitive processing. For example, early noninvasive EEG studies focused on event-related potentials (Handy, 2005; Luck, 2014), which were obtained from averaging multiple stimulus or response-locked trials to improve the signal-to-noise ratio and reduce background noise. Likewise, invasive recordings in primates were often limited to analyzing spike trains over time (Brown et al., 2004). However, both approaches ignored the role of background activity and discarded the rich information present in single trials (Stokes and Spaak, 2016). Although the discovery of



0015 **Fig. 3.2.** Communication-through-Coherence hypothesis. Three neuronal populations are depicted. The *first and third rows* highlight two downstream sensory regions: one represents an apple and the other one a pear. The *second row* illustrates a higher-order area that is connected to both populations. When two populations (*first and second rows*) are synchronized at an optimal phase, then excitatory volleys (*red ticks*) will arrive at the higher-order area at an optimal, highly excitable phase and information about the apple can be transferred. In contrast, the *third and second rows* are out of sync; hence, volleys arrive when the higher-order region is refractory due to inhibition (*blue ticks*) and no information is transferred. The interplay of excitation and inhibition thereby controls the oscillatory cycle of the population. Reproduced from Fries P (2015). Rhythms for cognition: communication through coherence. *Neuron* 88: 220–235. doi:10.1016/j.neuron.2015.09.034 with permission of Elsevier.

neuronal oscillations is linked to the discovery of the human EEG (Berger, 1929), their role has been mostly ignored for decades. The field took a pragmatic turn in the early 1990s, when several groups suggested that synchronized oscillatory brain activity could constitute a key mechanism of information processing and transfer in the cortex (Gray et al., 1989; Engel et al., 1991; König et al., 1995; Singer and Gray, 1995). Subsequently, the focus shifted away from event-related brain activity to studying ongoing background activity utilizing spectral analyses to explain how oscillatory dynamics shape subsequent cortical responses and behavior (Fries, 2005; Siegel et al., 2012; Engel et al., 2013; Helfrich and Knight, 2016).

00065 Initially, it has been hypothesized that synchronized neuronal activity might enable efficient feature integration or binding from different neuronal populations, offering a possible mechanism for how different task-relevant features are simultaneously encoded and integrated (Singer and Gray, 1995). Subsequently, the psychophysiological binding-by-synchrony hypothesis (Engel et al., 2001) has been extended into a more physiological model of information routing in the cortex by means of the communication-by-coherence hypothesis (Fig. 3.2; Fries, 2005).

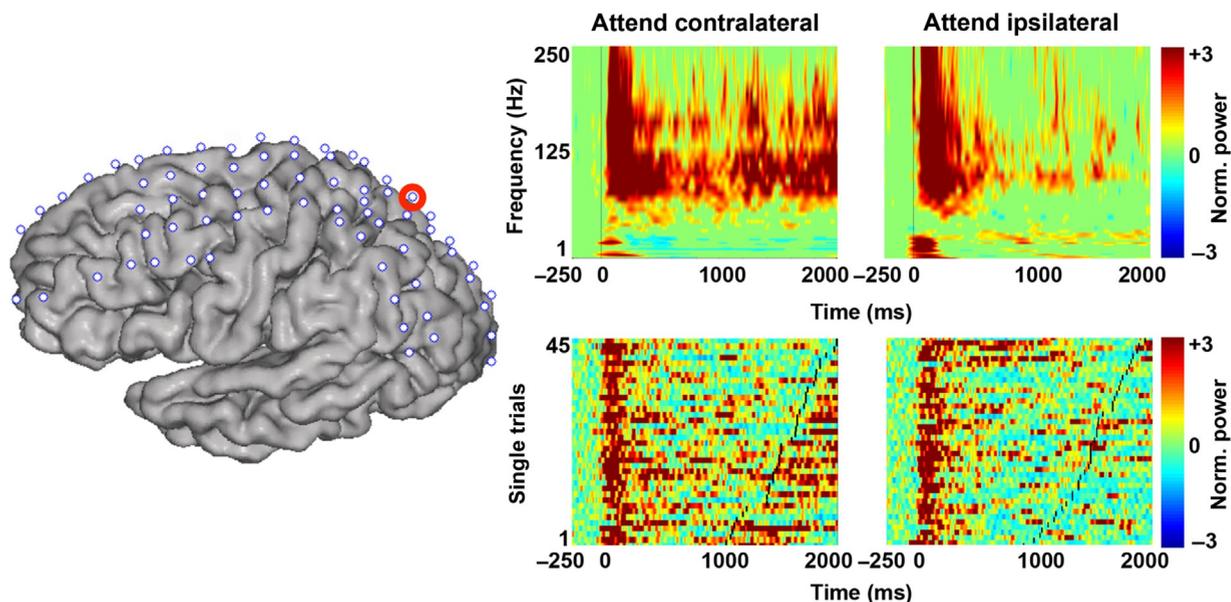
Recently, it has been postulated that different cognitive states might be encoded in distinct spectral fingerprints in large-scale cortical networks (Siegel et al., 2012) and that the cortex utilizes independent frequency bands and communication channels to effectively multiplex cortical computations by separating them in the frequency domain (Engel et al., 2013; Knight and Eichenbaum, 2013; Lisman and Jensen, 2013; Akam and Kullmann, 2014).

While invasive recordings in rodents and primates indicated that neuronal firing modulates the local field potential, the exact relationship remains unclear (Buzsáki, 2006; Buzsáki et al., 2012). Recently, it has been suggested that the LFP is not only a result of neuronal firing, but also constitutes a feedback mechanism to guide cortical spiking activity (Fröhlich and McCormick, 2010). While primate research has made major contributions to our current understanding of cortical physiology and how it shapes behavior, it is not fully understood whether these findings generalize to human behavior (Pesaran et al., 2008; Crowe et al., 2013).

First, invasive recordings in primate provide a better spatial resolution (submillimeter) range than invasive recordings in human epilepsy patients (subcentimeter) or noninvasive methods (multiple centimeters). Second, although the level of spectrally decomposed LFPs under 100 Hz could theoretically allow for a direct comparison between species (Buzsáki and Draguhn, 2004; Buzsáki et al., 2012), they often do not provide the reliability to link single-trial dynamics to behavior.

Hence, the discovery of high gamma (HG) or high frequency activity (HFA, 70–150 Hz) in the human cortex (Fig. 3.3) constituted a substantial advance in linking single-trial activity in humans to behavior (Crone et al., 1998; Edwards et al., 2005; Szczepanski et al., 2014).

Primate recordings indicated that HFA might be a suitable surrogate marker for multiunit activity (Ray and Maunsell, 2011). However, to date all the evidence has been obtained from recordings in sensory areas and it remains unclear if these correlations generalize to higher-order association cortices. Nevertheless, HFA analyses enabled researchers to adopt analytic approaches from the single-unit field and bridge human and primate research. For example, it has been well established that spikes are preferentially coupled to certain phases of low frequency LFP components (spike-field-coupling; Womelsdorf et al., 2007; Rutishauser et al., 2010; Vinck et al., 2012). Given that spikes and HFA are strongly correlated, this approach has been extended into studying the coupling between low-frequency oscillations and HFA in the human cortex (referred to as cross-frequency coupling (CFC); Canolty et al., 2006). In particular, phase-amplitude coupling (PAC) where the phase of slower oscillations predicts

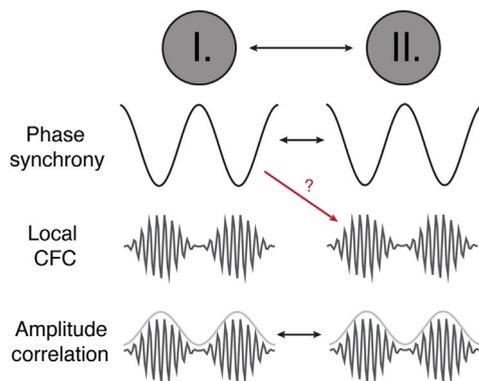


f0020 **Fig. 3.3.** High-frequency activity in human ECoG. An example parietal electrode from a single subject with implanted ECoG electrodes is depicted (*red circle*). The patient performed a lateralized attention task. *Left*: Electrode placement. *Right*: *Upper row*: Sustained high-frequency activity can be observed on the trial averaged spectrogram. Note the increase in the 70–250 Hz range, which is stronger for contralateral than ipsilateral covert attention shifts. *Lower row*: Single-trial stacked HFA responses. Every line depicts one trial; the *black dashed line* reflects the reaction time on every trial. Note that trials are sorted by reaction time. Note the increase in HFA relative to the cue, which was present for approximately 300–500 ms in all trials. Subsequently, the effect is less pronounced from 500 ms to the motor response but appears sustained on the trial-averaged spectrogram (*upper row*). However, note the different patterns between attend contralateral and ipsilateral to the grid electrode, which is present on the single trial level. Reproduced from Szczepanski SM, Crone NE, Kuperman RA et al. (2014). Dynamic changes in phase-amplitude coupling facilitate spatial attention control in fronto-parietal cortex. PLoS Biol 12: e1001936. doi:10.1371/journal.pbio.1001936 with permission from the authors under the Creative Commons Attribution (CC BY) license.

the amplitude of HFA has been studied in great detail (Canolty and Knight, 2010; Lisman and Jensen, 2013; Aru et al., 2015; Hyafil et al., 2015). Over the last decade, CFC has been interpreted as a metric that captures the temporal coordination within and across cortical regions and has been linked to a variety of cognitive functions (Hyafil et al., 2015; Helfrich and Knight, 2016). Notably, CFC and phase synchrony metrics or amplitude correlations, which are similar to fMRI functional connectivity metrics, are not fully independent from each other (Fig. 3.4), but might be systematically related (Hipp et al., 2012; von Nicolai et al., 2014). Recently, it has been demonstrated that CFC is sensitive to nonlinear sharp transients in the underlying signal and several groups have urged caution when interpreting CFC results (Aru et al., 2015; Gerber et al., 2016; Scheffer-Teixeira and Tort, 2016; Cole and Voytek, 2017).

s0025 **INTRACRANIAL ELECTROPHYSIOLOGY OF THE PFC—A GAME CHANGER**

p0095 Much of our understanding about the function of the PFC was obtained from carefully studying patients with circumscribed lesions in different prefrontal areas



f0025 **Fig. 3.4.** Interareal connectivity and cross-frequency coupling. Schematic illustration of how different connectivity metrics are related: two hypothetical populations (I and II) could be phase synchronous and exhibit local cross-frequency coupling. Hence, the amplitudes of the high-frequency activity should also be correlated over time, which might be reflected in interareal phase-amplitude coupling (PAC; *red arrow*). However, it is currently unclear whether these phenomena always interact or whether they could occur in isolation. Adapted from Helfrich RF, Knight RT (2016). Oscillatory dynamics of prefrontal cognitive control. Trends Cogn Sci 20: 916–930. doi:10.1016/j.tics.2016.09.007 with permission of Elsevier.

(Szczepanski and Knight, 2014). In addition, a multitude of imaging studies localized and thus confirmed the involvement of prefrontal regions to support higher cognitive functions (Sakai, 2008; Stuss and Knight, 2013). In a separate line of research, several groups have studied single-unit activity in primates, providing important insights into cognitive processing at the single neuron level (Miller and Cohen, 2001). However, both approaches are also inherently limited in their spatiotemporal resolution. While imaging and lesions provide information at the macroscale, studying SUA only provides insights on the microscale (Rainer et al., 1998; Wallis et al., 2001; Pesaran et al., 2008; Crowe et al., 2013), often limited to only one or two cortical regions. Here we argue that intracranial electrophysiology in humans bridges this gap on the mesoscale (Fukushima et al., 2015), in which novel recording and analysis techniques provided valuable insights into cortical coding and information transfer (Quiñan Quiroga and Panzeri, 2009; Panzeri et al., 2015). In order to highlight the power of the intracranial approach, we describe three exemplary studies where intracranial recordings substantially extended our understanding of cognition. These examples are by no means exhaustive, but provide a starting point to illustrate the strength of this approach: (1) the use of HFA to pinpoint cognitive processes in space and time; (2) the single-trial reliability; and (3) the precise timing information in large-scale networks. After the introductory examples, we will discuss various key concepts in more detail.

The role of Broca's area for speech production

In 1861, Broca described two patients with damage to the left inferior frontal gyrus, who exhibited severely impaired speech production. Since then, a number of fMRI studies have linked activity in Broca's area to a variety of language-related tasks. However, activations in Broca's area were not limited to speech production and several cases were reported where patients could still speak despite the obvious destruction of Broca's area (Dronkers et al., 1992, 2004).

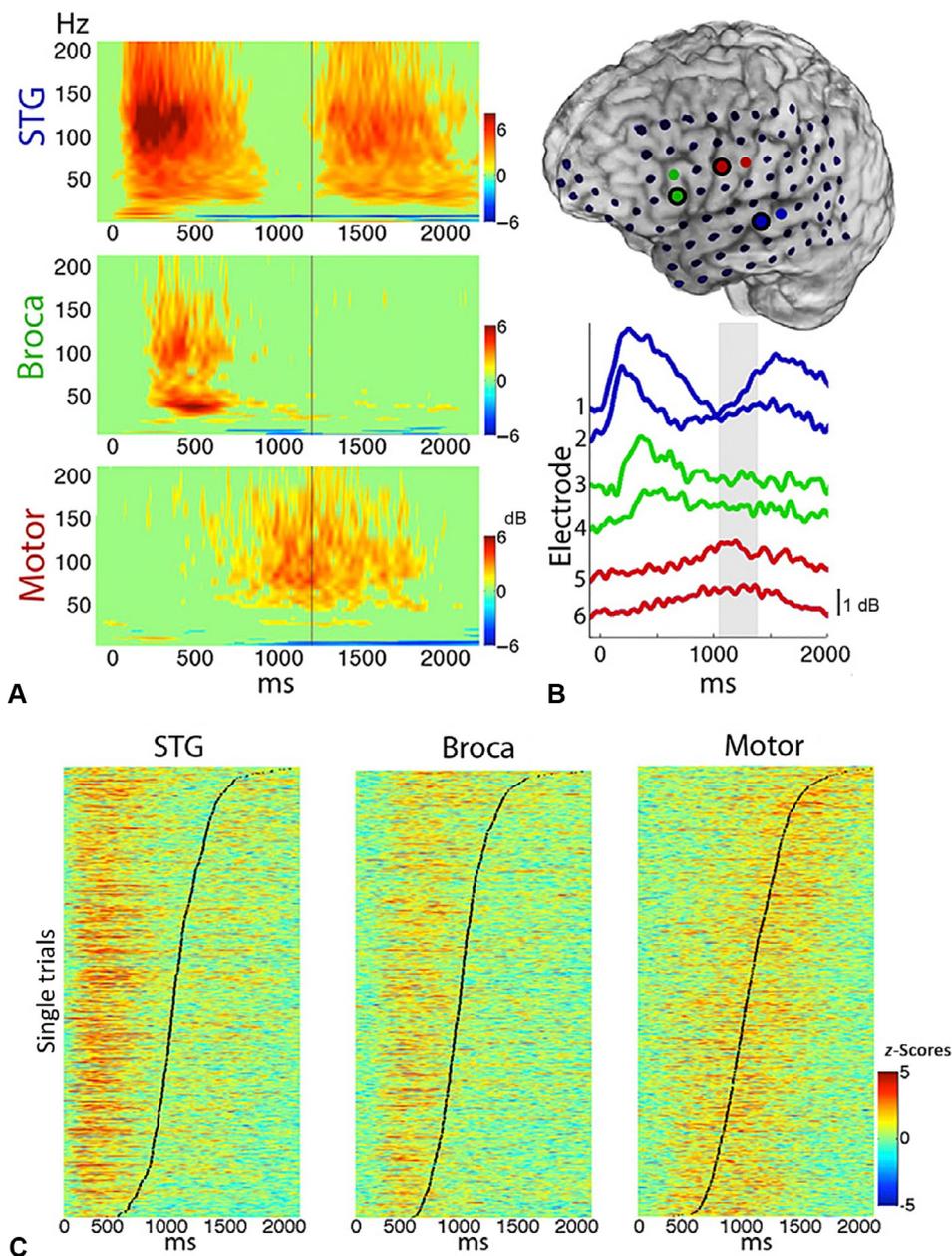
In a recent study, Flinker et al. (2015) recorded ECoG from epilepsy patients while they performed a cued word production task. Their results indicated that Broca's area mediates the transformation from sensory representation to spoken words through reciprocal connections with both temporal and motor cortex. However, contrary to the expected activation of Broca's area during speech production, they observed that it remained silent, while motor cortex was active. This provides direct evidence that Broca's area is not involved in speech production per se, but rather encodes the information and establishes an articulatory plan, which is then executed by motor cortex. Crucially, this effect was visible on single trials (Fig. 3.5).

Sustained neuronal firing as a correlate of working memory maintenance

Delay activity in the prefrontal cortex has been suggested to constitute the neuronal correlate of working memory to maintain information online (Fuster and Alexander, 1971; Christophel et al., 2017; Leavitt et al., 2017). However, several recent studies indicated that this view might be oversimplified (Sreenivasan et al., 2014; Rose et al., 2016). First, the sustained activity in the delay period could rather reflect an artifact of averaging across multiple trials, which were characterized by discrete activity bursts (Stokes and Spaak, 2016). Hence, averaging across multiple bursts might have resulted in a smooth trace that appeared sustained (Warden and Miller, 2007; Watanabe and Funahashi, 2007). Second, in a recent dual-task experiment an attentional modulation was added to the working memory experiment (Watanabe and Funahashi, 2014). The authors reported that the sustained delay activity was absent when attention was directed away from the memory task. However, the monkeys were still able to recall the items held in memory. These observations led to the hypothesis that working memory might be encoded in an activity-silent manner by transiently shifting synaptic weights (Stokes, 2015). Stokes and colleagues reasoned that if the task context or content of working memory are encoded in a static code, then a pattern classifier trained on previous time points should be able to predict the information held in memory on subsequent samples (Stokes et al., 2013; Spaak et al., 2017). However, they reported only limited evidence for this consideration. Rather, their results supported a dynamic, activity-silent code, which implied that pattern discrimination is only successful at a given time point but does not necessarily generalize across time. Implications of the findings will be discussed in detail later.

Representation of task-relevant information in large-scale networks

For decades, it has been thought that different brain areas are specialized and subserve distinct cortical functions. For example, distinct sensory regions encode different task-relevant aspects (e.g., color in V4 and motion in MT+), which are then integrated in higher-order frontoparietal association cortex (e.g., PFC). This notion has recently been challenged in an experiment where two monkeys performed a flexible categorization task (Siegel et al., 2015). As expected, the authors found that sensory information was encoded in early sensory regions and then flowed to higher-order frontoparietal association areas, while choice information first emerged in frontal areas and subsequently peaked in downstream



f0030 **Fig. 3.5.** Revisiting the role of Broca's area for speech production. (A) Trial-averaged responses at representative electrodes over superior temporal gyrus (STG), Broca's area, and motor cortex. During every trial, subjects listened to a word and then repeated it. Cortical activations were first observed in STG during word perception, then in Broca's area, and finally in motor cortex during word production. Note that Broca's area is only active prior to production onset, while STG is again active during word production, which is related to the perception of the spoken word. (B) *Upper*: Electrode coverage and electrode locations. *Lower*: Time-course of HFA activity. (C) Stacked single trials that were sorted relative to the reaction time (*black line*). Again, note the reliability of the signal-on-single trials. The activation of Broca's area is clearly visible as well as its sustained activity, which terminates just prior to the motor response. These findings clearly indicate that Broca's area is involved in sensorimotor transformations of speech, but not involved in actual speech production. Reproduced from Flinker A, Korzeniewska A, Shestyuk AY et al. (2015). Redefining the role of Broca's area in speech. *Proc Natl Acad Sci USA* 112: 2871–2875. doi:10.1073/pnas.1414491112 with permission from the authors.

regions. However, information about all task-relevant aspects was present in all sampled cortical regions, thus supporting the notion that information is distributed across large-scale networks. Analyses of peak latencies

indicated that at least some of the information is encoded in parallel. However, this study did not address whether information was redundant or if distinct features were encoded in different cortical regions. In addition, it is

currently not clear how information is transferred between regions. Similar findings were obtained from working memory tasks, where information about the items held in memory could be decoded from frontal as well as parieto-occipital regions, indicating that at least some information is redundant (Christophel et al., 2017; Leavitt et al., 2017).

REVISITING THE NEURON DOCTRINE

The neuron doctrine is one of the foundations of modern neuroscience and states that the single neuron constitutes the structural and functional unit of the CNS (Golgi, 1906). The doctrine was first conceptualized by Golgi in the 19th century and later received a multitude of experimental support, including the seminal work of Hubel and Wiesel (1962) and Barlow (1953), who suggested that individual neurons are highly selective and are only tuned to very specific features. While early recordings were only made from one or a few neurons at a time, modern neuroscience enabled scientists to record from tens to hundreds of neurons simultaneously. One intriguing observation was that a surprising number of randomly sampled neurons encoded task-relevant aspects. For example, several microelectrode studies recording from prefrontal cortex suggested that around 90% of the recorded cells are active during one or more task epochs (Warden and Miller, 2007; Watanabe and Funahashi, 2007; Barak et al., 2010; Stokes et al., 2013). Were these groups simply fortunate to have sampled from highly task-active populations, or does this population activity actually support cognitive processing?

In a theoretically different account from Golgi or Barlow, Hebb and others suggested that neuronal assemblies might constitute the functional unit of the nervous system (Hebb, 1949). This notion has received substantial experimental support in recent years by taking full advantage of large-scale recordings and novel methods to analyze network interactions and population-based information coding (Quiñones Quiroga and Panzeri, 2009; Yuste, 2015; Eichenbaum, 2017). Regarding prefrontal cortex, it has repeatedly been demonstrated that most randomly sampled neurons are task-active and that the same group of neurons exhibits highly context-dependent alterations in their firing rates (Warden and Miller, 2007; Meyers et al., 2008; Mante et al., 2013; Rigotti et al., 2013; Stokes et al., 2013). While information about all task-relevant aspects could be decoded from the population at all times during the task, individual neurons showed complex patterns, which could not be explained by a linear summation of two task-relevant variables (Meyers et al., 2008; Barak et al., 2010; Rigotti et al., 2013). These findings strongly supported the

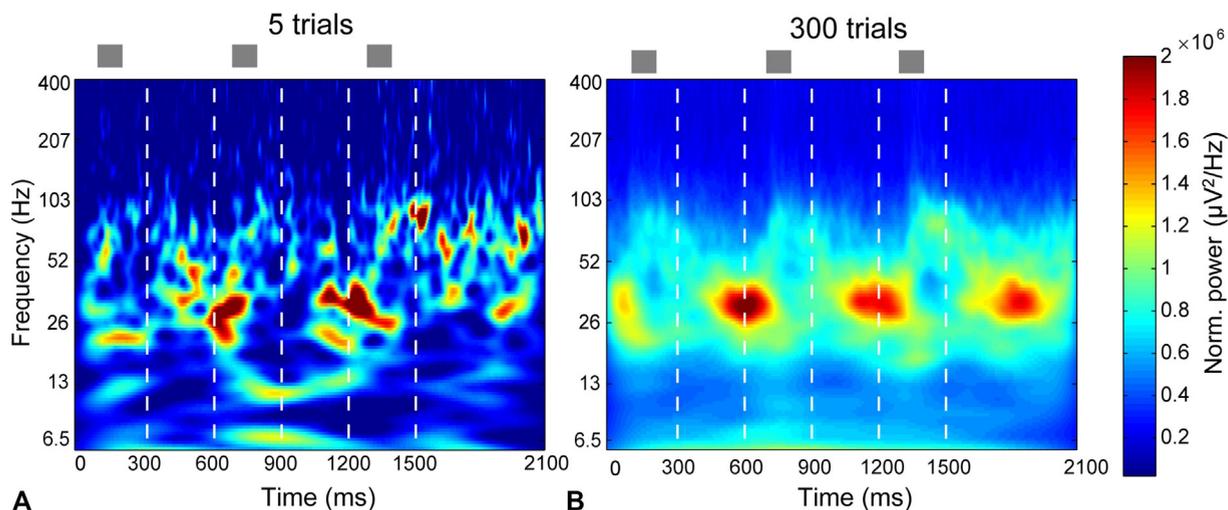
hypothesis that cell assemblies are the functional unit of the brain and code information in high dimensional neuronal representations (Fusi et al., 2016). Similar findings have been reported in the inferotemporal cortex of macaques or the hippocampus in rodents (Eichenbaum, 2017). Despite substantial evidence for population-based coding in rodents and primates, human single-unit research is still largely focused on single neurons and how they respond to one specific task-aspect (Fried et al., 2014; Kamiński et al., 2017; Kornblith et al., 2017; Mormann et al., 2017).

MIXED SELECTIVITY AND DYNAMIC CODING FOR COGNITIVE FLEXIBILITY

In the case of the PFC, two related key observations have gained interest in recent years. The first is population-based coding, where single neurons exhibit complex response patterns that depend on the current task context (Meyers et al., 2008; Barak et al., 2010; Rigotti et al., 2013; Stokes et al., 2013; Panzeri et al., 2015). This feature has also been described as mixed selectivity at the single cell level within an assembly. In particular, a neuron might respond to a specific object 1 in context A, but not object 2. If task demands or rules change (i.e., context B), then the same neuron might respond to object 2 instead, but not object 1 (Warden and Miller, 2007, 2010; Rigotti et al., 2013). This mechanism might support an adaptive mapping of any task onto a cell population according to current task demands and therefore support cognitive flexibility (Fusi et al., 2016).

Mixed selectivity also implies that the neuronal population can alter its current state into a number of possible complex configurations. These configurations can be represented in a N -dimensional coordinate system. Here, N corresponds to the number of possible task-relevant combinations. For example, in Rigotti et al. (2013), monkeys were presented with 2 consecutive objects out of a set of 4, yielding 12 possible combinations (objects A–B, A–C, A–D, B–A, B–C, B–D, etc.), which were presented in two different contexts. Hence, the maximal dimensionality N was 24—i.e., a maximum of 24 different configurations was needed to map every possible task–object relationship onto the population. This study highlights the behavioral relevance of high dimensional representations by demonstrating that the dimensionality is significantly lower in error trials. This was interpreted as evidence for the notion that current task demands need to be encoded by the cell assembly. Any errors during encoding lead to a breakdown of dimensionality and predict that the monkey will make a mistake.

The second concept is closely related and has been described as dynamic coding (Meyers et al., 2008; Stokes et al., 2013; Spaak et al., 2017). In the past,



0035 **Fig. 3.6.** The effect of analyzing trial-averaged responses. Single-trial dynamics are lost in population and trial averages. (A) Average across five trials during a working memory task reveals an inconsistent spectral patterning with bursts in multiple-frequency bands that are short lasting and irregular. (B) Average across 300 trials. Now the representation appears smooth and shows prominent dynamics in the beta band (~ 30 Hz), which do not necessarily reflect single-trial dynamics and might lead to erroneous interpretations about the underlying process. Reproduced from Lundqvist M, Rose J, Herman P et al. (2016). Gamma and beta bursts underlie working memory. *Neuron* 90, 152–164. doi:10.1016/j.neuron.2016.02.028 with permission of Elsevier.

sustained activity in the delay period has been thought to reflect a hallmark of working memory (Fuster and Alexander, 1971; Sreenivasan et al., 2014). Recently, it became clear that this sustained activity might actually reflect an averaging artifact (Lundqvist et al., 2016; Stokes and Spaak, 2016). While single trials might exhibit bursts of spiking or oscillatory activity, the averaging of hundreds of trials might actually smear out effects, which then appear as sustained (Fig. 3.6). Similar considerations might apply to decision-making processes (Latimer et al., 2015).

p0145 In order to ascertain whether the coding at the population level remains stable over time, Stokes et al. utilized a multivariate pattern classification approach (Stokes et al., 2013). They demonstrated that at time point t , a pattern classifier could successfully discriminate different trial types. Crucially, they also attempted to train the classifier on time point t and then classify later time points. While they found robust evidence for time-specific coding, the classifier did not generalize to later time points when being trained during cue presentation. However, this failure to generalize to later time points did not imply that no discriminative information was present, but rather suggested that the coding at the population level changed over time. Notably, they found evidence for a generalization in the delay period, pointing toward more stable population codes (Fig. 3.7). They suggested that this time-varying coding could most likely be attributed to shifts in synaptic weights (Stokes, 2015). While early processing requires a high dimensional active space, the system settles into a low dimensional, possibly

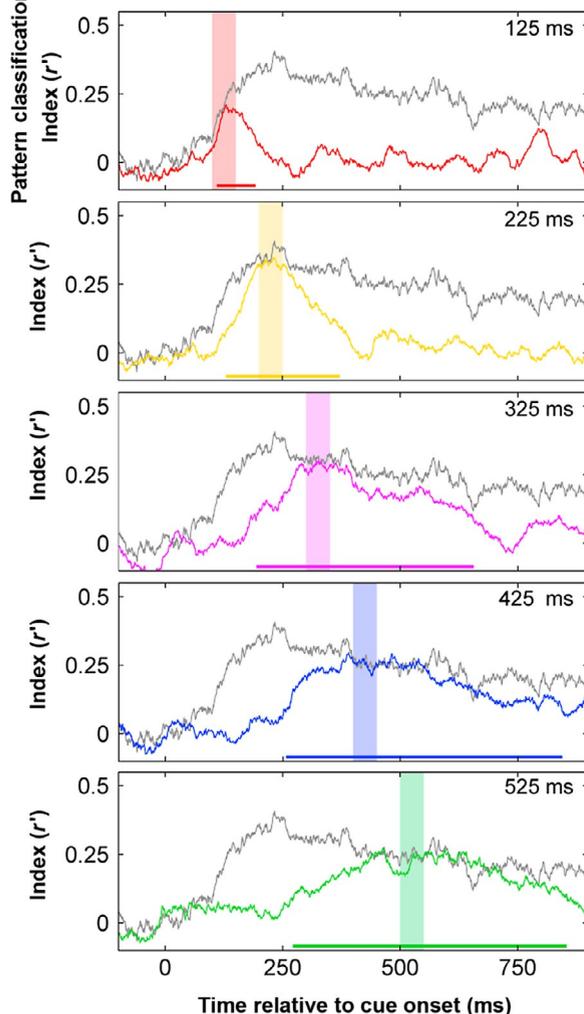
more energy-efficient, state after encoding, which would explain why population coding might change from dynamic to more stable codes.

Critically, a coding scheme at the synaptic level might be p0150 “activity-silent,” i.e., a set of cues, rules, or contexts does not induce significant differences in mean firing rates or oscillatory power (Stokes, 2015). In a related study, Buschman et al. demonstrated that encoding of different task rules was mediated by shifting phase relationships of oscillatory signatures at the population level (Buschman et al., 2012).

These findings raised the question of how activity-silent coding at the synaptic level could be quantified. p0155 Recently, Wolff et al. conceived a novel analytical approach, which was inspired by echolocation (Wolff et al., 2015, 2017). By presenting a task-irrelevant, high-contrast, visual impulse stimulus in the delay period, they evoked a strong visual response, which contained decodable information about the content of working memory, even when the content was not decodable prior to impulse presentation. These findings support the idea of activity-silent population encoding at the synaptic level. Taken together, both mixed selectivity and dynamic coding contradict the neuron doctrine (Eichenbaum, 2017); rather they highlight the importance of a population-based code to support cognitive flexibility and dynamic cognitive control (Yuste, 2015).

THE TIMESCALE OF COGNITION

We experience the world as continuous, while brain activity is inherently rhythmic (Helfrich and Knight, 2016). p0160



f0040 **Fig. 3.7.** Stable and dynamic coding in prefrontal cortex. Results from cross-temporal classifiers to distinguish different trial types and contexts. Cue onset was at time point 0. The time-point by time-point decodability is displayed in gray for reference. Here the decoding algorithm was trained on a 50-ms window of data (shaded area) and then tested on all time points during the trial. Color-coded significance bars are displayed below the respective trace. Note that in the first 225 ms (first two panels), the classifier only predicts trial type correctly in a narrow time window. In contrast, at later time points, training the classifier on 50 ms of data (panels 3–5) generalizes to other time points. This indicates that the population code is dynamic during initial encoding (0–500 ms) and more stable during the delay period (500 ms onward). Reproduced from Stokes MG, Kusunoki M, Sigala N et al. (2013). Dynamic coding for cognitive control in prefrontal cortex. *Neuron* 78: 364–375. doi:10.1016/j.neuron.2013.01.039 with permission of Elsevier.

This has led to the intriguing hypothesis that if neuronal oscillations constitute the neuronal basis for cognitive processing, then these rhythms should modulate perception and higher cognitive functions (Thut et al., 2012). To empirically examine this hypothesis, behavior is

typically sampled on a fine-grained temporal scale over several hundred milliseconds in small steps (Landau and Fries, 2012; Fiebelkorn et al., 2013). For example, in a recent study we probed visual target detection performance over 850 ms by sampling 25 discrete bins in 34-ms steps (Helfrich et al., 2017). We replicated the observation that target detection performance cycles are a function of the parieto-occipital alpha (8–12 Hz) phase (Busch et al., 2009; Mathewson et al., 2009, 2012; Spaak et al., 2014). Thus the average performance changed by up to 10% as a function of the presentation phase (Fig. 3.8). Next, we added an additional top-down cue that predicted the upcoming target in the preceding rapid visual stream. Previous lesion evidence had suggested that DLPFC lesion patients do not show a behavioral benefit from the predictive cue (Fogelson et al., 2009).

We hypothesized that if cognition operates in a rhythmic mode, then the alpha-dependent target detection performance should be modulated by a second rhythm (Song et al., 2014; Zoefel and Sokoliuk, 2014). We identified a delta (~4 Hz) signature that modulated perceptual alpha cycles in the top-down condition, but not in the absence of a predictive cue. Simultaneous source-reconstructed EEG recordings confirmed that the perceptual sampling in the alpha range originated from parieto-occipital areas, while the delta rhythm arose from the prefrontal areas and modulated posterior alpha activity in a top-down manner (Fig. 3.9).

Similar periodic fluctuations in behavior that reflect the timescale of endogenous processes have been found for visual perception (Mathewson et al., 2012; de Graaf et al., 2013; Spaak et al., 2014) and attention (Landau and Fries, 2012; Fiebelkorn et al., 2013), as well as for human decision-making (Wyart et al., 2012).

In particular, attention research (Carrasco, 2011) has shifted its focus away from studying how attention samples the spatial dimension (e.g., space or objects) and more toward investigating how attentional processes evolve over time (Buschman and Kastner, 2015). A series of studies (Landau and Fries, 2012; Fiebelkorn et al., 2013; Song et al., 2014; Landau et al., 2015) demonstrated that visual perception at a cued location is sampled at approximately 8–12 Hz, while unattended spatial positions are only monitored at a slower rhythm (~4 Hz). Jointly, these findings provide evidence that cognition operates in a rhythmic mode and exhibits fluctuations that can be attributed to periodic endogenous processes.

PREFRONTAL CORTEX DEPENDENT LARGE-SCALE NETWORKS

The PFC is widely connected to different cortical regions through reciprocal connections (Miller and Cohen, 2001). A long-standing hypothesis of prefrontal

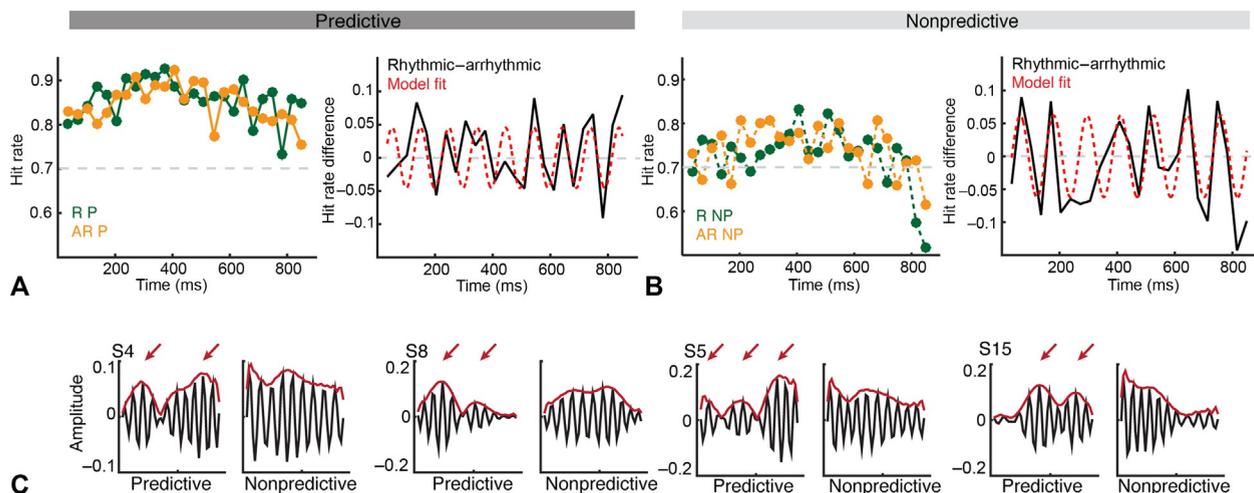


Fig. 3.8. The rhythmic nature of cognition. (A) Mean accuracies averaged across subjects for 25 distinct time bins (34–850 ms in 34-ms steps). Note the time-varying nature of the behavioral time course. Contrasting rhythmic and arrhythmic conditions in the predictive context are well approximated by a 10-Hz sine fit, thus highlighting the rhythmic sampling of the visual environment over time. (B) Contrast of rhythmic–arrhythmic for the nonpredictive condition. Same conventions as in (A). (C) Individual hit rate fluctuations in the alpha band exhibit slow rhythmic modulations in the predictive top-down condition (*red arrows*), which are not present in the control condition. These findings point toward the rhythmic nature of cognitive processing in the delta/theta range. Interestingly, the observed timescale is in line with the timing for conscious awareness in the classic experiments by Libet (2002). Reproduced with permission from Helfrich RF, Huang M, Wilson G, Knight RT (2017). Prefrontal cortex modulates posterior alpha oscillations during top-down guided visual perception. *Proc Natl Acad Sci USA* 114: 9457–9462.

executive control suggested that activity patterns in the PFC selectively bias neural activity in distant cortical regions to route information to task-relevant cortical regions (Pesaran et al., 2008; Crowe et al., 2013; Voytek et al., 2015). The influential Communication-through-Coherence (CTC) theory (Fries, 2005, 2015) suggested that the selective synchronization of task-relevant neuronal populations establishes transient coalitions of neuronal assemblies, which support cognition (Siegel et al., 2012). Crucially, phase alignment is thought to optimize the spiking activity; that is, a volley sent from population A arrives at an optimal, highly excitable, phase of population B. While the original CTC implied that two populations are optimally aligned at zero phase lags, several more realistic recent models take interareal conduction delays into account (Baldauf and Desimone, 2014; Bastos et al., 2015a). Furthermore, the original CTC could not explain how feedforward and feedback information could be transferred between two neuronal populations along the same anatomic pathways. More recently, the concept of oscillatory multiplexing provided a powerful solution (Watrous et al., 2013; Akam and Kullmann, 2014). Multiplexing implies that information along the same pathway might be transmitted on different frequency bands, similar to FM transmitters for radio reception where one can tune into different, simultaneously active channels. In recent years, several groups have provided evidence that distinct spectral signatures support bottom-up and top-down processing along the same

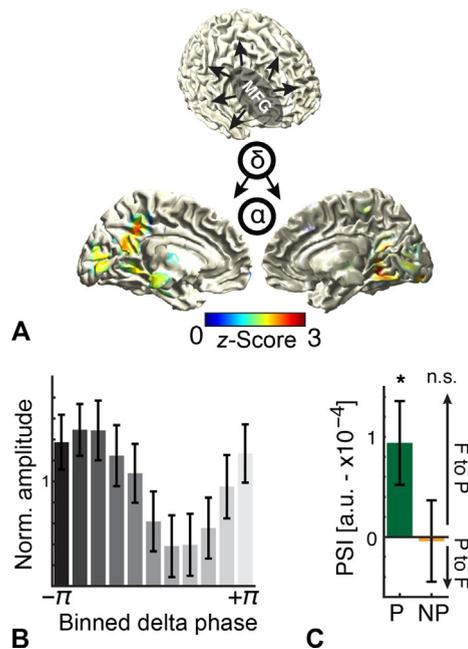
anatomic pathways (Bastos et al., 2015b; Michalareas et al., 2016). For instance, while gamma oscillations (30–80 Hz) are thought to reflect bottom-up processing, beta-band signatures (13–30 Hz) are often implicated in top-down processing to support conscious perception and goal-directed behavior (Buschman et al., 2012; Micheli et al., 2015; Lundqvist et al., 2016).

Several other influential theories have emphasized the role of, e.g., alpha oscillations (8–12 Hz) as a gating mechanism to block out irrelevant sensory information and optimize the cortical processing architecture on both the micro- and macrolevel (Klimesch et al., 2007; Jensen and Mazaheri, 2010; Klimesch, 2012; Jensen et al., 2014). Slow-frequency delta (1–4 Hz) and theta oscillations (4–7 Hz) have been linked to a number of processes, but they might play a pivotal role in context-dependent processing and memory formation (Anderson et al., 2010; Rutishauser et al., 2010; Lisman and Jensen, 2013; Watrous et al., 2013; Cavanagh and Frank, 2014).

We will now focus on PFC-dependent large-scale cortical and subcortical interactions to highlight the role of selective oscillatory synchronization and timed information transfer for cortical processing.

Prefrontal–cortical connectivity

The frontoparietal network, which is often referred to as the attention network (Buschman and Kastner, 2015; Scolari et al., 2015), is thought to provide the structural

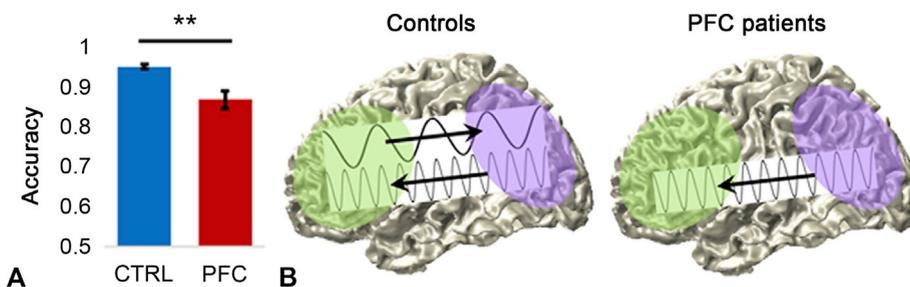


10050 **Fig. 3.9.** Prefrontal-dependent top-down control of posterior alpha activity. (A) Prefrontal top-down control of alpha activity (8–12 Hz) in ventromedial parieto-occipital cortex was mainly mediated by activity in the delta/theta range (~4 Hz) in the right middle frontal gyrus. (B) Posterior alpha amplitude (y-axis) was predicted by the phase of the frontal delta/theta signature (x-axis). Note the nonuniform amplitude distribution relative to the delta phase. (C) Directionality analyses indicated that this prefrontal driving was only present in the predictive, but not in the nonpredictive, condition. Reproduced with permission from Helfrich RF, Huang M, Wilson G, Knight RT (2017). Prefrontal cortex modulates posterior alpha oscillations during top-down guided visual perception. *Proc Natl Acad Sci USA* 114: 9457–9462.

foundation for a multitude of cognitive functions (Helfrich and Knight, 2016). While most of the evidence is still correlative in nature, several lesion or noninvasive brain stimulation studies aimed to provide causal evidence for the importance of frequency-specific interaction for cognitive processing (Herrmann et al., 2016; Thut et al., 2017).

For example, a recent lesion EEG study investigated the role of PFC for working memory performance. Johnson et al. replicated the commonly observed finding that PFC lesion patients had impaired memory recall performance (Duarte et al., 2005; Szczepanski and Knight, 2014; Johnson et al., 2017). Notably, their performance was still significantly above chance level, indicating that the PFC has a modulatory and not an exclusive role in supporting working memory. Subsequently, the authors demonstrated that bottom-up signals in the alpha-beta band (9–24 Hz) were intact in PFC lesion patients, but top-down signals from PFC to parieto-occipital areas in the delta-theta band (2–7 Hz) were absent in patients with PFC lesions. These findings support the notion that multiple, frequency-specific bidirectional networks support white matter (WM) (Fig. 3.10). Hence, DLPFC lesions only abolish top-down modulatory signals, while bottom-up processing remains intact and explained why patients still perform significantly above chance (>80% correct). These findings challenge classic PFC-centric models of WM and support theories of distributed memory maintenance in higher-order sensory areas (Sreenivasan et al., 2014; Leavitt et al., 2017).

Converging evidence from imaging, fiber tracking, brain stimulation, electrophysiology, lesions, and behavior indicates that processing in early sensory areas is



10055 **Fig. 3.10.** Bidirectional frontoparietal connectivity supports working memory. (A) Behavioral results. Memory recall performance was better in healthy controls than in DLPFC lesion patients. However, patients performed well above chance level (0.5), indicating that all patients were able to perform the task despite prefrontal damage. (B) Schematic illustration of two distinct bidirectional systems supporting WM. While the bottom-up (posterior to PFC; purple to green) system in the alpha/beta range remained intact in PFC patients, the top-down PFC-dependent delta/theta system was attenuated in patients. Since the PFC lesion patients still demonstrated task proficiency, the authors reasoned that the bottom-up system might be sufficient for WM, while the prefrontal system only exerts moderate modulatory influences in this task. Reproduced from Johnson EL, Dewar CD, Solbakk A-K et al. (2017). Bidirectional frontoparietal oscillatory systems support working memory. *Curr Biol* 27: 1829–1835. doi:10.1016/j.cub.2017.05.046 with permission of Elsevier.

PFC-dependent (Barceló et al., 2000; Voytek and Knight, 2010; Voytek et al., 2010; Szczepanski and Knight, 2014; Marshall et al., 2015a,b; Helfrich et al., 2017). For example, it has been demonstrated that prefrontal damage reduced neuronal activity in extrastriate cortex of the lesioned hemisphere as early as at 125 ms after stimulus presentation (Barceló et al., 2000). In addition, it has been reported that the volume of frontoparietal WM tracts correlates with their ability to lateralize behaviorally relevant alpha and gamma oscillations in a lateralized spatial attention task (Marshall et al., 2015a). Hence, transient (Marshall et al., 2015b) or permanent (Voytek and Knight, 2010) deactivation of regions in DLPFC has a profound impact on the oscillatory architecture in distant cortical sites (Helfrich and Knight, 2016).

To date most studies have focused on frequency-specific interactions, which did not explain how information could be transferred across different temporal scales. Neocortical cross-frequency coupling (Fig. 3.4; Canolty et al., 2006; Canolty and Knight, 2010) was described a decade ago. Subsequently, CFC was used to capture interactions in the frontoparietal network during working memory processing (Friese et al., 2013), selective spatial attention (Szczepanski et al., 2014), or top-down guided contextual processing (Helfrich et al., 2017).

Prefrontal–subcortical connectivity

In addition to being widely connected to multiple cortical regions, the PFC is also linked to subcortical structures such as the hippocampus (Anderson et al., 2010; Brincat and Miller, 2015; Place et al., 2016), the cingulate (Voloh et al., 2015), and thalamus (Sweeney-Reed et al., 2014, 2015). Here, we first focus on prefrontal–thalamic interactions, which have not been widely studied, given the difficulty to record electrophysiological signals from the thalamus in humans.

In recent years, interest in the thalamo–cortical interactions has been fueled by several findings that suggested that the thalamus regulates cortical information flow and might be an important relay station to coordinate cortical networks. For example, Saalman et al. demonstrated that thalamic control of two distant cortical sites (V4 and TEO: temporo–occipital cortex) induced zero phase-lag synchronization at the cortical level (Saalman et al., 2012). This finding was extended to prefrontal–thalamic interactions during rule-guided attentional control (Schmitt et al., 2017). This provides evidence that the thalamus plays a crucial role in controlling cortical excitability (Guo et al., 2017). This is in line with the observation that thalamo–cortical connectivity depends on the general arousal state as measured by pupillometry. Stitt et al. reported that different frequency

bands mediate feedforward and feedback interactions between thalamus and cortex: connectivity in the delta/theta band (~4 Hz) was driven by the thalamus and monotonically increased with increased pupil size indexing higher arousal levels. In contrast, connectivity in the alpha band was driven by neocortical regions and was inversely modulated by arousal: high alpha synchronization in states of low arousal, and low alpha synchronization in states of high arousal (Stitt et al., 2017).

Invasive recordings from epilepsy patients offer the rare opportunity to record directly from the human thalamus. For example, Sweeney-Reed et al. took advantage of simultaneous intracranial thalamic recordings and external EEG recordings (Sweeney-Reed et al., 2014, 2015). They reported that successful memory encoding is associated with stronger thalamocortical phase synchronization in the theta band. These rare clinical opportunities provide significant insights into thalamus-dependent large-scale dynamics underlying higher cognitive functions.

Prefrontal-dependent large-scale dynamics

In this chapter, we did not cover prefrontal–cingulate (Voloh et al., 2015), –hippocampal (Brincat and Miller, 2015), or –striatal (Antzoulatos and Miller, 2014) interactions, and the examples in this chapter are by no means exhaustive. We refer the interested reader to other recent reviews on the topic (Helfrich and Knight, 2016). Currently, most observations are only correlative in nature and several pressing questions have not been addressed yet. For example, it is unclear how neuronal populations actively tune into one or another frequency channel to extract information (Knight and Eichenbaum, 2013). In addition, no mechanism has been described for how a cell assembly can simultaneously process top-down and bottom-up influences. Does mixed selectivity of single neurons play a key role or do cell assemblies contain specialized subunits that process top-down and bottom-up influences separately? Eventually, the field needs a better understanding of how timed transfer of information is established in the human brain, to understand how cognitive flexibility is supported at the neuronal level. In the future, this will help to assess the pathophysiology of a variety of neuropsychiatric disorders such as attention deficit hyperactivity disorder (ADHD), obsessive–compulsive disorder (OCD), or schizophrenia, which likely reflect network disorders (Voytek and Knight, 2015). Therefore, several attempts have been made to modulate oscillatory patterns in vivo to better understand their relevance for behavior and potentially have novel tools to nonpharmacologically treat neuropsychiatric diseases.

ENTRAINED COGNITION: DRIVING OSCILLATIONS TO UNDERSTAND BEHAVIOR

Neuronal oscillations are readily visible in a variety of electrophysiological recordings, ranging from noninvasive scalp EEG to invasive LFP recordings in primates (Buzsáki, 2006; Buzsáki et al., 2012). While numerous studies provided correlative evidence for their role in cognitive processing, a causal demonstration in humans remained difficult (Thut et al., 2011a). Novel noninvasive brain stimulation techniques offer the opportunity to stimulate the cortex rhythmically and thereby modulate oscillatory patterns and subsequent behavior (Herrmann et al., 2016; Thut et al., 2017). The two most commonly used approaches are rTMS and tACS. However, the exact mechanisms of action of both methods are currently not fully understood. Several theoretical accounts argued that rhythmic cortical stimulation entrains cortical generators by phase alignment (Thut et al., 2011a, 2012; Ali et al., 2013). For example, multiple rTMS pulses are thought to reset and align the phase of ongoing oscillatory activity, i.e., the ongoing oscillation becomes entrained and now cycles in sync with the external driving force (Thut et al., 2011b; Hanslmayr et al., 2014). Crucially, entrainment in dynamic systems implies that this effect outlasts stimulation offset (Herrmann et al., 2013; Fröhlich et al., 2015). Note that this approach aims at assessing frequency-specific contributions and is fundamentally different from the often employed 1 Hz or theta-burst TMS protocols, which are applied over minutes, to temporarily make a cortical region active or inactive (“virtual lesion” approach), to make causal inferences about its function (Herrmann et al., 2016).

In the case of tACS, it has been hypothesized that sinusoidal stimulation waveforms utilizing weak electric currents (1–2 mA) enhance network resonance at the applied stimulation frequency (Ali et al., 2013; Helfrich et al., 2014; Neuling et al., 2015). However, in order to be successful, the frequency of the external driving force needs to match the endogenous frequency. It has been demonstrated that 10–30 min of stimulation induce outlasting network effects, possibly through mechanisms similar to short-term synaptic plasticity (Zaehle et al., 2010; Neuling et al., 2013; Kasten et al., 2016).

Driving brain oscillations in the prefrontal cortex have been used to test frequency-specific causal contributions to a variety of cognitive functions. For example, Hanslmayr et al. tested the role of theta, alpha, and beta oscillations over the left inferior frontal gyrus for memory recall performance (Fig. 3.11; Hanslmayr et al., 2014).

Correlative evidence has linked all three spectral signatures to memory processes; however, only rTMS at beta frequencies significantly impaired recall performance.

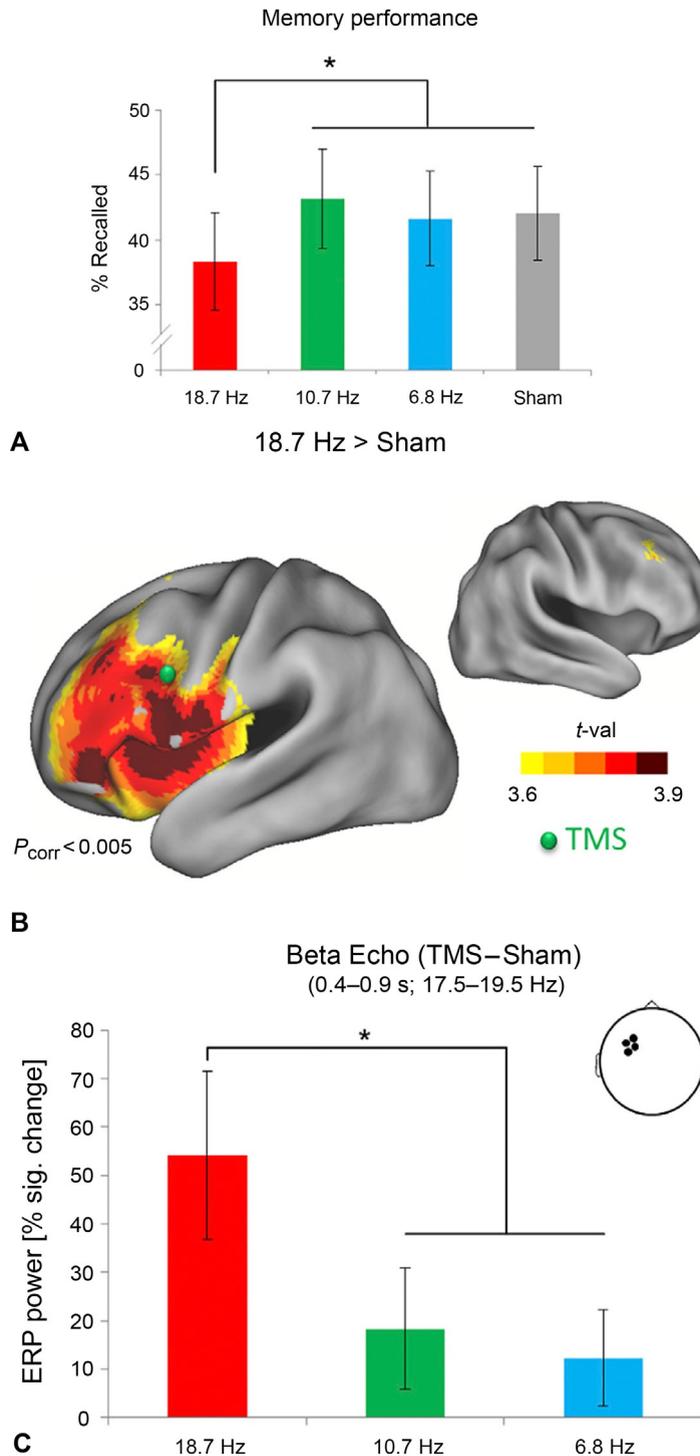
Even though theta oscillations have been implicated in memory processes, stimulation in that frequency did not modulate recall performance in this study. In contrast, multiple tACS studies reported that beta tACS remained ineffective in modulating WM performance (Braun et al., 2016), but demonstrated that theta-band tACS might be effective in modulating WM performance (Vosskuhl et al., 2015; Alekseichuk et al., 2016, 2017; Chander et al., 2016). Evidently, the field is still in its infancy and preliminary results often remain inconclusive, which can partially be attributed to the state-dependence of neuromodulatory approaches (Neuling et al., 2013; Alagapan et al., 2016; Hanslmayr and Roux, 2017).

Notably, several groups have begun to take advantage of direct electric stimulation (DES) on the cortex of epilepsy patients with implanted electrodes who undergo presurgical evaluation. DES is a standard procedure in the preoperative mapping of motor and speech regions and is routinely delivered in biphasic pulses at 50 Hz. Again, results are mixed and while a few groups found that stimulation enhanced memory performance (Suthana et al., 2012), others reported impaired memory performance (Jacobs et al., 2016). Recently, it became clear that this approach is highly state-dependent, too (Ezzyat et al., 2017; Hanslmayr and Roux, 2017). A shortcoming of DES is that stimulation patterns are not functionally motivated, i.e., they are not frequency matched to modulate a distinct spectral signature of a cognitive process, which might enhance its efficacy in future studies (Alagapan et al., 2016).

Taken together, the field of (noninvasive) brain stimulation holds the potential to establish a causal relationship between electrophysiological signatures and human behavior and will likely gain more interest in the future to enhance or restore cognitive functions in the aged or diseased brain.

OSCILLOPATHIES AND DISORDERS OF NETWORK SYNCHRONY

Many neuropsychiatric diseases have traditionally been described and understood at the cellular or molecular level, such as Parkinson’s disease (PD), Alzheimer’s disease, or epilepsy. However, despite substantial effort no cellular or molecular mechanisms have been observed for a variety of disorders such as schizophrenia, depression, ADHD, or OCD, and the underlying anatomic structures appeared intact in imaging studies. Therefore, it has been suggested that selected neuropsychiatric disorders might be caused by impaired network communication (Voytek and Knight, 2015). While every cortical region appears functional when analyzed independently, their coordinated interplay might be disturbed, thus giving rise to a variety of neuropsychiatric symptoms.



f0060 **Fig. 3.11.** Prefrontal beta entrainment impairs memory recall. (A) Behavioral results. When left IFG was entrained at beta frequencies, then subsequent recall performance was impaired. Stimulation in the theta or alpha range did not have an effect. (B) Source-reconstructed increased beta activity as a result of rTMS entrainment indicated that the effect was spatially and (C) spectrally specific. Reproduced from Hanslmayr S, Matuschek J, Fellner M-C (2014). Entrainment of prefrontal beta oscillations induces an endogenous echo and impairs memory formation. *Curr Biol* 24: 904–909. doi:10.1016/j.cub.2014.03.007 with permission of Elsevier.

s0090 **Neuropsychiatric disorders might reflect network disorders**

p0270 One of the model diseases that might be understood as a network disorder is schizophrenia, since multiple genetic mutations have been linked to clinical symptoms. In addition, pharmacotherapy in schizophrenia is often not effective, indicating that the aberrations giving rise to clinical symptoms are highly complex. In recent years, a multitude of studies indicated that the variability in clinical symptoms and their fluctuations across days, months or years correlates with the variability in electrophysiological signatures in large-scale networks (Andreou et al., 2015; Ćurčić-Blake et al., 2017; Hunt et al., 2017). In particular, two frequency bands have been implicated: Delta and gamma oscillations. It has been hypothesized that the coupling between sensory cortices, prefrontal areas, mediotemporal lobe structures, and the thalamus is impaired. Crucially, both impaired and elevated coupling have been observed: positive symptoms, such as auditory hallucinations, might reflect increased synchrony in the gamma band from auditory to prefrontal areas (Herrmann and Demiralp, 2005; Andreou et al., 2015), while decreased cortical delta connectivity is thought to reflect impaired network integration (Hunt et al., 2017). Hence, the coordination of information flow from sensory areas to cortical association cortex seems to be aberrant. Similar network-based models have been proposed for ADHD (Uhlhaas and Singer, 2012, 2015; Calderone et al., 2014). Several recent reports indicated that this spatiotemporal coordination is impaired in ADHD (Vollebregt et al., 2016), especially between alpha and gamma activity in the frontoparietal attention network (Jensen et al., 2014). In the case of OCD, deep brain stimulation on subgenual areas has proven to be beneficial, in particular when WM tracts and not distinct nuclei are being stimulated (van Westen et al., 2015). Hence, activity might spread to several relevant regions in the network and rebalance excitatory–inhibitory balance and synchrony (Voytek and Knight, 2015).

p0275 The recent developments in linking impaired oscillatory brain activity to neuropsychiatric diseases have triggered revisiting other diseases in light of these new findings. For example, in the case of PD, the aberrant network oscillation in the delta/theta band becomes visible in the tremor frequency. In addition, it has been demonstrated that high-frequency DBS in PD changes oscillatory activity in the beta band in motor cortex (Swann et al., 2015; Cole et al., 2017). Evidently, clinical findings can be reinterpreted in the framework of network neuroscience and can advance our understanding of neuropsychiatric disorders.

s0095 **How to restore oscillatory balance and network synchrony**

p0280 If aberrant neuronal oscillatory activity is causally involved in clinical symptoms, then an intriguing hypothesis is that modulation of these oscillatory patterns should improve symptoms and clinical scores. In the case of PD, it has been shown that peripheral tracking of the cortically generated tremor allows determining its frequency and instantaneous phase (Brittain et al., 2013). Following this, Brittain et al. used tACS to stimulate the motor cortex at the same frequency. They showed that if motor cortex is stimulated at an opposite phase angle, tremor amplitude is significantly reduced through phase cancellation. If the phases were aligned, the tremor amplitude was enhanced.

p0285 Currently, the first clinical trials are being conducted to test whether tACS may modulate aberrant oscillatory patterns in schizophrenia (STILL2 study: Stimulation to Improve auditory HaLLucinations). In contrast to the more common transcranial direct current stimulation (tDCS) approach, which has been widely criticized in recent years (Horvath et al., 2015, 2016), tACS offers the opportunity to tailor stimulation protocols to distinct spectral signatures and individualize interventional protocols by means of frequency, intensity, and duration according to individual structural and functional metrics (Thut et al., 2017). If successful, this approach provides a nonpharmacologic treatment of neuropsychiatric disorders to complement DBS (Philip et al., 2017).

s0100 **OUTLOOK AND FUTURE DIRECTIONS**

p0290 In this chapter, we outlined how electrophysiology in humans and primates has contributed to our current understanding of the prefrontal cortex physiology. The field of network neuroscience is slowly replacing the classic neuron doctrine (Yuste, 2015; Eichenbaum, 2017). In this last section, we would like to highlight that testing future hypotheses using novel methods does not necessarily require additional data collection. As data sharing and open science become more widely accepted (Ioannidis et al., 2014; Chambers et al., 2015; Eglen et al., 2017; Munafò et al., 2017), scientists have the opportunity to test new hypotheses on existing datasets to provide additional insights. In the following text, we outline this approach on one exemplary dataset. In particular, non-linear signal analyses have gained importance in recent years and will be discussed in detail. We believe that challenging established facts constitutes a hallmark of scientific progress toward a better understanding of the specific role of the prefrontal cortex for cognition.

s0105 **A multimodal and multifaceted approach to understanding the PFC**

p0295 Understanding the physiology of the prefrontal cortex requires recording techniques that span multiple scales: across species, across spatial, and across temporal scales. Every method has advantages and disadvantages to answer specific questions. In the field of invasive electrophysiology, one often has to adapt the scientific question to the recording environment. For example, the electrode coverage in epilepsy patients is solely dictated by clinical considerations, and thus only rarely provides access to, e.g., primary visual cortex (Self et al., 2016) or the thalamus (Sweeney-Reed et al., 2014). In contrast, given that the majority of epileptic cases have a seizure onset zone in medial temporal cortex and adjacent regions, consistent coverage can be expected over medial and lateral temporal cortex, as well as over frontal regions, such as DLPFC, OFC, anterior cingulate, SMA, and medial PFC.

p0300 Similar considerations hold true for primate research. While electrode placement in primates can be adjusted according to the scientific question, primate research entails a different set of ethical considerations and difficulties. Therefore, it is important to extract as much information as possible from a single dataset using a variety of analytical approaches. We outline how one dataset could be mined for different questions using multiple analytical approaches, which ultimately leads to a better understanding of the underlying processes.

p0305 We exemplify this approach by focusing on a dataset that was first reported by Warden and Miller, in which two monkeys were trained on a working memory task, where two pictures were presented sequentially (Warden and Miller, 2007). Memory performance was either assessed in a recognition task, where the monkeys had to indicate whether a second sequence matched the first sequence or not. In a second recall task, the monkey had to pick the two pictures in the correct sequence from a three-item array. Recordings across multiple sessions were made from single neurons and LFPs in DLPFC.

p0310 In the first paper, the authors analyzed how the firing rates of individual neurons contributed to recall performance. They reported that most prefrontal neurons responded to both stimuli. However, the exact relationship was complex: representations of the first object were altered by the addition of the second object. However, they did not observe a clear pattern across different neurons, suggesting that the items held in working memory are not encoded by single neurons but by coding at the population level (Warden and Miller, 2007).

p0315 In the first follow-up paper reexamining this dataset, they demonstrated that this complex coding was also modulated by task context, i.e., whether the monkey

performed the recall or recognition task (Warden and Miller, 2010). Most prefrontal cells encoded both the task and the objects in a highly complex fashion, again supporting the notion that neuronal populations are functional units and not single neurons.

In order to test whether the population encodes all task-relevant parameters, a second follow-up study utilized machine-learning techniques to decode information from the population (Rigotti et al., 2013). They found that every task-relevant aspect could be decoded from the population. Crucially, they demonstrated that individual neurons exhibited a mixed selectivity, i.e., one neuron would only respond to the first object in the recall context and only to the second object in the recognition task. Importantly, these responses did not reflect a linear summation, but were instead highly nonlinear in nature (Fusi et al., 2016). This indicated that neural representations are complex and encoded in a high dimensional space in prefrontal cortex, which was predictive of task performance. However, while the results provided insights into how different task-relevant features are encoded at the population level, it remained unclear how the temporal order of the objects is held in working memory.

To address this, the authors extended their analyses from studying single neurons to assessing the temporal relationship of spikes and the underlying LFP in another follow-up study (Siegel et al., 2009). Previously it has been suggested that LFP oscillations provide a temporal reference frame to encode the temporal order of objects or events. Indeed, in support of this hypothesis, they found that information about the first object peaked significantly earlier in the cycle of a beta oscillation (~32 Hz) than information about the second object. These findings supported the idea that WM content is not represented in sustained firing rates but is maintained in an activity-silent manner embedded into oscillatory activity at the population level (Stokes, 2015).

In a more recent study, the group also demonstrated that discrete, short-lasting bursts of activity support the read-out of working memory on a trial-by-trial basis (Lundqvist et al., 2017), supporting a novel model of working memory (Lundqvist et al., 2011, 2016). Importantly, activity in the beta (20–35 Hz) and gamma range (55–120 Hz) was predictive of task performance on a trial-by-trial basis.

Taken together, multiple analytical approaches, ranging from single neuron spiking to multivariate decoding approaches, information theoretical measures or spectral and connectivity analyses, jointly provide insights into the functional architecture of higher cognitive functions. We are convinced that reanalysis of previously collected, highly complex datasets using novel methods will help to unravel the spatiotemporal dynamics of prefrontal-

dependent operations and ultimately lead to a better understanding of neurophysiology of the prefrontal cortex.

s0110 **Analysis of nonlinear neural dynamics**

p0340 In recent years it became obvious that previously employed analytic approaches are insufficient to capture complex dynamics underlying human behavior. We briefly outline two approaches to study nonlinear dynamics.

p0345 First, spectral analyses of oscillatory brain activity are increasingly popular and have significantly advanced our understanding of how information is encoded and transferred in large-scale cortical networks. A particular focus has been on the phase of band-limited oscillatory signals, which is circular in nature and hence cannot easily be analyzed using linear models. Therefore, circular statistics have been used to unravel periodicities in electrophysiological signals and behavior (Berens, 2009). Multiple methods have been introduced to either assess circular-circular correlations to describe phase-synchronous processes in distant cortical sites (Lachaux et al., 1999; Nolte et al., 2004; Vinck et al., 2012), or to capture circular-linear interactions as frequently utilized in cross-frequency-coupling analyses (Canolty et al., 2006; Tort et al., 2008).

p0350 A second approach to assess nonlinear dynamics of neuronal populations is based on machine learning algorithms, which are able to separate complex patterns by projecting them into a high dimensional space (Meyers et al., 2008; Quian Quiroga and Panzeri, 2009; Jafarpour et al., 2013; Panzeri et al., 2015). The outcome of such pattern classifiers or decoding algorithms indicates that there is enough information present in the data to successfully separate two or more task categories. While pattern classification provides valuable insights into what information is encoded and when it is decodable, it often remains difficult to visualize these highly dimensional patterns in regular 2-D or 3-D representations (Meyers et al., 2008; Barak et al., 2010; Stokes et al., 2013). Therefore, multiple groups used additional dimensionality reduction techniques, such as principal component analysis, to limit their analyses to components that explain most of the variance (Quian Quiroga and Panzeri, 2009).

s0115 **Challenging classical models of PFC-dependent processing**

p0355 Over the last decade, novel methods for signal analyses and multisite recording techniques yielded a wealth of information that provided valuable insights into the neurophysiology of the prefrontal cortex. During this process, several established concepts were challenged, such as the neuron doctrine, the role of sustained firing

for cognitive processing, and cortical division into highly specialized subunits. Instead, it became clear that network neuroscience might constitute a new paradigm to study cognitive functions and we expect that several other well-established cognitive constructs will be revisited in light of the most recent developments. Ultimately, all models that assume a neural process is stationary might not stand the test of time.

For example, visual attention has been extensively p0360 studied in the spatial domain (Carrasco, 2011). The current taxonomy distinguishes spatial from object-based or feature-based attention, which might be independently modulated by endogenous priors and high-level predictions (Chun et al., 2011). Recently, the field became more interested in the temporal features of attention (Buschman and Kastner, 2015). Given the most recent findings, attention might be better described as a rhythmic process where distinct spatial locations are sampled periodically over time (Fiebelkorn et al., 2013). In this view, the brain might sample more frequently from a spatially cued location. When temporal expectations are high and attention can be directed to a certain point in time, this endogenous rhythmic process might align its optimal phase to maximize stimulus processing through endogenous entrainment or phase resetting (Slama and Helfrich, 2017). Furthermore, conceptualizing attention as a rhythmic process might explain attentional lapses and fluctuations over time.

It is part of the scientific process that established p0365 knowledge is revisited and put under close scrutiny when new evidence becomes available. Even though the discovery of the human EEG is inevitably linked to the discovery of neuronal oscillations (Berger, 1929), their functional relevance in guiding neocortical spiking was only established recently (Fröhlich and McCormick, 2010). Critically, oscillations can be observed across several spatial scales: for example, on the microscale in LFPs or single-unit firing patterns, as well as on the macroscale in human M/EEG and sometimes in behavior. We suggest that oscillatory neural activity might constitute a candidate mechanism to bridge findings from various species and recoding environments (Buzsáki and Draguhn, 2004; Buzsáki et al., 2013). However, it is currently unclear if frequency-specific motifs actually reflect distinct canonical cortical computations and if they are comparable across spatial scales (Haegens et al., 2011; Spaak et al., 2012). While oscillations were largely ignored for decades in favor of studying event-related potentials and neuronal spiking activity, the most recent technological advancements permit a more detailed characterization (Kam et al., 2016). Hence, we are convinced that spectral analyses will have an increasing impact on the field of network neuroscience.

CONCLUSIONS

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p0370 Over the last three decades, scientific interest in the prefrontal cortex and its intrinsic computations has steadily increased. While lesion and imaging evidence clearly attributed many cognitive functions to the prefrontal cortex, it remained unclear how prefrontal cortex gives rise to complex behavior and human mental abilities. Novel methods and sophisticated analysis methods are beginning to unravel the role of neuronal assemblies in cognition. In particular, intracranial electrophysiology allows the imaging of cognitive processes at an unprecedented spatiotemporal resolution. Milestones of the last decade include the findings that neuronal assemblies constitute the functional unit of the nervous system, and not the single neuron. Importantly, in higher-order cortical areas, such as the prefrontal cortex, neurons exhibit mixed selectivity and utilize dynamic codes to encode information at the population level. Network neuroscience is an emerging paradigm for neuroscience and has the potential to bridge findings from several species and spatial scales (Yuste, 2015). Eventually, a better understanding of the underlying physiology will help to characterize the cortical states that support higher cognitive functions, generate complex goal-directed and contextually adjusted behavior, and potentially underlie mental diseases.

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