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Human brain oscillations: from physiological mechanisms to analysis and cognition

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Abstract

In the cognitive neuroscience community there is a strong and growing interest in the function of oscillatory brain activity. Brain oscillations can readily be detected with MEG which also allows for indentifying the sources and networks producing the activity. The aim of this chapter is first to describe the physiological mechanisms responsible for generating brain oscillations in various frequency bands and regions. We will focus on insight gained from the animal literature and physiologically realistic computational modeling. Next, we will explain the signal-processing tools typically applied to characterize oscillatory brain activity from human electrophysiological data in the context of cognitive paradigms. The final section will address the main ideas on the functional role of brain oscillations in various frequency bands. This discussion will be focused on recent findings applying MEG.

Keywords: magnetoencephalography, brain oscillations, signal processing, time-frequency analysis, functional and cognitive relevance of oscillations, computational modelling, biophysical modelling, alpha oscillations, beta oscillations, gamma oscillations, delta oscillations, theta oscillations.

1. Introduction

Oscillations in the brain are produced by coordinated electrophysiological activity in large groups of neurons. Human brain oscillations were first discovered in 1929 by Hans Berger by measuring the electrical potentials between two electrodes placed at the scalp (Berger, 1938). When the subject was asked to close her eyes, Berger observed a strong ~10 Hz rhythmic activity in the electrical potential over time. Modulations in the alpha rhythm were also observed in response to simple cognitive manipulations (Fig. 1). The oscillatory activity in the 10 Hz band is termed the *alpha rhythm* or the *Berger rhythm*. Given that such brain oscillations can be readily measured at the scalp and observed with the naked eye, they must be a consequence of thousands of neurons oscillating in synchrony. As such, it is conceivable that brain oscillations will have a strong impact on how neuronal spiking is coordinated in both space and time. The coordination of

neuronal spiking by oscillatory brain activity is thus important to investigate in the quest to understand the physiological basis of cognition.

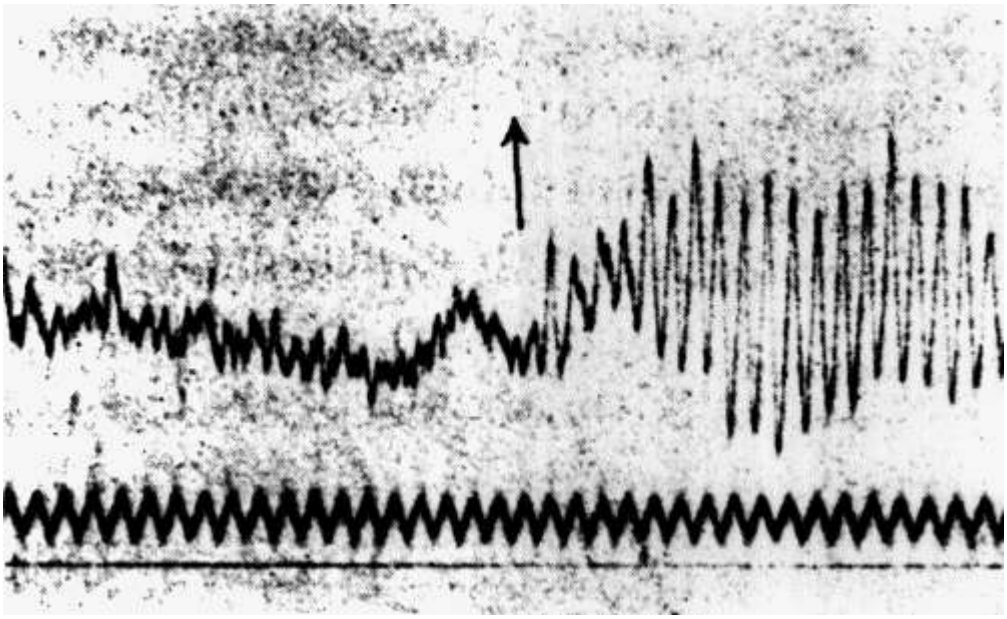

Fig. 1. An early EEG recording performed by Hans Berger. Prior to the arrow the subject is performing a mental arithmetic task. After the task stops, alpha returns. (Niedermeyer, 1997)

Human brain oscillations have been known for almost a century and have been investigated with various degrees of vigor over the years (Shaw, 2003). However, recently there has been a surge in the interest in oscillatory brain activity. This is partly explained by intracranial animal recordings relating spike timing to ongoing oscillations measured in the local electrical potential. These studies have revealed that spike timing is locked to the phase of the ongoing oscillations in various brain regions and frequency bands (Fries et al., 2001) (O'Keefe and Recce, 1993) (Bollimunta et al., 2008) (Pesaran et al., 2002). What also has kindled the interest in brain oscillations is the fact that they are strongly modulated during cognitive tasks. There is now a rich literature reporting on the modulation of brain oscillations by a wealth of tasks spanning from simple perception to higher levels of cognitive processing such as language comprehension (Buzsáki, 2006). In particular, MEG recordings using hundreds of sensors have made it possible to identify and locate the source of the brain oscillations (Hari and Salmelin, 1997) (Siegel et al., 2012) (Varela et al., 2001) (Tallon-Baudry and Bertrand, 1999) (Vrba and Robinson, 2001) (Singh et al., 2002). Further, the theoretical basis of the functional role of neuronal activity coordinated by oscillations is in rapid development (Fries et al., 2007) (Jensen et al., 2012a) (Fell and Axmacher, 2011) (Lisman, 2005) (Mehta, 2001). These developments, in combination with improved computer speed and the development of signal-processing tools, have now made human electrophysiological recordings focusing on brain oscillations a strong research area.

The aim of this chapter is first to describe the physiological mechanisms generating oscillations in various frequency bands. We will then describe how these oscillations can be measured and quantified in humans. Finally we will discuss current ideas on the functional role of brain oscillations for cognitive processing. Each section will be organized according to the conventionally defined frequency brands. However, it should be made clear from the onset that

these frequency bands are somewhat arbitrarily defined. It is currently debated to what extent distinct brain oscillations should be defined according to frequency band or according to function.

2. Physiological mechanisms

We have probably all had the following experience: after a play or a concert the audience is applauding. While the audience initially is clapping at a different pace and out of synchrony, they suddenly enter a mode where everybody is clapping in synchrony in a rhythmic manner. What happens is a self-organizing phenomenon where the dynamics emerge from interactions between the individual persons in the audience without external organization. A key requirement for this phenomenon is communication between the individuals in the audience. The communication is constituted by auditory perception of the clapping sounds heard from the other persons. A second key requirement is an inherent drive to clap in pace with the rest of the crowd or, stated differently, the timing of the clapping of an individual is adjusted in phase and frequency according to the summed clapping sound from the audience. Likewise, neurons coupled in a network often show the emergence of spontaneous oscillations (Buzsáki, 2006) (Traub et al., 1999) (Wang, 2010). In this case, the communication is constituted by the synaptic interactions between the neurons. The phase- and frequency-adjustments are determined by how the electrical membrane dynamics respond to the synaptic currents. Spontaneous neuronal oscillations have been defined in a wide range of frequency bands. We will here discuss the different physiological mechanisms thought to be responsible for determining the characteristic frequencies of these oscillations and the neuronal synchronization properties underlying them.

2.1 Gamma oscillations

Neuronal synchronization in the gamma band (30-100 Hz) has been intensively studied by both *in vivo* and *in vitro* recordings (Buzsaki and Wang, 2012) (Traub and Whittington, 2010). Further extensive theoretical work has been done in order to understand the dynamical principles creating these oscillations.

Much empirical work has focused on gamma oscillations in various animals and brain regions. For instance there has been a strong interest in the gamma activity generated in the visual system. In cats, monkeys and humans, gamma oscillations can be observed in response to visual gratings (Gray et al., 1989) (Bosman et al., 2012) (Hoogenboom et al., 2006). Another line of research has focused on gamma oscillations in the rat hippocampus (Chrobak and Buzsaki, 1996). In particular it has been found that the power in the gamma band is locked to the phase of theta oscillations in the behaving rat (Bragin et al., 1995) (Belluscio et al., 2012) (Colgin et al., 2009). Importantly, it is also possible to identify the gamma oscillations in slice preparations of the rat and mouse hippocampus. This has allowed for both pharmacological and genetic manipulations aimed at identifying the core mechanism determining neuronal synchronization in the gamma band. This work has then informed computational modeling which has identified the dynamical properties determining both frequency and synchronization properties (Buzsaki and Wang, 2012).

The theoretical work has resulted in two key mechanisms which can produce gamma band oscillations, termed the "interneuronal network gamma" (ING) mechanism and the "pyramidal—interneuronal network gamma" (PING) mechanism (Whittington et al., 2000) (Tiesinga and Sejnowski, 2009).

The ING-mechanism (sometimes also referred to as the I-I, inhibitory-inhibitory, model) refers to gamma oscillations produced by interactions between interneurons alone communicating through gamma-aminobutyric acid (GABA) synapses. These oscillations can be observed in hippocampal slice preparations where the AMPA and NMDA synaptic inputs from pyramidal cells are blocked by respectively CNQX and APV (Whittington et al., 1995), thus proving that input from pyramidal neurons is not required for the generation of gamma. To observe the oscillations in slice preparations it is essential that the activity of the interneurons is boosted by cholinergic and metabotropic glutamate receptor agonists. The oscillations are abolished if a GABAergic antagonist is applied. The important theoretical insight is that inhibitory interactions alone can serve to synchronize a neuronal population (Van Vreeswijk et al., 1994).

The basic ING mechanism can be understood as follows. Consider one neuron coupled to itself by a GABAergic synapse, receiving some tonic excitatory input. After the neuron fires, the GABAergic feedback will hyperpolarize the membrane potential. The duration of the hyperpolarization is determined by the kinetics of the $GABA_A$ receptor and will typically last 10-20 ms; i.e. the duration of a gamma cycle at 50-100 Hz. When the GABAergic hyperpolarization wanes, the cell will fire again (Fig. 2A). Now consider two inhibitory interneurons mutually coupled with GABAergic connections. If they both fire at about the same time, the GABAergic connections will provide mutual inhibition. When the inhibition wanes, the cells will fire simultaneously (Fig. 2B). Thus zero-lag synchronization emerges. One might also consider the alternative case when the two neurons fire out of phase. In this case the first neuron might inhibit the second, delaying its firing. When the second neuron fires it will inhibit the first (Fig. 2C). This results in anti-phase synchronization. The conditions for zero-lag and anti-phase synchronization have been studied in the context of physiologically realistic parameters (Van Vreeswijk et al., 1994) (Gerstner et al., 1996). As it turns out, the kinetics of the $GABA_A$ receptor is a main player in determining the synchronization properties. Importantly, for physiologically realistic parameters, zero-lag synchronization is typically the most stable model (Van Vreeswijk et al., 1994) (Wang and Buzsaki, 1996). This synchronization scheme is also stable to delays in synaptic transmission. In short, when two interneurons are mutually coupled with GABAergic synaptic input they will typically enter a mode in which they rhythmically synchronize their firing. The frequency of firing is determined by the kinetics of the GABAergic feedback. Now consider what happens when a third or more inhibitory interneurons are added to the network. They will also fire synchronously with the rest. This mechanism explains how gamma oscillations can emerge from a network of interneurons only.

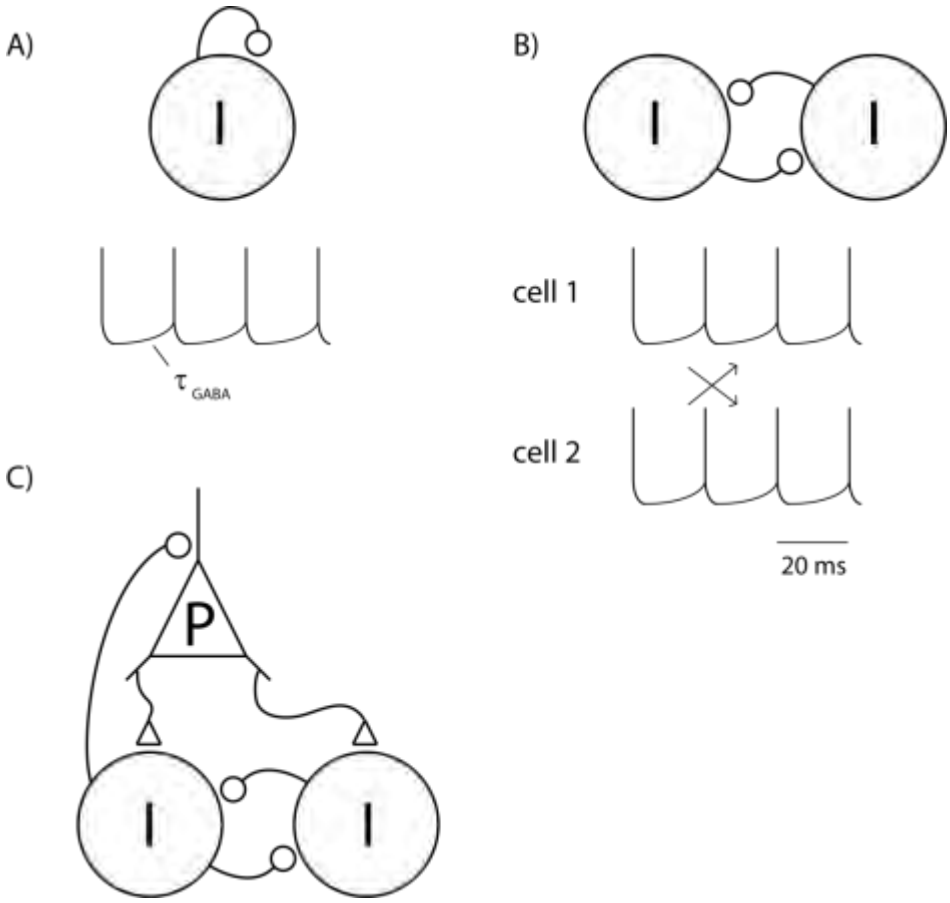

Fig. 2. The ING and PING mechanisms for neuronal synchronization in the gamma band (A) Consider one inhibitory neuron coupled to itself with a GABAergic synapse. If sufficiently depolarized, it will fire rhythmically with a frequency determined by the kinetics of the GABAergic feedback. (B) Consider two inhibitory neurons mutually coupled. When coupled they might fire either in phase or in anti-phase. It turns out that synchronized firing (in phase) typically is the most dynamically stable mode given realistic physiological parameters. This constitutes a mechanism for neuronal synchronization in the gamma band that generalizes to larger populations of interneurons. It is termed *interneuronal network gamma* (ING). (C) A second mechanism for the fast oscillations involves pyramidal neurons, and is termed *pyramidal interneuronal network gamma* (PING). According to this mechanism the pyramidal neurons periodically excite the interneurons, which in return induce synchronized inhibitory post-synaptic potentials (IPSPs) in the pyramidal neurons.

The PING mechanism (also referred to as the E-I, excitatory-inhibitory, model) constitutes another important principle by which neuronal oscillations can emerge in the gamma band. In contrast to the ING mechanism, the PING mechanism employs two different populations of cells: one excitatory and one inhibitory, reciprocally connected to each other (Whittington et al., 2000) (Wilson and Cowan, 1972) (Ermentrout and Kopell, 1998) (Borgers and Kopell, 2003). In the PING mechanism, AMPAergic projections of the excitatory population onto the inhibitory population provide fast excitation of the latter cells. These inhibitory cells, in turn, provide fast inhibition of the excitatory cells through GABAergic synapses. When the inhibition on the excitatory cells wears off, the excitatory cells fire. The excitatory firing results, a short delay later, in inhibitory firing, thus bringing the network into an oscillatory state. For this oscillatory state to

happen, the strength of inhibition and excitation needs to be properly balanced. Note that the short delay between excitatory and inhibitory firing is the crucial factor for determining the oscillatory properties in this network (Borgers and Kopell, 2003). This delay is composed of both axonal conduction and synaptic delays (Leung, 1982).

For both ING and PING models GABAergic interneurons are key players, a finding which is corroborated by the observation that GABA concentration in the brain predicts an individual's peak gamma frequency (Muthukumaraswamy et al., 2009). Even though either of these two mechanisms could in principle explain all gamma oscillation phenomena in the brain, there is ample evidence that both of them are at work. For instance, when synaptic inhibition onto inhibitory cells is disabled in the mouse hippocampus, gamma activity is not significantly affected, providing evidence that some mechanism other than ING is at work (Wulff et al., 2009). In contrast, it is known that gamma oscillations are also prominent in structures that do not have dense excitatory-to-inhibitory connections (Brown et al., 2002;Fujisawa and Buzsaki, 2011), indicating that PING cannot be the whole story. Thus, whether the PING or the ING mechanism is dominating might depend on the brain region and species (Tiesinga and Sejnowski, 2009) (Buzsaki and Wang, 2012).

Given the likelihood that inhibitory interneurons are crucial for generating gamma oscillations, is anything known about the specific *type* of inhibition involved in this mechanism? Inhibitory interneurons can be broadly classified along two dimensions: fast-spiking versus non-fast-spiking, and soma-targeting versus dendrite-targeting. Several strands of evidence indicate that fast-spiking, soma-targeting basket cell interneurons (specifically, those that express parvalbumin (Kawaguchi et al., 1987)) are crucial in the generation of gamma rhythms (Bartos et al., 2007). These cells are abundant (Freund and Buzsaki, 1996), form extensive interconnections amongst one another (Gulyas et al., 1999), and a single basket cell can project onto more than one thousand pyramidal cells (Cobb et al., 1995). These conditions enable basket cells to impose their gamma rhythm onto a pyramidal cell network; the population activity of the pyramidal cells then is reflected in the local field potential (LFP) and MEG signal. Furthermore, gamma activity is associated with strong perisomatic current sinks, consistent with the soma-targeting properties of basket cells (Mann et al., 2005). Finally, fast-spiking basket cells have resonance properties in the gamma range (Pike et al., 2000) (Cardin et al., 2009) and typically produce ~1 spike per gamma cycle, phase-locked to the population rhythm (Gloveli et al., 2005). Further evidence shows that gamma-generating interneurons are likely coupled through shunting inhibitory synapses and by gap junctions, which increases their robustness against heterogeneous input (Vida et al., 2006) (Bartos et al., 2007).

Apart from gamma oscillations, another high-frequency component of LFP and MEG signals can be distinguished. Sometimes referred to as *high gamma*, relatively broadband high-frequency activity (>85 Hz) is also known as *epsilon* activity (Freeman, 2007) (Belluscio et al., 2012) or the chi band (Miller et al., 2008). It is currently unclear to what extent this activity should be considered a rhythm. The high-frequency broadband spectral components might reflect the spectral fingerprint of a neuronal spiking (Manning et al., 2009) (Belluscio et al., 2012).

2.2 Beta oscillations

Typically, beta oscillations (14-30 Hz) are considered to be generated by similar mechanisms as the gamma rhythm. A large-scale simulation of a network generating beta oscillations has been implemented (Traub et al., 1999), based on *in vitro* observations of hippocampal slices that alternate between gamma and beta states. It has been shown that the essential features of this large-scale network can be reproduced in a much simpler network, which bears strong resemblance to the PING mechanism of gamma generation (Kopell et al., 2000).

Imagine again the PING network described earlier, in which alternating balanced inhibitory and excitatory bursts between two coupled populations result in a network oscillating at gamma frequency. It turns out that only two changes need to be made to this model for it to generate beta oscillations: first, a slow potassium after-hyperpolarization (AHP) conductance is added to the excitatory cells, and, second, the excitatory cells have recurrent connections to themselves. When an excitatory cell has fired in this regime, it cannot fire again in the next gamma cycle, because then the AHP conductance prevents the cell's membrane potential from reaching threshold. Only on the next cycle can the cell fire again. This phenomenon is known as "beat-skipping" and results in the excitatory cells synchronizing at a beta frequency that is half the frequency of the interneuronal gamma rhythm. Note that because the inhibitory cells receive phasic excitatory input from the pyramidal cells, when one pyramidal cell fires, other pyramidal cells on the next gamma cycle will be silenced by the recurrent inhibitory connection. This leads to a regime where, although each individual pyramidal cell fires in a beta rhythm, the population activity is still of gamma frequency. The additional change to the model, the addition of recurrent connections between excitatory cells, ensures the synchronization: because the excitatory cells excite one another, they will fire before the inhibition from the GABAergic cells arrives. The latter route requires two synapses, while the recurrent connection is monosynaptic. Thus, a "PINB" (pyramidal-interneuronal network beta) mechanism might explain the occurrence of beta oscillations in local neuronal networks (Kopell et al., 2000), such as in the hippocampus.

Just as PING is not the whole story for gamma, so PINB is not the whole story for beta. Beta oscillation amplitude over human sensorimotor cortex is increased when benzodiazepines are administered, while the oscillation frequency is decreased (Jensen et al., 2005). Benzodiazepines mainly act by increasing GABAergic conductances. In a PINB-regime, increasing GABAergic conductances has the effect of decreasing the spiking frequency of the inhibitory cells, thus allowing more of the excitatory cells to fire, which in turn then excites the inhibitory cells more, leading to an equilibrium in which the net effect on network frequency is negligible. Therefore, the PINB mechanism cannot explain the robustly observed effect of benzodiazepines on beta oscillations. In contrast, an "INB" mechanism, analogous to ING for gamma, is able to explain these findings: in this mechanism, excitation of the inhibitory cells is tonic, so the period of the inhibitory cells' firing is determined only by the recurrent inhibitory connections. Since these become stronger under administration of benzodiazepines, the period of the inhibition becomes longer, in line with the observed results. As the period increases, a larger fraction of pyramidal cells will be released from inhibition during the refractory period. This explains the increase in beta power and decrease in frequency with benzodiazepines in sensorimotor areas observed in humans (Jensen et al., 2005).

2.3 Theta oscillations

The mechanisms described above for the generation of gamma and beta oscillations are primarily *local* models: they describe how oscillations of a particular frequency can arise through interaction of neuronal populations within the same brain structure. This allows for related models to account for gamma and beta activity in different structures such as the hippocampus, entorhinal cortex, or neocortex. The lower-frequency theta oscillations (4-8 Hz), primarily (though not exclusively) observed in hippocampus, are typically thought to be generated by an interaction between several brain regions, and might not sufficiently be explained by a local model (Wang, 2010).

Classically, the medial septum-diagonal band of Broca (MS-DBB) has been regarded as the crucial brain structure for the generation of the hippocampal theta rhythm, a notion which is corroborated by the observation that lesioning or inactivating the MS-DBB effectively obliterates theta in the rat brain (Stewart and Fox, 1990). The MS-DBB provides a tonic cholinergic drive to the hippocampus which greatly influences the amplitude of the hippocampal theta rhythm (Lee et al., 1994). In addition, GABAergic interneurons in the MS-DBB project selectively onto hippocampal interneurons and these projections likely provide the phasic entrainment (Freund and Antal, 1988;Buzsaki, 2002). Although originally the MS-DBB was regarded as *the* pace-making structure for theta oscillations (i.e., it was thought that the MS-DBB generates theta by itself and then imposes its theta rhythm onto the regions to which it projects), later studies have found that interactions between the MS-DBB and the hippocampus, as well as intra-hippocampal processes, are just as essential for theta generation. For instance, it turns out that an *in vitro* preparation of an entire isolated hippocampus is still capable of generating theta oscillations (Goutagny et al., 2009). Furthermore, dendritic inhibition of pyramidal cells by oriens lacunosum-moleculare (O-LM) interneurons, the presence of slow $GABA_A$-receptors on hippocampal cells, and the value of several specific active membrane conductances all are important for the occurrence of hippocampal theta oscillations (Buzsaki, 2002) (Rotstein et al., 2005) (Kopell et al., 2010) (Wang, 2010).

2.4 Alpha oscillations

Alpha oscillations (8-12 Hz) can be robustly observed in both the thalamus and the neocortex. Which of these two regions is the primary pacemaker of the alpha rhythm is still under debate. Generators of the alpha activity have been found with certainty in both thalamus and in neocortex (Lopes da Silva et al., 1980) (Bollimunta et al., 2008) (Bollimunta et al., 2011). The neocortical alpha activity measured by MEG is likely to stem from an interaction between the thalamic and neocortical generators.

Most is known about the generation of thalamocortical (TC) alpha oscillations. The lateral geniculate nucleus (LGN) of the thalamus contains a particular set of TC neurons, the high-threshold bursting neurons, which we are called HTC neurons. These neurons, coupled through gap junctions, fire bursts of spikes in synchrony with alpha oscillations in the field potential (Hughes and Crunelli, 2005). However, this cannot be the whole story of TC alpha, since the main projections conveying visual information from thalamus to cortex are from relay-mode cells (Llinas and Jahnsen, 1982), and not HTC cells. So how do the HTC and relay-mode cells interact? Extensive physiological and computational work has converged on the following model (Lorincz et al., 2009) (Vijayan and Kopell, 2012). HTC cells rhythmically excite thalamically local

GABAergic interneurons, probably through axon collaterals. This causes these interneurons to also fire at alpha frequency. Depending on the strength of tonic excitation, the interneurons can fire in one of two modes: a rhythm of single spikes near the trough of an alpha cycle, or a rhythm of spike bursts near the peak of alpha. The interneurons project extensively to the relay-mode cells, thus resulting in an alpha-frequency occurrence of IPSPs on their membrane potential. Because of the two modes of firing of the interneurons, the relay-mode cells can send their information to the cortex in two distinct temporal framing regimes, i.e. at different alpha phases (Lorincz et al., 2009;Vijayan and Kopell, 2012).

Apart from alpha activity, sleep spindles are also reflected in the frequency range of 8-12 Hz. These are thought to be generated by mechanisms related to the thalamocortical alpha oscillation, with some important differences: cells of the reticular nucleus are believed to be crucial for the spindle rhythm, and spindle activity emerges only in a regime of widespread (as opposed to sparse) inhibition, as would be expected for a sleep rhythm (Destexhe et al., 1993) (Terman et al., 1996).

2.5 Delta oscillations

Delta oscillations (1-4 Hz) are prominent during sleep, just like the spindle rhythm. A model has been proposed in which these two rhythms are generated by the same neuronal circuitry: an interaction between thalamic reticular (RE) cells, thalamocortical (TC) cells, and neocortical excitation of the reticular cells. In the generation of spindles, RE cells inhibit TC cells through $GABA_A$ and $GABA_B$ receptors. The TC cells project with excitatory connections to the cortex and the RE cells, and the cortex excites the RE cells. A network in this configuration generates spindle activity. When the conductance of the RE cells is changed such that they become less sensitive to the excitatory input of the TE cells, this causes the fast inhibition of the TE cells through $GABA_A$-receptors to be functionally removed. The slow inhibition through $GABA_B$ is unaltered. This gives rise to a rhythm in the delta frequency range during sleep (Terman et al., 1996). Delta activity also occurs during wakefulness (e.g. (Lakatos et al., 2008)); however, few if any models have been developed for the generation of delta during wakefulness.

2.6 Cross-frequency interactions

In addition to observing oscillations in distinct frequency bands, one can also observe *interactions* between those oscillations. In section 3.4, the different types of cross-frequency interactions that can be observed are outlined. The neuronal mechanisms underlying cross-frequency interactions are currently not well understood. One possibility for the observed coupling between the hippocampal theta rhythm and the neocortical gamma rhythm (Sirota et al., 2008) is that the hippocampal theta rhythm is imposed onto fast-spiking interneurons in the neocortex by direct anatomical projections (Tierney et al., 2004) (Gabbott et al., 2002). These interneurons are crucial for the generation of the gamma rhythm, as explained in the section on gamma activity above. The number of interneuron network spikes per gamma cycle is proportional to the measured gamma amplitude in the local field potential (and thus the MEG signal). Since the interneuron network spike rate is determined by the input to the network, whenever this input is time-varying at a certain low frequency (i.e., theta), the gamma amplitude will be modulated at the same frequency (Spaak et al., 2012b) (Wulff et al., 2009).

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3. Methods for characterizing oscillations

An oscillation as measured by MEG can most simply be thought of as a stationary sinusoidal signal, varying across time at a particular frequency. However, such pure signals do not exist in the brain, but rather neural data are mixes of sinusoidal oscillations at varying frequencies whose peak amplitudes vary over time. This section describes how to compute meaningful quantities from these signals that characterize their frequency dependence and dynamics. Although the oscillations are recorded in the time domain (i.e. a signal that varies over time), often they can be better defined in the frequency domain (i.e. a signal whose amplitude and phase vary over frequency). The power spectral density (PSD) of a time series describes how its power (amplitude squared) is distributed with frequency. In this section, first we will describe the transformation of the raw (recorded) time series to the PSD and how the PSD is optimally computed for neuroscience applications. Second, we will describe how oscillations can alternatively be treated in the time domain and lastly, methods for computing within- and cross-frequency interactions. For further references on methods and computation, please see (Muthuswamy and Thakor, 1998;Mitra and Pesaran, 1999;Gross et al., 2013).

3.1 Power spectral density of oscillatory activity

Any time series can be re-written as a sum of sine waves with each wave having a frequency at the appropriate amplitude and phase. Vice versa, by knowing the amplitudes and phases of the waves, the original time series can be reconstructed. The amplitude and phase of the sine waves for all relevant frequencies can be determined from the Fourier Transform. Power is defined as the magnitude of the signal squared per time; thus the power spectral density describes how the squared amplitude for a given time window is distributed with frequency.

For discrete, digitized signals, such as those obtained from MEG, EEG, and invasive electrophysiological systems, the discrete Fourier Transform (DFT) is used to compute the amplitude and phase estimates for a finite number of frequencies. Thus, the PSD is the square of the DFT of a given discretized signal. The DFT is typically computed by the Fast Fourier Transform (FFT), a computationally fast and practical algorithm. Limits on the maximum frequency and the spacing of the estimated frequencies exist. First, the maximum frequency possible to be quantified, also called the Nyquist frequency, is half of the temporal sampling rate. For example, using a 1000 Hz sampling rate means that the maximum frequency at which information is estimable is at 500 Hz. If the underlying time signal contains information at a frequency higher than the Nyquist frequency, this information will bleed in at lower frequencies (termed “aliasing”), thus making this information irrecoverable and will corrupt the estimates at lower frequencies. Thus, it is imperative to low-pass filter the analog continuous signals prior to discretizing (Smith, 1997). Indeed most commercial data acquisition systems will apply anti-aliasing filters via a lowpass filter at typically 1/4-1/3 of the sampling frequency. The second limit when converting recorded data to the frequency domain is the spacing between discrete frequencies. This spacing is referred to as the Rayleigh frequency and is equal to the inverse of the length of the temporal sampling window. For any finite signal, estimates of oscillatory power can only be obtained at integer multiples of the Rayleigh frequency (for example, for a 400 ms

data segment, estimates will be obtained at 2.5 Hz, 5 Hz, 7.5 Hz, etc.) (Mitra and Pesaran, 1999) (Pesaran, 2008).

In theory, the estimate of the power spectrum from the FFT of a finite data segment is biased, as the true spectrum can only be obtained from an infinitely long segment. In practice, however, directly applying the FFT to longer segments of data is less desirable for at least three reasons. It will require long computational time, it assumes stationarity of the underlying signal, and also it does not exhibit the expected property of a decrease in variance with increased data length. For a long segment, the noise will be represented at a high spectral resolution determined by the Rayleigh frequency, but not be averaged over nearby frequency bins. As such, while the frequency resolution increases with long data length, the noise variance of the spectral estimate is not improved. *Welch's method* is one way to circumvent these concerns, by first "windowing" (i.e. cutting the data into N shorter equal-length segments) and then computing the power spectra per segment followed by averaging the spectra (Welch, 1967). Fig. 3 illustrates this, first by showing a long (20 s) time segment of a 20 Hz oscillation with added pink noise (Fig. 3A); a 1 s subset is shown in Fig. 3B. (Pink noise is noise drawn from a signal with a power spectral density following 1/f, in other words inversely proportional to frequency). If the FFT of the 20 s data is calculated (Fig. 3C), the peak at 20 Hz is strong, but also the noise is strong. In contrast, if the Welch method is used, whereby the FFTs of 20 (N=20) segments, each 1s long, are computed and averaged, the result is a smoothing over N adjacent frequency bins. This smoothing reduces the main peak at 20 Hz, but also reduces the noise, by the expected ratio of $1/\sqrt{N}$. Effectively, one compromises frequency resolution when averaging over N bins, but typically the increased signal-to-noise ratio is preferred over a small Rayleigh frequency, since neural oscillations typically fluctuate in frequency. (Note that in Fig. 3, the short 1 s segments were padded to a length of 20 s prior to FFT; padding is discussed further down).

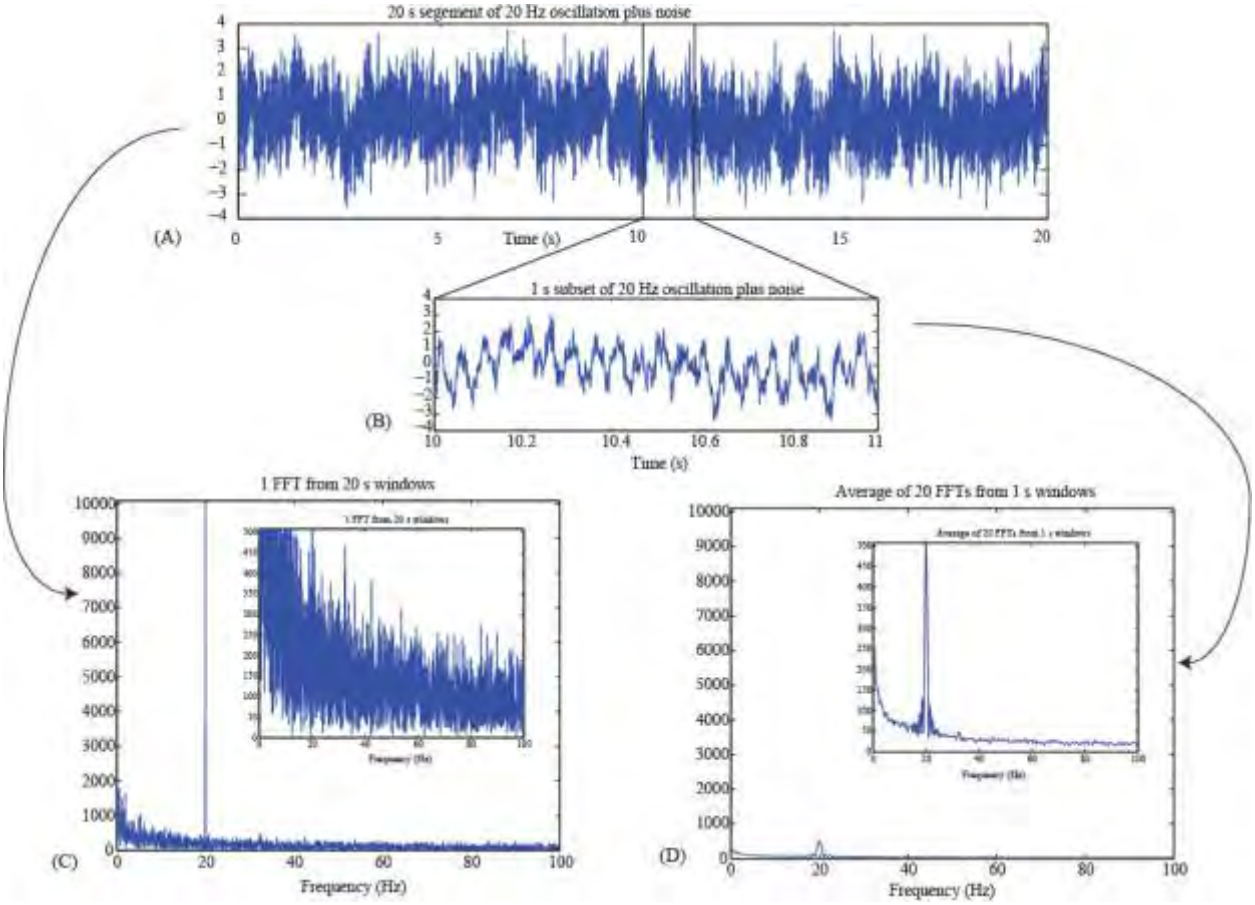

Fig. 3. Illustration of the averaging/smoothing over frequency provided by the Welch method using averaged spectra from shorter time windows. (A) A simulated 20 s long signal created from the addition of a 20 Hz sinusoid plus pink noise. (B) A zoomed in view of 1 s of the simulated signal. (C) The FFT of the data in (A). The inset is the same figure with a different y-scale. (D) The average of the 20 FFTs obtained from dividing the signal in (A) into 20 separate 1 s duration segments, with padding to 20 s length. The inset is the same figure with a different y-scale, but same y-scale as the inset in (C).

Segmenting has the further advantage of only assuming/requiring short-time stationarity within one segment, as variation over segments can be examined for non-stationarity. However, care should be taken that the segments do not become too short, as the practical minimal data segment length to sufficiently capture an oscillation is suggested to be about 3-5 times the length of the period of the frequency of interest. Thus, for example, a segment not much shorter than 400 ms should be used to estimate the power and/or phase at 10 Hz. Longer time segments may be advised if characterization of precise frequency estimates are desired (e.g. determining the peak frequency of the alpha oscillation during an eyes-closed resting condition to within 0.5 Hz precision would require a 2 s window). However, at least two concerns become apparent with the use of shorter time windows. The first is the increased Rayleigh frequency. In the example above, sacrificing a Rayleigh frequency of 0.05 Hz from a 20 s window to 1 Hz from a 1 s window is usually acceptable for most research questions; however, a Rayleigh frequency of 5 Hz, resulting from a window length of 200 ms, may not be sufficiently precise. To mitigate this, one may *"pad"* a time window with extra zeros resulting in a desired Rayleigh frequency. New information has not been gained at these intermediary frequency bins; the improved frequency resolution is a

consequence of spectral interpolation. However, padding allows a spectrally smoothed representation to be depicted. In the situation of unequal time segments, for example due to unequal trial lengths between stimulus and response time, padding each segment to an equal length is necessary if these trials are to be averaged in the frequency domain and thus at the same frequency bins. The effect of padding is illustrated in Fig. 4, described below.

A second problem with shorter time windows is that more blurring (spectral leakage) of the PSD can occur. The original Fourier Transform assumes an infinitely long signal with periodic components. However, when a segmented time window is used, this is implicitly the multiplication of a boxcar-shaped window (zeroes everywhere except a segment of ones) with the original signal. Since multiplication in the time domain is equivalent to convolution in the frequency domain, the FFT of a windowed time series appears as the convolution of the FFT of the original signal (for example, a stick, or delta function, at 20 Hz for a pure 20 Hz sinusoid) with the FFT of a boxcar, which is a sinc function. The resulting power spectral density contains power in the "tails" of the sinc function, outside the main peak of 20 Hz. This is illustrated in the example in Fig. 4. The time domain (left column) and frequency domain (right column) of several signals are shown. Fig. 4A and 4C show sinusoids at 20 Hz and 21.5 Hz, respectively with a sampling rate of 1000 Hz for duration of 1 s. The Rayleigh frequency is thus 1 Hz and the 20 Hz sinusoid can be well captured in the PSD as a sharp peak at 20 Hz and no power elsewhere (Fig. 4B). However, since the 21.5 Hz sinusoid contains its power at a frequency not at a multiple of the Rayleigh frequency, then the corresponding PSD exhibits a blurred peak near the true frequency but also power in other bands quite some distance from the true peak (Fig. 4D). The situation is worsened by using a shorter time window of 200 ms (sufficiently long to capture at least three periods of oscillation for both 20 Hz and 21.5 Hz), as shown in Fig.s 4G and 4I. The Rayleigh frequency is now 5 Hz; the PSD at every 5 Hz is shown in Fig.s 4H and 4J indicated by the black circles. The blue lines in these subfigures are computed from "zero padding" the 200 ms signal to a full 1 s length (as depicted in Fig.s 4G and 4I). In Fig. 4H, the PSD of the 20 Hz sinusoid is again well captured with the peak power at 20 Hz and no power at the other sampled frequencies for the time window 200 ms; however, the FFT of the padded signal shows the leakage effects of the boxcar window. Furthermore, in Fig. 4J the bleeding of power to frequencies away from the true 21.5 Hz is strong, both in the unpadded (black circles) and padded (blue line) results.

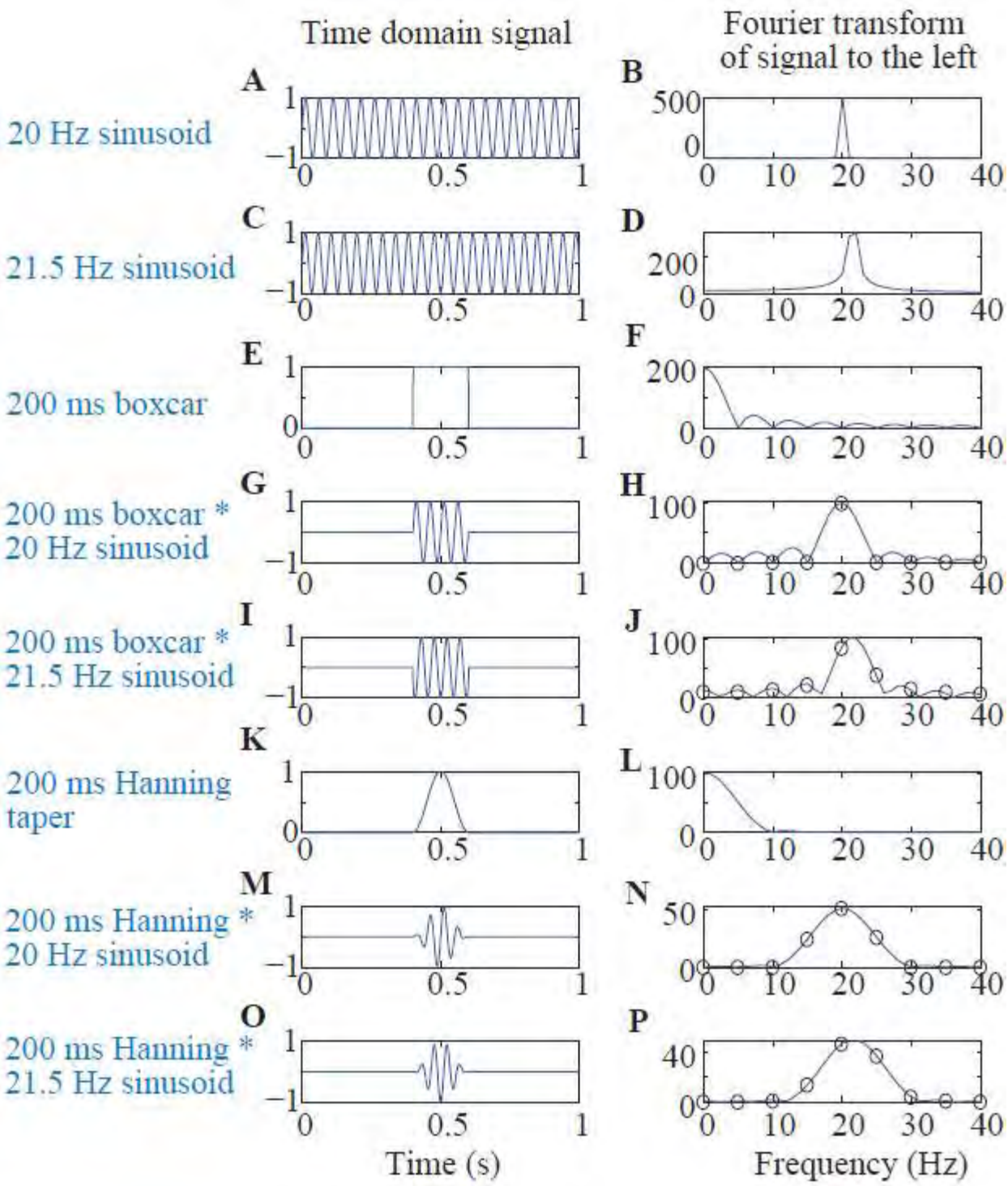

Fig. 4. Effect of window length, zero padding, and tapering on short window Fourier Transform. A) 20 Hz sinusoid over 1 s. B) FFT of A. C) 21.5 Hz sinusoid over 1s. D) FFT of C; note the spectral leakage. E) Boxcar window of length 200 ms. F) FFT of E. G) Sinusoid from A multiplied by boxcar from E. H) Blue line is the FFT of 1 s padded segment from G; black circles are the FFT from the 200 ms segment without padding. I) Sinusoid from C multiplied by boxcar from E. J) Blue line is the FFT of 1 s padded segment from I; black circles are the FFT from the 200 ms segment without padding. Again notice the bleeding. K) Hanning taper of length 200 ms. L) FFT of K. M) 20 Hz sinusoid from A multiplied by Hanning taper of K. N) FFT of M, with the blue line resulting from padding to 1 s and

the black circles from no padding of the 200 ms segment. O) 21.5 Hz sinusoid from C multiplied by the Hanning taper of K. P) FFT of O, with the blue line resulting from padding to 1 s and the black circles from no padding of the 200 ms segment. The Hanning taper effectively resolved the leakage but with the trade-off of increased spectral smoothing.

An operation known as *tapering* can be used to mitigate the effect of the bleeding into far-away frequencies due to shorter time windows. Tapering is the explicit multiplication of the signal with some taper or window function, rather than relying on the implicit multiplication with a boxcar. Smoothing the sharp rise/fall of the boxcar edge leads to reduced leakage into further away frequencies. Tapering results in local smoothing of the peak frequency and thus assumes similarity of power in nearby frequencies (an assumption which is usually justified when analyzing brain signals). A common function used is the Hanning taper. A 200 ms version of the Hanning taper with zeros padded on either side is shown in Fig. 4K and its FFT is shown in Fig. 4L. When multiplying the windowed sinusoids by the Hanning taper (Fig.s 4M and 4O), the resulting FFT of the sinusoids (Fig.s 4N and 4P) now appear as the stick (delta function) at 20 Hz or 21.5 Hz convolved with the smooth curve of Fig. 4L, rather than convolved with the bumpy curve of the sinc function in Fig. 4F. The short window of 200 ms still limits the Rayleigh frequency to 5 Hz and there is still some bleeding at nearby frequencies (e.g. at 15 Hz and 25 Hz); however, the leakage at 10 Hz and 30 Hz is greatly reduced. It is often recommended to demean before FFT as the baseline (DC) component can leak to other frequency bands.

The choice of which taper to use is based on the assumptions of the underlying true PSD. The Hanning taper illustrated minimizes the spectral leakage in the tails (also referred to as leakage in the side lobes) but results in a fairly wide blur around the true spectral peak (also referred to as a wide main lobe). Ideally, the taper choice should match the expected underlying spectral width. For example, in the alpha band of 8-12 Hz with a 4 Hz bandwidth, the Hanning taper over a 400 ms window gives a suitable match of the width of the main lobe (in fact, one roughly twice as narrow as that depicted in Fig. 4L, since the longer that the Hanning taper is in time, the narrower the lobe is in frequency). Other functions such as the Hamming taper can also be used. The Hanning, Hamming and other tapers differ from each other in their characteristics of relative suppression of the leakage in near and far frequency bands and width of the main lobe. Please see (Smith, 1997) for a detailed discussion.

When considering neural responses in the gamma band, they are often broadband, for example from 60-80 Hz. In this case, one commonly uses a set of tapers, known as the Slepian or discrete prolate spheriodal sequences (DPSS) or simply “multitapers” (Slepian and Pollak, 1961), which are a set of mutually orthogonal vectors with optimal desired spectral properties. The number of tapers used is determined by the length of the time window (Δt) and the desired frequency bandwidth (Δf), with the formula: $K = 2*\Delta t*\Delta f - 1$, where K is the number of tapers (Percival and Walden, 1993). Ideally at least three tapers should be used. A set of four DPSS are shown in Fig. 5. The result of using the multitaper method is a wider but specific passband with minimal leakage in the stopbands. In other words, the spectral properties are ideal for a broadband but yet band-limited response in the gamma band. The choice of data segment length and desired bandwidth of the multitapers is important, but to advise specific settings that are generally applicable is not possible. Rather, iteration and initial exploration of the data is recommended, for example, to determine whether a wide-band response is actually two distinct bands near each other. Further discussion of Fourier analysis for neural signals can be found in (Pesaran, 2008).

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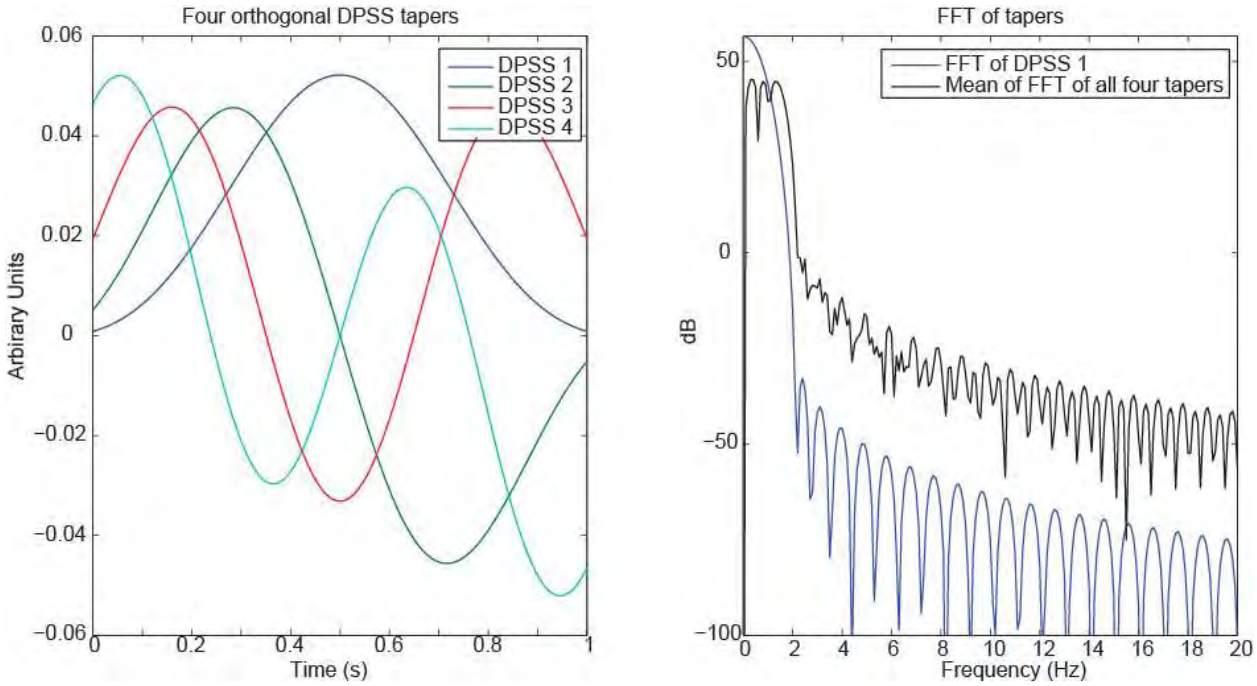

Fig. 5. Orthogonal DPSS tapers over a 1 s window (left) and their spectral density (right), with zero padding to 10 s length. The black line in the right figure is the average of the FFT of each taper, which indicates the effective result of using all four together.

3.2 Time domain characterization of oscillations

Rather than computing the FFT of a time-windowed signal to obtain its PSD across all frequencies, another option is to band-pass filter the data so as to obtain a time domain signal containing only frequencies of some band of interest. The success of this method depends on the characteristics of the filter which, similar to the discussion of tapers above, depend on passing the desired frequencies (in the "pass-band") with as close to unity gain as possible and suppressing the non-desired frequencies (in the "stop-band") with as close to full attenuation as possible (see Fig. 6). The "transition-band" refers to the frequencies in between the pass-band and stop-band for which the gain is neither zero nor unity. Four filter types are named according to the relative position(s) of their pass-band and stop-band: low-pass (Fig. 6), high-pass, band-pass and band-reject. In reality, filters are not perfect, and thus three important characteristics of filters are roll-off between the pass-band and reject-band, amount of ripple in the pass-band, and amount of attenuation in the stop-band. For more information on digital filtering, please see (Smith, 1997).

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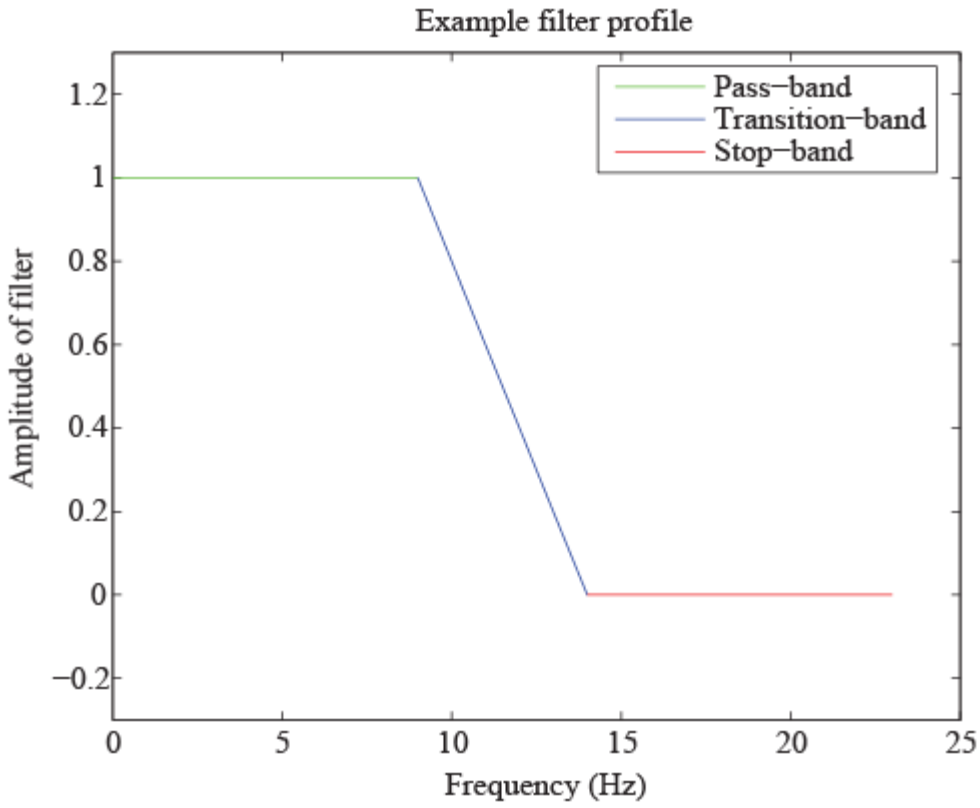

Fig. 6. Portions of a low-pass filter which correspond to the pass-band (unity amplification), transition-band (neither unity amplification nor full suppression), and the stop-band (full suppression). Similarly, a high-pass, band-pass and band-stop filter can be constructed.

While the characterization above (low-pass, high-pass etc.) applies to the desired behavior of the filter, another characterization of filters is the type of implementation used: ”infinite impulse response” (IIR) or “finite impulse response” (FIR). We do not intend to provide a mathematical explanation of these types and how they differ, but rather to introduce and discuss trade-offs of commonly used filters in neuroscience. For further details please see (Smith, 1997). The Butterworth filter is a commonly used IIR filter. Some considerations as to whether to use an IIR or FIR filter are that IIR filters tend to have a flat frequency response but a shallow drop-off in the frequency domain and indirect control over time and frequency resolution, whereas FIR filters tend to have precise control over time and frequency resolution and a sharp drop-off in the frequency domain, but have an “oscillating” response in the frequency stop-band. The order of the filter is important as well, as it relates to the amount of temporal lag of the convolution kernel as well as computation time. One important criterion is to use a filter that will preserve the phase of the signal (a “zero-phase filter”) since the phase of the oscillation can be of important functional importance. A zero-phase filter is often implemented by applying two linear-phase filters in succession, where the second “un-does” the phase shift of the first. However, it is important to know that no filter is perfect and thus by applying the same filter twice to obtain zero-phase, the amplitude is reduced twice as strongly in the pass-band. Thus when comparing amplitudes across conditions, it is imperative to use the same filtering and other preprocessing.

Filters may still have a ringing artifact (Gibbs ringing) of the filtered time series near sharp transitions in the signal, even though optimal filters aim at reducing this artifact. Thus, it is suggested to filter a segment of data longer than needed and discard the transition effects at the edges. The length of the discarded segment depends on the severity of the artifacts, but often 50-100 ms at each end is sufficient. This longer, edge-trimmed segment then can be further cut into shorter segments according to the same guidelines given above (at least 3-5 times the length of the period of oscillation) and a sum of squared amplitudes can be computed for the power of that particular time segment and frequency band according to the filter. Thus, in contrast to the FFT where all frequencies are obtained in one computation and at precise frequencies determined by the window length, this time-domain method allows for power over a window for the breadth of a frequency band to be computed, subject to the precision of the filter used. Note that filtering is for computational reasons often computed in the frequency domain using the FFT approach.

A possibility of probing the data characteristics from the band-pass filtered time domain signal is to compute its instantaneous phase and amplitude envelope (Fig. 7), using the Hilbert Transform (Bruns et al., 2000). In the limit that the time-varying signal is a perfect sinusoid, then the Hilbert transform would provide the same results as the FFT approach at a particular frequency for an infinitely long segment. The Hilbert transform can be useful to obtain the instantaneous phase estimate for an oscillation which, as recorded from a distant sensor as in MEG, may well be a mix of several oscillating neurons at nearly the same frequency. Additionally, the Hilbert amplitude envelope itself may be filtered to assess at what frequency the envelope is modulating (e.g. commonly observed in the range of 0.01-0.1 Hz (Hipp et al., 2012)).

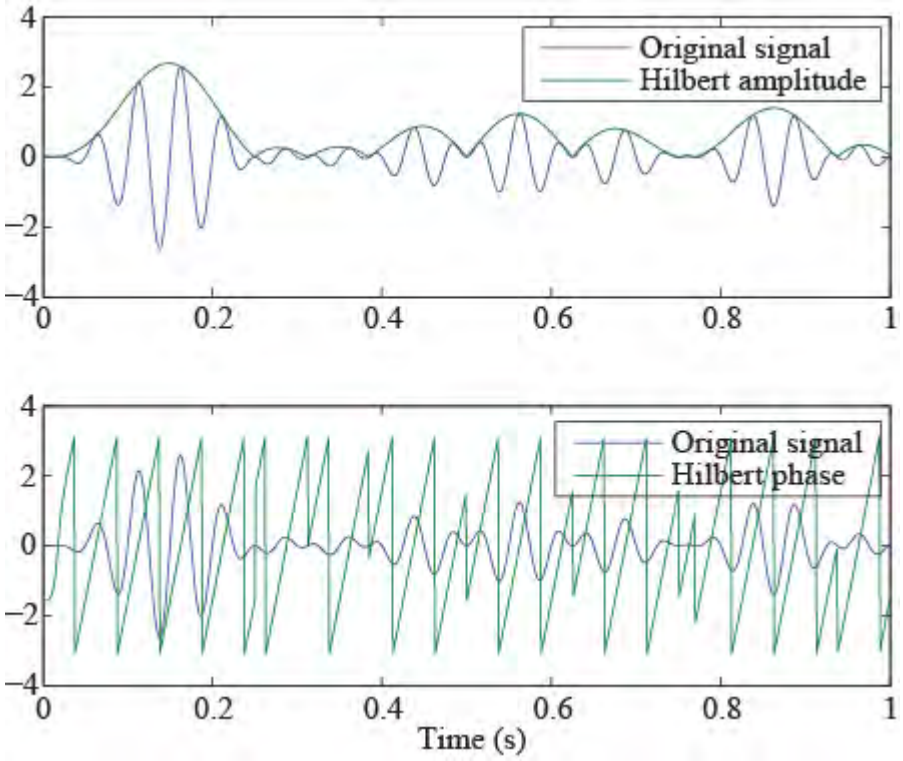

Fig. 7. The blue line shows a 20 Hz oscillation modulated by lower frequencies. The green line in the top panel shows the Hilbert amplitude of this signal and the green line in the bottom panel shows the Hilbert phase.

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3.3 Computation of time-frequency representations of oscillations

For many neuroscience applications, it is desired to compute the PSD over a range of frequencies and investigate how the PSD changes over time relative to some aspects of the task. Considering modulations in oscillatory power this way is referred to as a time-frequency representation (TFR) of power. The TFR is computed using a sliding time window. The length of each time segment in the window is determined as discussed before, but the time scale over which the changes in power may occur can be faster than the segment length; thus overlapping segments are often used. For example, 400 ms segments may be computed with the central time point in steps of 50 ms. The overlap helps mitigate the dampening effect that tapering has on the power at the edges of the time segment; the loss of power at the edges of one segment is less of a concern if the edges are the middle of another computed segment. The window length of the segments may be kept the same for all frequencies examined (Fig. 8A) as long as the window length is sufficiently long for the lowest frequency. Alternatively, as shown in Fig. 8B, a different window length may be used for every frequency so that the number of periods of oscillation remains fixed (for example, keeping 4 cycles fixed leads to a 400 ms window for 10 Hz, 200 ms window for 20 Hz, and so on). Keep in mind that if a multitaper approach is used for computing the PSD of broadband gamma, the time window should be kept constant over the frequencies, as the multitapers interact over the range of frequencies. Also due to the difference in spectral width of the generated oscillations, the lower bands (e.g. 1-30 Hz) and higher bands (e.g. 20-100 Hz) are often computed separately using, respectively, Hanning and multitapers.

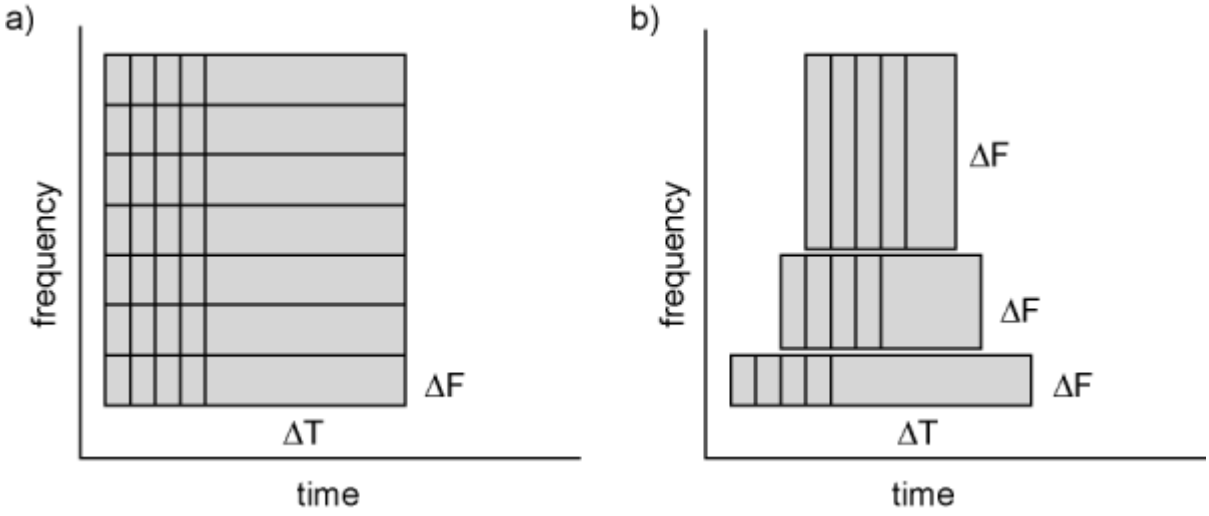


Fig. 8. Illustration of how time-frequency windows may be selected. (A) A fixed time width (ΔT) and fixed frequency width (ΔF) can be used. The center of each time window may be shifted in a time shorter than ΔT. (B) Variable time and frequency widths may be used where the area of the time-frequency window remains constant. As the time width (and temporal smoothing) is reduced at higher frequencies, the spectral width and smoothing are increased. This figure is reproduced from the tutorial on time-frequency analysis on the wiki page of the FieldTrip analysis toolbox (http://fieldtrip.fcdonders.nl/tutorial/timefrequencyanalysis).

Wavelets are another computational method which may be used to compute the TFRs of power. They use a set of basis functions across multiple frequencies and times, that qualitatively

each look like a burst of oscillatory activity at a given time and frequency, beginning and ending with zero amplitude. The exact shape of the wavelet depends on the type, of which there are many. One common type is the Morlet wavelet created by a sinusoid tapered by a Gaussian window centered at a specific time point (Fig. 9 left panel). The wavelet transform then uses the wavelet basis set (typically optimized for discrete signals with a discrete wavelet transform) to estimate power and phase at each frequency over time (Fig. 9). Wavelets have the property that the product of the bandwidth and window length remains constant, ensuring a constant time-frequency "area" of which the power is computed; the value of this product is user-specified. Note that Fourier analysis using sliding time windows, filtering plus Hilbert transform, and the wavelet transform are mathematically equivalent, given specific sets of parameters (Le Van Quyen et al., 2001;Bruns, 2004).

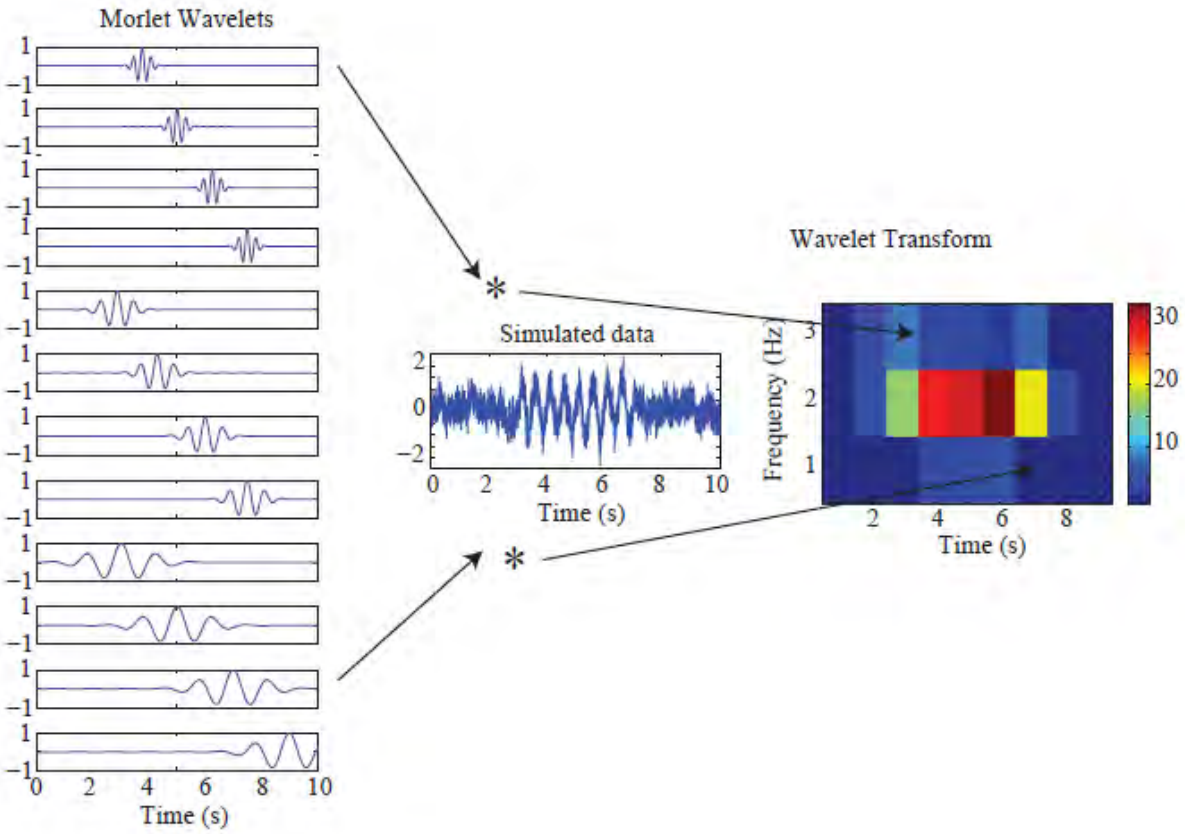


Fig. 9. Morlet wavelets and their use to create a time-frequency representation of data. (Left) A set of Morlet wavelets, with four different central points over three different frequencies. (Middle) example data with an oscillation at a frequency close to that of the middle frequency of the wavelets. (Right) The time-frequency representation of the spectral (vertical) and temporal (left to right) variation of each wavelet with the data.

3.4 Characterizing cross-frequency interactions

The physiological mechanisms of interactions across frequencies have been briefly described earlier in this chapter and may be quantified in various ways, each emphasizing different aspects of the interaction. Cross-frequency coupling can occur in various ways, involving the phase or

amplitude (power) of a lower frequency band and the phase, amplitude or frequency in a higher-frequency band ((Colgin et al., 2009); Fig. 10A).

One well studied type of cross-frequency coupling is phase-amplitude coupling (PAC), i.e. coupling of the phase of the lower frequency (LF) (Fig. 10B-C) to the amplitude of the high frequency (HF) (Fig. 10B-D). Eight metrics to compute PAC are compared in (Tort et al., 2010) and reviewed in (Canolty and Knight, 2010), of which we provide here a summary. As shown in Fig. 10B-E, reproduced from (Tort et al., 2010), a phase-amplitude histogram can be computed from the amplitudes of the higher frequency binned according to the phase of the lower frequency. Metric 1 (heights ratio; HR) uses this histogram directly to compute the ratio of the relative difference between the highest and lowest amplitudes; thus the HR metric lies between 0 and 1. Rather than just using the bins with the highest and lowest amplitudes, Metric 2 instead uses the whole distribution to compare against a uniform distribution (Tort et al., 2008;Tort et al., 2009), via a modulation index (MI) computed from the Kullback-Leibler (KL) distance (a method to compute a distance between probability distributions), denoted MI-KL. Metric 3 uses the PSD of the high frequencies to explore for possible PAC with any number of low frequency bands (Cohen, 2008). However, note that a simple presence of power at low and high frequencies does not mean that there is phase-coupling in the same bands. Metric 4 uses a complex-valued time series created by the amplitude at high frequencies and the phase of the low frequencies; the mean vector length (MVL) of this new signal in the complex domain then indicates the extent to which amplitudes of high frequency activity are clustered in a particular phase of the low frequency oscillations (Canolty et al., 2006). Metric 5 computes a phase-locking value (PLV) between the phase of the low frequency signal and the phase of the envelope of the high frequency signal (Cohen, 2008) (Penny et al., 2008). Metric 6 computes the correlation of the high frequency envelope to low frequency signal, referred to as the envelope-to-signal correlation (ESC); this can be modulated to use only the cosine of the phase of the low frequency component removing its amplitude, thus a normalized ESC (NESC). However, ESC and NESC are phase-dependent and cannot detect a 90° phase difference. To get around his problem, (Penny et al., 2008) proposed Metric 7, which improves on the phase-specificity of ESC by adding a sine component and using a general linear model (GLM) to determine the dependence of the high frequency envelope on any phase of the low frequency signal. Finally, metric 8 computes a coherence spectrum between the amplitude envelope of the high frequency and the original unfiltered signal (Osipova et al., 2008).

(Tort et al., 2010) compared these eight metrics (see their Table 1) for properties of tolerance to noise, dependence on the amplitude of the low frequency, sensitivity to a multimodal histogram distribution, and sensitivity to width of the modulation distribution of the phase-amplitude coupling histogram. Specifically, measures that are only sensitive to the phase-locking will miss out on information of the extent of high frequency envelope modulation. Furthermore, the metric should be independent of the phase at which the high frequency envelope is maximal or minimal or if indeed multimodal. The metric should also have relative tolerance to noise and insensitivity to the absolute amplitudes of the low frequency or envelope of the high frequency signals. They conclude that their method of MI-KL performs optimally on these four considerations, and gives results that match intuitively with quantification of phase-amplitude coupling. The MI-KL metric is limited to examine only one low frequency band at a time, but of

course the MI-KL of the same high frequency to several different low frequency bands may be computed independently.

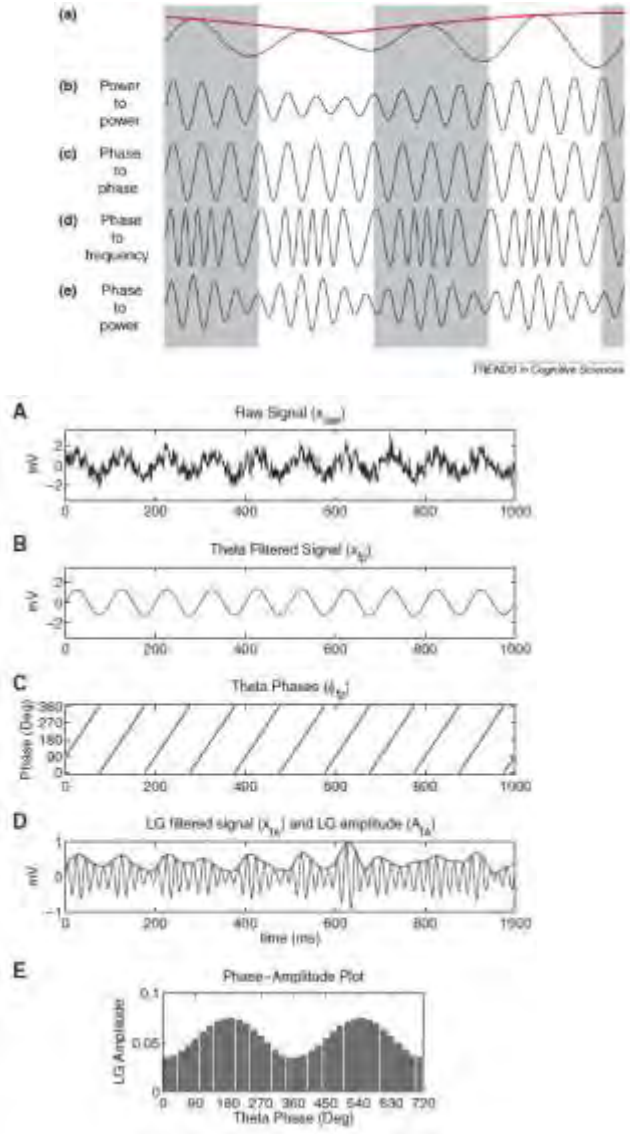


Fig. 10. A) Demonstration of four ways in which a higher frequency can be modulated by a lower frequency (reproduced from (Jensen and Colgin, 2007)). B) Analysis pipeline and example results for computing phase-amplitude coupling, with the lowest panel showing the histogram of amplitudes of the higher frequency binned according to phase of the lower frequency (reproduced from (Tort et al., 2010)).

Amplitude-amplitude (or power-power) coupling may be computed in several manners, although not so much variability or flexibility exists as it does for phase-amplitude coupling. One method includes computing the Hilbert amplitude envelope for two different frequencies and correlating them over time or trials. Note that the time series of the Hilbert envelope itself will fluctuate at a frequency much lower than the underlying frequency from which it is computed; thus, in order to compute a correlation a sufficiently long time window to capture several cycles is needed (e.g. 10 s for the alpha activity). This can be therefore useful in resting state paradigms

(de Pasquale et al., 2010;Brookes et al., 2011b;Hipp et al., 2012). Alternatively, it may be desired to assess whether the power at a particular time relative to a task from two different frequencies are co-modulated over trials (de Lange et al., 2008;Mazaheri et al., 2009). In this case, either the frequency domain or time domain methods for computing a PSD may be used.

Phase-phase coupling (PPC) means that the phase of an oscillation in one frequency is coupled to the phase of an oscillation in another frequency; in other words, a fixed number of high frequency cycles occurs every low frequency cycle. Once again, several methods exist to quantify this coupling. Bispectral analysis quantifies how two oscillations can nonlinearly interact to generate a third frequency. This metric has been used successfully in EEG data (Sigl and Chamoun, 1994) (Shils et al., 1996) (Schack et al., 2002). However, like coherence between two signals of the same frequency, the amplitude is involved as well, thus not a strict phase-phase coupling measure. If the two frequencies (n and m) are harmonics of the same fundamental frequency (such that n*f1 = m*f2), then a modified n:m phase synchronization index is computed as $\omega_{n,m} = n*\varphi_1 - m*\varphi_2$ (Tass et al., 1998) (Guevara and Glass, 1982). (Palva et al., 2005).

3.5 Concluding remarks

We have demonstrated that transforming the original time domain signal to the frequency domain allows for a rich characterization and efficient computation of the data to obtain a time-frequency representation of power. Considering the time signal as a sum of sinusoids each with its own amplitude and phase can promote a greater conceptual understanding. Considering cross-frequency interactions provides a new and exciting manner for analyzing oscillatory activity. Attention to details such as window length, tapering, spectral leakage and spectral smoothing will ensure an optimal representation of the data.

4. Functional role of brain oscillations

4.1 Gamma oscillations

Oscillatory activity in the gamma band (30-100 Hz) is typically associated with active neuronal processing of information. We will here first review the theoretical notions for how gamma activity might organize neuronal processing in time. We will then bring forward some examples demonstrating how the gamma activity can be investigated and interpreted in the context of MEG studies on cognition.

One of the key mechanistic ideas of the gamma band activity is related to synaptic integration. Imagine a group of neurons projecting to a downstream region. In order for a single neuron in the receiving region to fire, it must receive synaptic input from several of the neurons in the sending network. However, these inputs need to be somewhat synchronized to add up sufficiently. Typically an excitatory postsynaptic current lasts for about 10-20 ms. This implies that neurons in sending regions that synchronize in the gamma band (1/[20 ms] - 1/[10 ms] corresponding to 50 - 100 Hz) provide a strong feed-forward drive (Tiesinga et al., 2004) (Salinas and Sejnowski, 2001) (Fig. 11). This framework is supported by the observation that the engagement of a given brain region often is reflected by a gamma band power increase. This has for instance been reported in LFP recordings in animal preparations (Gray et al., 1992). When a

visual grating is presented to the monkey, strong gamma band synchronization is observed in visual regions including V1 and V4 (Gail et al., 2000) (Fries et al., 2001) (Rols et al., 2001) (Buffalo et al., 2011) (Bosman et al., 2012). Further the timing of neuronal firing is tightly coupled to the phase of the gamma band oscillations. Importantly, the degree of gamma band synchronization might act as a mechanism for gain control (Tiesinga et al., 2004). Tighter synchronization in the sending regions leads to a stronger feed-forward drive. This notion is reflected by an increase in spike-field coherence in the gamma band when covert attention was allocated to the respective visual field (Fries et al., 2001) (Buffalo et al., 2011). Further, the tightness of the synchronization will be reflected as an increase in the electrical fields in the gamma band. This has been demonstrated in several human studies using EEG and MEG in which the gamma band activity increases with attention (Bauer et al., 2012) (Gruber et al., 1999) (Siegel et al., 2008).

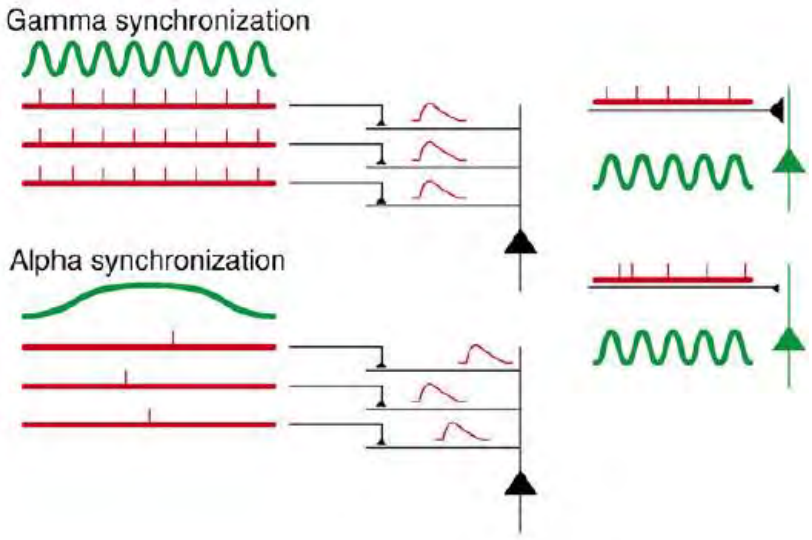


Fig. 11. Neuronal synchronization promotes a stronger feed-forward drive due to the temporal integration of synaptic input. This time-window of temporal integration is determined by the GABAergic feedback and is in the order of 10-20 ms, which makes synchronization in the gamma band optimal for providing a feed-forward drive. A slower rhythm like the alpha rhythm will provide a less tight synchronization and provide a less effective feed forward drive (reproduced from (Jensen et al., 2007)).

While these findings mainly pertain to the gamma activity in a given region ("the sender") it has also been proposed that communication between regions is a consequence of the dynamics in both the sender and the receiver. This theory is termed "communication through coherence" (Fries, 2005). It proposes that to achieve optimal communication, the sender and the receiver need to oscillate coherently such that an incoming synaptic input co-occurs with the maximally excitable gamma phase in a receiving neuron (Fig. 12). Likewise communication between the two regions can be blocked by adjusting the phase relationship such that incoming spikes arrive at the least excitable gamma phase. In general the framework is consistent with the notion that communication between brain regions should be reflected in gamma band coherence (Bressler, 1996) (Varela et al., 2001). Recently the theory has received some experimental support from intracranial recordings in monkeys (Bosman et al., 2012;Grothe et al., 2012). While these

findings are in support of the theory, long-distance coherence in the gamma band has been difficult to reliable identify in human MEG recordings, albeit there are several reports (Siegel et al., 2012). Interestingly there are now several papers on phase-synchronization in the theta and alpha band facilitating long-distance neuronal communication in both animals and humans (Colgin, 2011) (Liebe et al., 2012) (Palva and Palva, 2011) (Saalmann et al., 2012). More work is required in order to determine the generality of communication through coherence and which frequency bands best reflect communication.

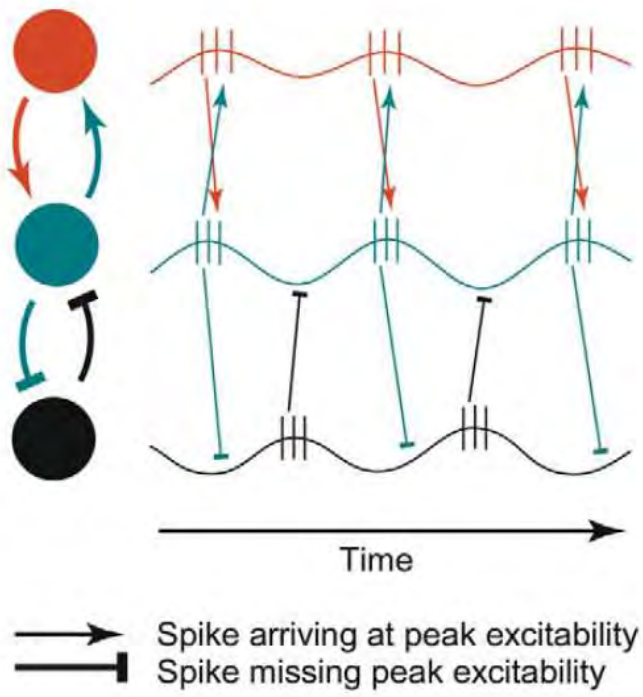


Fig. 12. A schematic illustration explaining communication through coherence. The red and the green cells are phase-locked in such a manner that spiking in one set of cells will coincide with the excitation by the gamma phase in the other cells. This allow for the cells to communicate. The phase relationship between the red and black cells is such that the incoming spikes will be missing the excitable phase. Thus information is only exchanged between the red and green cells. Reproduced from (Fries, 2005).

Beyond neuronal communication, it has been proposed that gamma band synchronization is needed for solving the "binding problem" (Gray et al., 1989;Engel and Singer, 2001) (Engel et al., 1999) (Tallon-Baudry and Bertrand, 1999). It should be mentioned that this framework pre-dates the ideas on communication by gamma band synchronization. Typically when we perceive an object it is composed of several parts. In order to perceive the object as one, we need to perceptually combine the parts. Obviously binding needs to be done in a fast and flexible manner. The "binding-by-synchronization" hypothesis proposes that binding is achieved by neuronal synchronization in the gamma band. In other words, neurons coding for different parts will fire synchronously in order to form an ensemble that is perceived as one object (Fig. 13). This theory has received some experimental support (Gray et al., 1989) (Engel et al., 1997;Castelo-Branco et al., 2000); however, it has also been criticized (Roelfsema, 1998;Burns et al., 2011). One point of

criticism pertains to the observation that gamma band activity changes frequency with stimulus contrast (Ray and Maunsell, 2010). This poses a challenge to the binding theory since an object can be perceived as one, even if it is composed of parts of different contrast. It is of interest to point out, that a recent paper reported that an ensemble of neurons synchronizing in the beta band (~30 Hz; also termed lower gamma band) reflected the dynamic formation of representations for rules implementing stimulus-response mappings in prefrontal cortex (Buschman et al., 2012). In this study, the formation of representations seems to be reflected by neuronal synchronization. Although this does not pertain to perceptual binding per se, it does demonstrate that synchronization could play an important role for the dynamic formation of neuronal representations. Further research applying multi-unit and field recordings need to be performed to determine the general importance of gamma synchronization and binding.

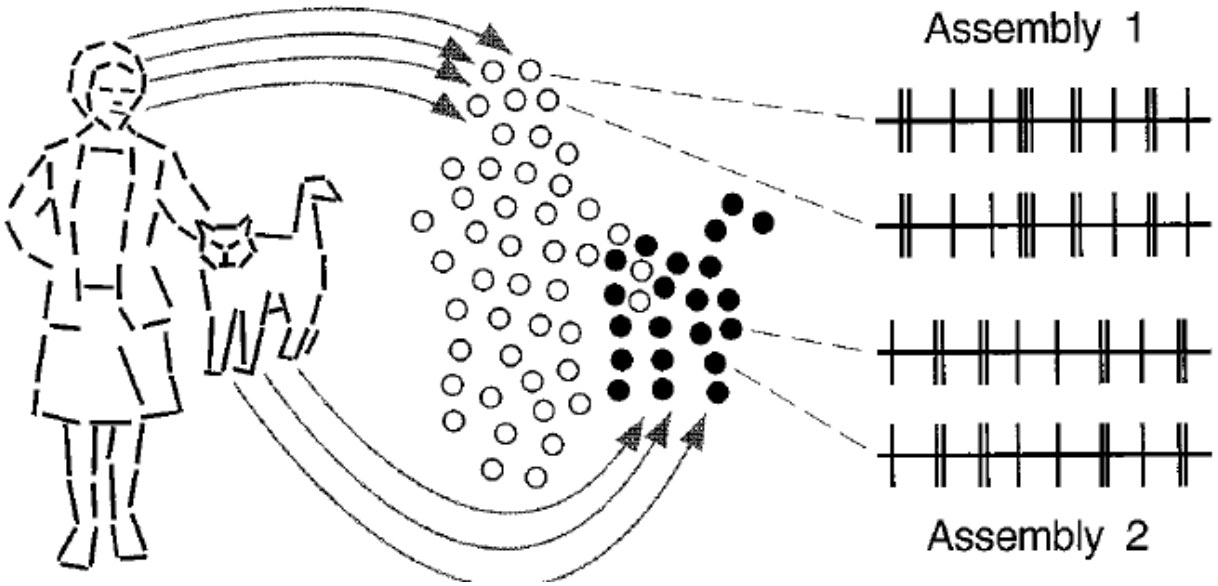


Fig 13. Perceptual binding by neuronal synchronization in the gamma band (reproduced from Engel 1999). Cells whose receptive fields (RFs) correspond to locations of parts of the same object will synchronize with each other, binding those parts of the visual field together.

To summarize, there are several influential theories on the functional role of gamma band oscillations. What these theories have in common is that they implicate gamma band synchronization in neuronal processing. There are now numerous studies demonstrating robust gamma band activity observed with MEG. We will mention a few here. Visual gamma band activity can be induced by gratings presented to the subject (Hoogenboom et al., 2006;Muthukumaraswamy and Singh, 2013)(Fig. 14a). This gamma activity is highly robust and remains stable when tested over days (Muthukumaraswamy et al., 2010). Interestingly, the properties of the spectra in the gamma band are highly reproducible over monozygotic twins (van Pelt et al., 2012). This suggests that the frequency and synchronization properties are strongly linked to the physiology in a given subject. Further, sustained gamma band oscillations have been observed in human visual areas during working memory maintenance (Jokisch and Jensen, 2007) (Roux et al., 2012) (Van Der Werf et al., 2009) (Fig. 14b). These findings are consistent with intracranial monkey recordings also demonstrating sustained gamma band activity during working memory maintenance (Pesaran et al., 2002). This was observed in LFP power but also in the coupling between neuronal spiking to the phase of ongoing gamma oscillations. Gamma band activity has also been associated with the successful encoding of long-term memory. Stronger induced gamma activity was observed in response to the presentation of items that were later remembered compared to forgotten (Gruber et al., 2004) (Osipova et al., 2006) (Meeuwissen et al., 2011). These findings are possibly linked to the observation that synaptic plasticity (long-term potentiation) can be improved when the inducing stimulus is coupled to the phase of the gamma oscillations (Wespatat et al., 2004). Finally it should be mentioned that MEG studies have found gamma band activity not only in the visual system. Reliable gamma band activity modulated by attention has also been observed in the somatosensory system (Bauer et al., 2006). Also, gamma band activity in the auditory system has been intensively investigated (Knief et al., 2000) (Pantev et al., 2003) (Kaiser and Lutzenberger, 2005).

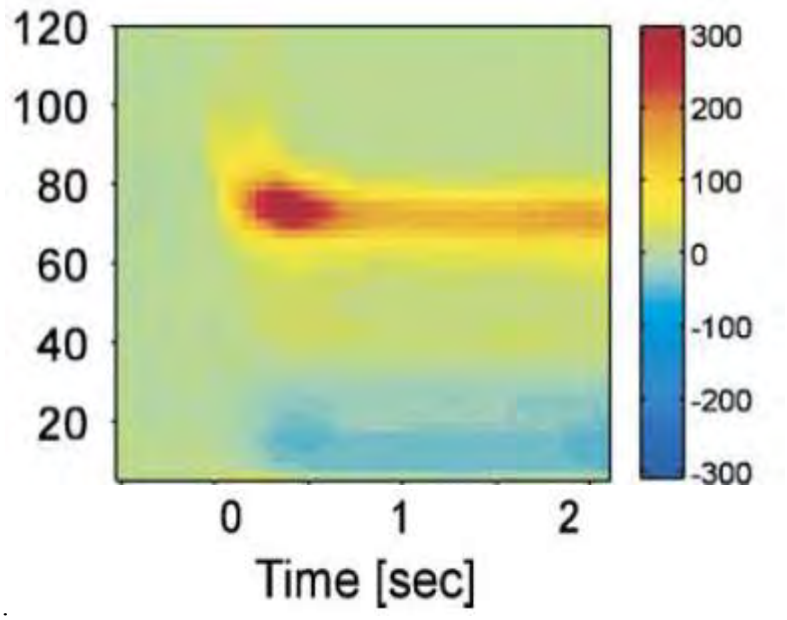
In conclusion gamma activity can be reliably detected using MEG. Further, the gamma band activity is often observed to be modulated by various cognitive manipulations. Animal recordings indicate that the gamma band activity is a consequence of a temporal organization of neuronal firing. As both theories and experiments develop we will gain further insight into the functional role of gamma oscillations.

4.2 Alpha oscillations

Oscillatory activity in the alpha band was first reported by Hans Berger in 1929 (Berger, 1938). Given that the alpha band activity emerges during rest and increases when subjects close their eyes, it has been associated with a state of rest. It has also been termed an idling rhythm, i.e. reflecting a state in which subjects are not engaged in a particular task but yet wakeful. This notion has recently lost ground in favor of the idea that alpha oscillations reflect active inhibition in a given region, although several indications from older studies actually are in support of this notion. For instance (Adrian, 1944) showed that alpha band activity in posterior regions increases when attention was allocated from the visual to the auditory modality (Fig. 15). An EEG study by

Ray and Cole (1985) showed a relative increase in alpha band power when attention was allocated to an internal task compared to the environment (Ray and Cole, 1985). These types of observations were not consistent with the resting or idling notion of the alpha band activity. As a result of studies manipulating attention between the auditory and visual modality, it has been proposed that the alpha band activity reflected active inhibition of the visual system (Foxe et al., 1998). There are now numerous papers supporting the alpha inhibition hypothesis and we will here mention a few of those (for reviews see (Foxe and Snyder, 2011) (Klimesch, 2012) (Jensen and Mazaheri, 2010).

A)



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B)

Appeared in Magnetoencephalography. From Signals to Dynamic Cortical Networks
Supek, Selma, Aine, Cheryl J. (Eds.) 2014, pp. 359-404; ISBN 978-3-642-33044-5

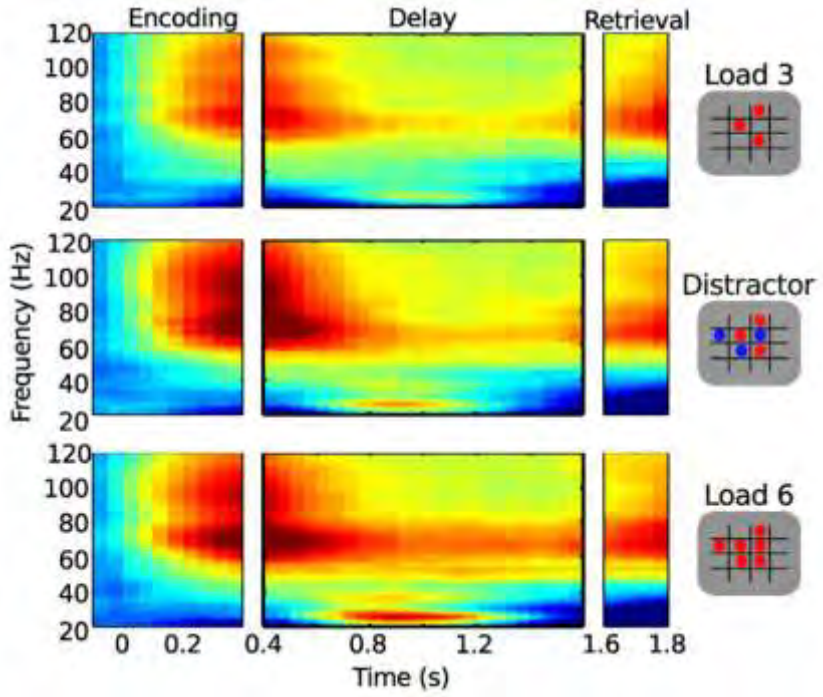

Fig 14. (a) Robust gamma band oscillations induced by visually presented moving gratings. Their sources were localized to visual cortex (reproduced from (Hoogenboom et al., 2006)). (b) Sustained gamma band oscillations observed during working memory maintenance (Roux et al., 2012).

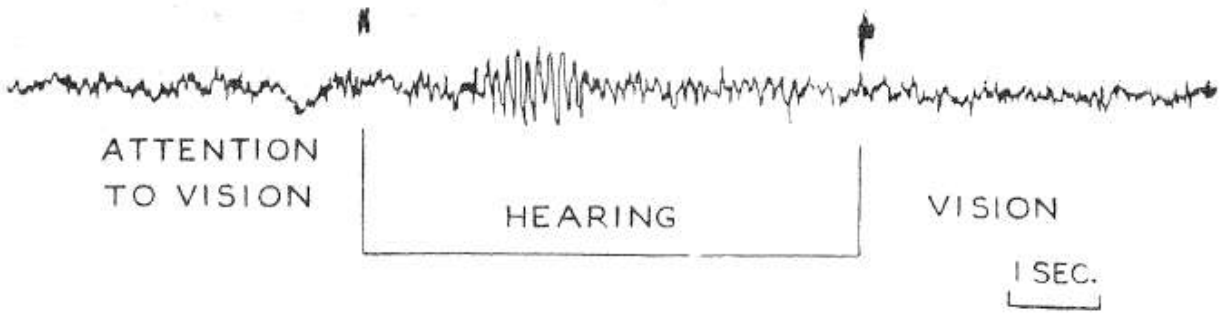

Fig. 15. An example of an EEG study in which subjects were asked to shift attention between vision and hearing. The alpha power increased with an increase in attention towards hearing. (Reproduced from Adrian 1944)

There are several lines of direct evidence showing that the alpha activity is associated with a decrease in neuronal activity. When relating spiking neurons to the field potential of ongoing oscillations in monkey recordings, a robust phasic modulation has been shown (Bollimunta et al., 2008) (Haegens et al., 2011b) (Buffalo et al., 2011) (Saalmann et al., 2012). Further it was demonstrated in sensorimotor regions that as firing rate decreases, alpha power increases (Haegens et al., 2011b). In recordings from the monkey visual system, a negative correlation between alpha and gamma power was demonstrated (Spaak et al., 2012a). Combined EEG and fMRI recordings have consistently demonstrated a negative correlation between alpha power and the BOLD signal (Laufs et al., 2003) (Goldman et al., 2002). The perception of phosphenes induced by transcranial magnetic stimulation (TMS) has been related to the ongoing EEG signal. It was found that phosphene perception decreases as alpha power increases (Romei et al., 2008).

These studies provide direct physiological support for a region specific inhibitory role of the alpha band activity.

Considerable effort has also been put into investigating the functional role of the alpha band activity using EEG and MEG. In particular, MEG has allowed studying the region specific properties of the alpha band activity. One of the challenges to the idling hypothesis stems from working memory paradigms, applying a variation of the Sternberg task. In these studies it has been demonstrated that the alpha activity systematically increases with memory demands (Jensen et al., 1999;Klimesch et al., 1999) (Fig. 16A). This is a highly robust finding that has been shown with EEG, MEG and even concurrent EEG and fMRI recordings using various kinds of stimuli (Tuladhar et al., 2007b;Scheeringa et al., 2009;Park et al., 2011). The increase in the alpha power with working memory demands is in stark contradiction to the resting or idling notion of the alpha activity. It has been proposed that the alpha power increase reflects either the active maintenance of the working memory representations (Palva and Palva, 2007) or active inhibition of posterior regions (Klimesch et al., 2007) (Foxe and Snyder, 2011). This inhibition would serve to decrease the processing of potentially interfering information and thus allocate resources to working memory maintenance. This hypothesis was recently tested in a working memory study in which distracters were presented during the retention interval in a modified Sternberg task (Bonnefond and Jensen, 2012). The timing and type of the presented distracters could be anticipated by the subjects. A clear increase in alpha activity was shown to occur just prior to the arrival of the distracter (Fig. 16B). Furthermore, trials with longer response times to the memory probe were associated with a weaker pre-distracter alpha increase. These findings demonstrate that the posterior alpha activity serves an active role in filtering out distracting information. The alpha activity has also been shown to be strongly modulated with regard to attention allocated to the left or the right hemifield (Worden et al., 2000). When attention is directed to the left hemifield the alpha power is decreased over the right posterior hemisphere. Importantly, the alpha activity is relatively greater in the left hemisphere (and vice versa). These findings suggest that the right hemisphere is engaged while the left is inhibited. This hemispheric lateralization has been shown to have behavioral consequences for visual detection (Thut et al., 2006) (Gould et al., 2011) (Händel et al., 2010). Importantly, the alpha activity in the hemisphere ipsilateral to the direction of attention predicted performance to a greater extent than the alpha decrease contralateral to the direction of attention.

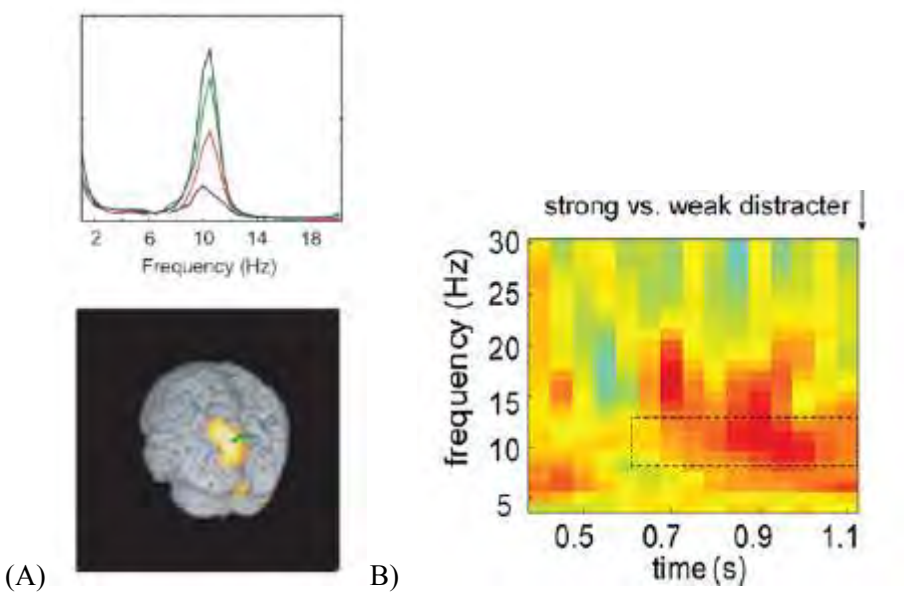

Fig. 16. (A) It has been consistently demonstrated that the posterior alpha activity increase systematically with working memory load. This finding is in contradiction to the resting or idling notion of the alpha activity (reproduced from (Tuladhar et al., 2007a)). (B) Distracters were presented in the retention interval of the Sternberg task. The alpha activity increased just prior to the anticipated distracter. This increase was predictive of performance (reproduced from (Bonnefond and Jensen, 2012)).

The functional role of alpha activity generalizes beyond the visual system. The primary sensorimotor system is known to strongly modulate alpha band activity (Pfurtscheller and Neuper, 1994;Hari and Salmelin, 1997). The somatosensory alpha band rhythm is also referred to as the mu rhythm. Sensorimotor alpha activity is also lateralized hemispherically with respect to attention to left and right hands. This has for instance been observed in a somatosensory working memory task in which subjects had to attend to electrical stimuli presented to one hand. The alpha activity which localized to the primary sensorimotor cortex decreased contralaterally to the stimulated hands, whereas it increased ipsilaterally. Importantly the ipsilateral alpha increase was the best predictor of performance (Haegens et al., 2010). These findings suggest that the active inhibition of task-irrelevant, but potentially interfering, regions is the best predictor of optimal performance. The notion that alpha activity reflects the inhibition of distracting information in the somatasensory system was directly tested in a study where target stimuli were presented to one hand and distracters were presented to the other (Haegens et al., 2012). The alpha activity in the somatosensory cortex contralateral to the hand with the distracters was the best predictor of target detection. Interestingly alpha band activity associated with the inhibition of motor responses has also been identified in the motor system (Sauseng et al., 2009). Alpha activity has also been identified in the auditory cortex using intracranial recordings in humans and MEG (Gomez-Ramirez et al., 2011). In older MEG studies this activity was called the tau rhythm (Lehtela et al., 1997). In more recent studies the functional role of the auditory alpha activity has been investigated (Weisz et al., 2011;Muller and Weisz, 2012). These studies suggest that the alpha activity also plays an inhibitory role in the auditory system.

In sum, these studies strongly point to an inhibitory role of the alpha activity. This alpha activity serves to suppress the processing in regions not required for a given task. Importantly, if the suppression is insufficient, performance is suboptimal. While this functional role seems to apply to the visual, somatosensory and auditory sensory systems, it might generalize to other regions. MEG may be particularly sensitive to activity produced in sensory regions. Intracranial recordings would help to elucidate the generality of the function of alpha oscillations . A recent study reported alpha activity in the prefrontal cortex of monkeys performing a rule-based stimulus-response mapping task (Buschman et al., 2012). Importantly, the alpha band synchronization in prefrontal cortex was associated with the suppression of the rules not to be applied.

The studies mentioned so far have only addressed the functional role of the *amplitude* or *power* of the alpha activity. This functional description is incomplete since the *phase* of the alpha oscillations strongly modulates neuronal firing as well (Bollimunta et al., 2008) (Haegens et al., 2011b) (Saalmann et al., 2012). Consistently, the BOLD signal evoked by visual stimuli has been shown to depend on the phase of ongoing alpha oscillations (Scheeringa et al., 2011). Several recent studies have investigated how the phase of the alpha oscillations modulates perception. It has been demonstrated that alpha phase in relation to stimulus presentation is predictive of hard-to-detect stimuli (Busch et al., 2009;Mathewson et al., 2009). Also, the detection of phosphenes evoked by TMS is dependent on the phase of ongoing alpha oscillations (Dugue et al., 2011). A recent working memory study demonstrated that alpha phase could be adjusted in anticipation of an incoming stimulus (Bonnefond and Jensen, 2012). These studies can all be interpreted as the alpha activity allowing for windows of processing. This notion can be reconciled with the alpha inhibition hypothesis: the stronger the alpha, the shorter the time-window ("duty cycle") of processing. A recent theory has developed these ideas in the context of attention of visual processing (Jensen et al., 2012b). The phasic modulation of processing is also likely to have consequences for communication between brain regions (Palva and Palva, 2011). If the information processing is constrained to certain alpha phases in sending regions, a receiving region could benefit in terms of adjusting its phase accordingly. In support of this notion, a recent intracranial monkey study demonstrated phase-synchronization between several visual regions organized by the pulvinar (Saalmann et al., 2012).

4.3 Delta oscillations

There are several EEG and MEG studies reporting on the modulation of delta oscillations in various tasks (Basar et al., 2001;Handel et al., 2007;Handel and Haarmeier, 2009;Knyazev et al., 2009;Knyazev, 2012); however, there are only a few explicit ideas on the mechanistic role of the delta oscillations (Lakatos et al., 2005;Lakatos et al., 2008). One dominating idea is that the phase of the delta oscillations determines the excitability of the network. In tasks where incoming input can be anticipated, the phase of the delta oscillations can change. This provides a gating mechanism allowing for either blocking or facilitating a given anticipated input. This mechanism has been demonstrated in monkey recordings to operate in cross-modal integration paradigms (Lakatos et al., 2008). A monkey received a stream of alternating visual and auditory input spaced at 300 ms. The monkey had to attend to either the visual or the auditory input. As the monkey attended to the visual input, the delta activity measured in visual cortex adapted in phase to the

timing of the visual stream. When attention was allocated to the auditory stream, the delta phase adjusted such that the excitability in visual cortex was no longer high when the input arrived. Further, induced gamma activity reflecting the processing of the input was found to be phase-locked to the delta phase. The demonstration that the phase of the slower delta oscillations control the gamma activity has also been reported in MEG studies (Handel and Haarmeier, 2009). In future work it would be interesting to further uncover the mechanistic role of delta oscillations, particularly in tasks where the timing of input can be anticipated.

4.4 Theta oscillations

Substantial insight on the mechanistic role of theta oscillations has been gained from multi-electrode recordings in behaving rat. It is now possible to record single unit activity from about 100 cells while simultaneously acquiring local field potentials (Wilson and McNaughton, 1993). This allows for relating spiking activity of a population of cells to local field oscillations. One of the most important insights from this work is the discovery of phase coding of hippocampal place cells. Place cells code for specific regions in an environment as the rat is exploring. The area in the environment in which a given place cell fires is termed the place field (O'Keefe and Dostrovsky, 1971). As the rat enters a place field, the respective place cell will first fire at late phases of the theta cycle. As the rat advances, the firing will occur at earlier and earlier phases. This phenomenon is termed theta phase precession (O'Keefe and Recce, 1993). From an ensemble of place cells it is possible to reconstruct the position of the rat; however, when taking the theta phase of firing into account, the reconstruction error is further reduced (Jensen and Lisman, 2000) (Harris et al., 2003). The evidence for phase coding in the rat hippocampus has promoted the development of biophysical models accounting for the phenomena (Burgess and O'Keefe, 2011) (Lisman and Redish, 2009) (Mehta et al., 2002). Several of these models are based on time-compressed representations being activated sequentially within a theta cycle. The principle of phase coding has consequences for communication between regions. A region receiving phase coded information must also receive information about the phase of the theta oscillations in order to make use of the code (Jensen, 2001). This can be achieved through theta phase synchronization between regions exchanging a phase code. In support of this notion, phase synchronization between the hippocampus and other regions has been reported in numerous studies. For instance, the hippocampal theta oscillations have been found to be phase-locked to theta activity in prefrontal cortex (Siapas et al., 2005). This phase-synchronization is modulated by the memory component in a navigation task (Jones and Wilson, 2005;Colgin, 2011). Further, the hippocampus has been found to be synchronized to the striatum and the amygdala (Tort et al., 2008;Battaglia et al., 2011) (Seidenbecher et al., 2003). Theta oscillations related to information exchange between regions have also been observed in other animals. For instance, theta phase-synchronization between V4 and prefrontal cortex was reported in a monkey study on working memory maintenance (Liebe et al., 2012). This synchronization was observed both in the local field potentials as well as in the spike trains.

Theta oscillations do not only modulate neuronal spiking, but also oscillations in higher frequency bands. In the rat hippocampus, gamma power in different frequency ranges is modulated by the phase of the theta oscillations (Bragin et al., 1995) (Belluscio et al., 2012). Importantly theta modulated gamma band synchronization in different frequency ranges has been

shown to route information from either the entorhinal cortex or the CA3 to the CA1 region (Colgin et al., 2009).

Intracranial recordings in humans have also reported theta band activity from both neocortical and hippocampal regions. These recordings are performed using either electrocorticographic or depth electrodes (Kahana et al., 2001;Sederberg et al., 2003;Lega et al., 2012;Burke et al., 2013;Watrous et al., 2013). The intracranial theta band activity has mainly been related to working and long-term memory processing. Interestingly, the intracranial theta activity is also phase-locked to gamma power exactly as seen in the rat (Canolty et al., 2006;Canolty and Knight, 2010).

In human extracranial EEG and MEG recordings, the theta band activity is observed most strongly over the frontal midline (Mitchell et al., 2008). In particular, frontal midline theta activity has been reported to increase with memory load in both the N-back and the Sternberg tasks (Scheeringa et al., 2009) (Gevins and Smith, 2000;Jensen and Tesche, 2002).

Frontal midline theta activity has also been associated with error-processing. Several studies using go/no-goparadigms have reported an increase in frontal midline theta after a wrong motor response has been elicited. It remains unclear how the frontal midline theta relates to the error-related negativity, but there might be a tight relation (Luu et al., 2004;Mazaheri et al., 2009;van de Vijver et al., 2011). In general, the frontal midline theta is thought to reflect executive processes related to updating after a perceptual error (Cohen and van Gaal, 2013) .

It remains unknown to what extent the frontal midline theta activity, associated with working memory maintenance and error processing, relates to the theta activity reported in rats. Nevertheless, both the frontal midline and the hippocampal theta activity are thought to be associated with the temporal coordination of neuronal processing.

4.5 Beta oscillations

Beta oscillations are strongly associated with the motor system (Baker, 2007). They have been recorded both in animals and in humans. Typically beta oscillations decrease in power in anticipation of sensori-motor processing (van Ede et al., 2011). Thus one might think that beta oscillations are associated with suppression. Nevertheless, beta oscillations have also been associated with the exchange of information between motor cortex and the muscle (Kilner et al., 2000;van Elswijk et al., 2010). During isometric muscle contraction, strong coherence is observed in the beta band between the EMG and the motor cortical EEG or MEG signal (Baker, 2007). The motor cortical beta oscillations are not only synchronous with muscle activity but also with basal ganglia areas and the subthalamic nucleus (Hirschmann et al., 2011) (Litvak et al., 2011) (Jenkinson and Brown, 2011). Thus, while it is clear that cortical beta oscillations play an important role for coordinating the timing of spiking between neocortex and motor units, the precise functional role remains elusive. A recent paper proposed that the beta oscillations are involved in setting the *status quo*, i.e. maintaining the state of an extended network (Engel and Fries, 2010). This idea is consistent with the observation that restating state networks observed with MEG often are reflected by functional connectivity in the beta band (Hipp et al., 2012) (Brookes et al., 2011a).

Higher level cognitive studies in both humans and monkeys point to a role for beta oscillations in decision making. During critical decision periods and updating, beta increases have

been observed in prefrontal regions in both monkey and human recordings (Haegens et al., 2011a) (Spitzer et al., 2010). Along those lines, the motor cortical beta activity has been proposed to be involved in the accumulation of evidence when perceptual decisions, and motor responses on those decisions, have to be made (Donner et al., 2009). The findings on decision making and beta oscillations give a strong processing connotation to the beta band activity which somehow is in contrast to observed functions of the motor cortical beta activity. Future work is required to determine if activity in the beta band is associated with only one function, or whether beta oscillations in different regions are associated with different functions.

5. Future perspectives and conclusions

Hopefully it is clear from this chapter that oscillatory brain activity is observed in a wide range of species. Further, the brain oscillations seem to play an important role in coordinating neuronal processing. This coordination is achieved by a phasic modulation of neuronal firing. The degree of phasic modulation is determined by the magnitude of the oscillations. Further, from human studies, various kinds of cognitive tasks result in reliable modulation of oscillatory activity in different frequency bands. These observations make integration possible in which neuronal firing is related to behavior by considering temporal coordination organized by brain oscillations.

Future work is required to further uncover the functional role of brain oscillations. New technologies and the integration of techniques will facilitate these efforts. For instance, the application of optogenetics will allow for driving oscillatory activity in order to study their causal role (Tiesinga and Sejnowski, 2009). Likewise, entrainment can be applied in humans using TMS and transcranial alternating current stimulation (tACS) in association with cognitive paradigms (Thut et al., 2012). While oscillatory activity is particularly strong in sensory regions, it remains unclear which brain regions are involved in controlling the oscillations. While the fronto-striatal network is likely to play a strong role in the top-down control, the mechanisms by which this control is exercised is unclear. Several approaches can be applied to identify the frontal control network. For instance, EEG combined with fMRI can be applied to identify prefrontal and deep brain regions associated with the modulation of posterior regions. Recording MEG and the structural MRI in the same subjects makes it possible to associate oscillatory modulations with anatomy. Finally, pharmacological manipulations hold a strong promise for isolating the physiological mechanisms associated with top-down control of oscillatory activity. In particular, manipulating the cholinergic and dopaminergic system is of importance (Bauer et al., 2012) (Noudoost and Moore, 2011). In short, substantial insight has been gained on understanding the functional role of oscillatory brain activity; however, many questions remain open. Integration of evidence where human data are interpreted in the light of animal recordings and the combination of techniques hold a strong promise for making further advances.

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