Satu Palva *Editor*

Multimodal Oscillation-based Connectivity Theory

Springer

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ISBN 978-3-319-32263-6 ISBN 978-3-319-32265-0 (eBook)
DOI 10.1007/978-3-319-32265-0

Library of Congress Control Number: 2016942271

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG Switzerland

Preface

The system-level neuronal mechanisms that coordinate temporally, anatomically, and functionally distributed neuronal activity into coherent cognitive functions in the human brain have remained poorly understood. Synchronized neuronal activity coordinates and regulates neuronal processing in local neuronal circuits and could hence be a system-level biological mechanism governing the coordination of anatomically distributed processing in perception, action, and cognitive processes.

In humans, neuronal oscillations and synchronization can be recorded non-invasively with electro- and magnetoencephalography (EEG and MEG) that have excellent temporal and good spatial resolution when combined with source-reconstruction methods. Although EEG and MEG recordings have revealed that local oscillations characterize task-dependent neuronal activity and predict behavior, less is known of the role of large-scale neuronal synchronization in the coordination of neuronal processing in support of cognitive processes as the analysis of large-scale synchrony from noninvasive MEG recording has been slowed down by several technical challenges. Estimating the role of large-scale synchrony in cognitive processes has been hindered by several technical difficulties, and only in recent years has it been shown that large-scale inter-areal synchronization may have a critical role in cognitive processing. In this book, the leading authors in the field describe how recent technical advances have paved the way for several major breakthroughs in the analyses and observations of human noninvasive MEG data.

In the first chapter, the research of groups of J. Matias Palva and myself describes the technical challenges in the analyses of large-scale synchronization from MEG data and approaches to overcome them. In the fourth chapter, we then discuss empirical data using these novel approaches for MEG data analyses and what they reveal about the roles of local and large-scale synchronization in visual attention, working memory, and conscious perception.

The same theme is carried on in the second and third chapters, in which the dynamical network states and synchronization are discussed as predictors of conscious sensory perception by the groups of Nathan Weisz and Lawrence Ward. The chapter written by Peter Uhlhaas and Frederic Roux takes an additional view of the topic by discussing the observations of thalamo-cortical oscillations and synchronization in MEG data. A different theme is covered by Fernando Maestu and colleagues who discuss the role of oscillations and synchronization in neuroaesthetics.

As discussed in these chapters, neuronal oscillations and large-scale synchronization are hence crucial in normal cognitive functioning. However, in several neuropsychiatric diseases, development of the nervous system, including neuronal oscillations and synchronization, is abnormal and thought at least partially to explain the deficits in the cognitive functions. This aspect is discussed in the chapters "Development of Human Neurophysiological Activity and Network Dynamics" and "The Role of Functional Networks in Neuropsychiatric Disorders" by Sam Doesburg, Fernando Maestu, and Leonides Canuet together with their colleagues.

I would like to warmly thank all the authors for their contributions to this book. This book covers extensively the functional significance of neuronal oscillations and synchronization in healthy and diseased human brain.

I wish you a good and instructive time in reading this book.

Helsinki, Finland Satu Palva
March 2016

Contents

Measuring Large-Scale Synchronization with Human MEG and EEG: Challenges and Solutions

Felix Siebenhühner, Muriel Lobier, Sheng H. Wang, Satu Palva, and J. Matias Palva

1 Introduction

1.1 Measuring Neuronal Oscillations and Synchronization in Noninvasive Electrophysiological Recordings

During the past two decades, a number of seminal studies have shown that synchronous neuronal activity and neuronal oscillations can mechanistically support the coordination of neuronal processing across distributed neuronal assemblies (Fries 2015; Singer 1999, 2009).

Neuronal oscillations occur in a wide range of frequency bands (at least 0.01−200 Hz) associated with distinct cognitive functions (Buzsaki and Draguhn 2004) and can be characterized by their amplitude, phase, and frequency. Behaviorally relevant oscillations characterize all scales of the nervous system and can be measured at millisecond temporal resolution by electrophysiological recordings. Spatial resolutions range from macroscopic (1–3 cm) in magneto- and electroencephalography (MEG and EEG) over mesoscopic (1–10 mm), such as in human intracranial EEG (iEEG), to microscopic levels in extracellular field potentials and neuronal membrane potentials accessible with microelectrodes in animal models. The amplitude of neuronal oscillations in macro- and mesoscopic recordings is largely determined by the fraction of local neurons that receive coherent synaptic inputs or operate coherently as a synchronized assembly among less coherent neurons. Amplitude, hence, is primarily a measure of local synchronization. Phase, on the other hand, quantifies the temporal evolution of the oscillatory cycle (see Fig. 1b) and is essential for the assessment of the phase-locking of local oscillations to internal or external events. Importantly, it is also critical for

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S. Palva (ed.), *Multimodal Oscillation-based Connectivity Theory*,
DOI 10.1007/978-3-319-32265-0_1

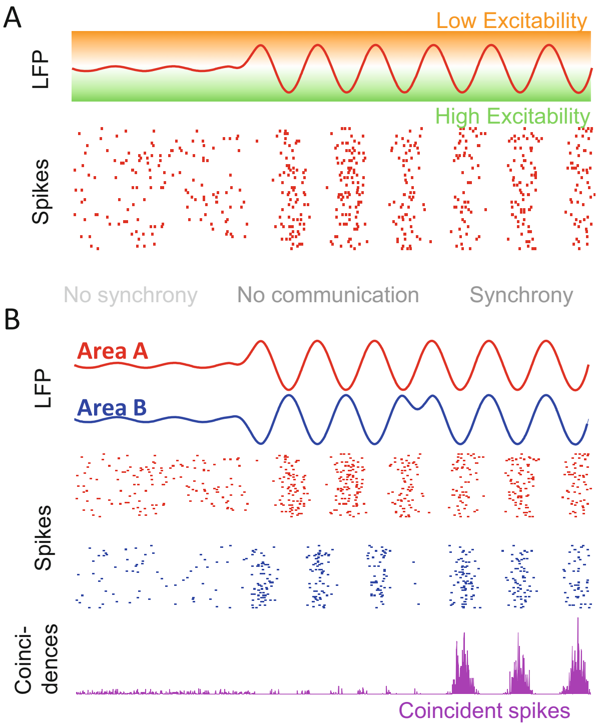

Fig. 1 Oscillations facilitate intra- and inter-areal synchronization. (**a**) Oscillations reflect local synchronization of neuronal spiking within a population. (**b**) Synchronization of two different neuronal populations at a specific phase difference enables communication. In this example, synchrony is enabled at zero phase difference, so neurons in both populations are spiking coincidentally and inhibited at 180° phase difference. Note that depending on the distance between the populations, synchronization can also occur at non-zero phase differences

determining whether signals from two regions have a consistent phase relationship (i.e., synchronized): a statistically nonrandom inter-areal phase relationship indicates phase synchronization.

1.2 Overview of the Confounds in the Estimation of Synchrony in Electrophysiological Recordings

While sensor-to-sensor analyses of MEG and EEG data have indicated that task demands for cognitive integration are associated with long range synchronization of neuronal oscillations (Palva and Palva 2012), these analyses not only suffer from confounds introduced by signal mixing and source amplitude modulations but also yield essentially no information about the anatomical structures generating the signals. In contrast, invasive recordings provide precise information on the anatomical location of the sources of neuronal oscillations and avoid confounds due to signal mixing. Their relevance to cortex-wide phase synchrony is, however, limited due to the sparse sampling of cortical locations that they offer. Despite methodological challenges that will be detailed below, MEG and EEG recordings can be used with source reconstruction methods to investigate the cortex-wide networks of phase synchrony (Palva et al. 2005, 2010, 2011; Palva and Palva 2012). Of these two, MEG offers a better spatial resolution as it is not confounded by the volume conduction and high resistivity of the skull, but combining MEG and EEG improves the detectability of some sources because MEG and EEG have distinct sensitivities (Sharon et al. 2007).

1.3 Problem Statement and Outline

In this chapter, we will first outline the data analysis "pipeline" for MEG and EEG from preprocessing to filtering and inverse modeling (Sect. 2). We will assess the basic interaction metrics that can be used to estimate pairwise interactions and their inherent advantages and disadvantages (Sect. 3). Section 4 will present the causes and consequences of linear mixing arising from volume conduction and signal mixing, the most profound challenge arising in MEG/EEG data analysis, and how sensitive different interaction metrics are to this problem. In Sect. 5, the advantages and challenges of all-to-all connectivity mapping will be discussed, and in Sect. 6, we will introduce methods of edge bundling to minimize the effects of signal mixing and improve the ratio of true to false positives.

2 The MEG/EEG Data Analysis Pipeline

2.1 Preprocessing of MEG/EEG Data

Identifying behaviorally relevant patterns of inter-areal correlations or synchronization in MEG/EEG data can be confounded by numerous sources of artifacts. We outline next the preprocessing steps that are essential for excluding extracranial signal sources and artifacts. MEG/EEG data are usually recorded while participants are carrying out a cognitive task of interest or, if applicable, are in a resting state. In a step often referred to as preprocessing, the sensor-space raw data are cleaned or de-noised using manual and/or automatic procedures. In the next step, the preprocessed sensor-space time series are filtered in order to estimate their oscillatory components in relatively narrow frequency bands. Using an appropriate source reconstruction technique, the time series of cortical sources are then estimated. These cortical time series are then used to compute the strength of inter-areal correlations or synchronization between each pair of cortical areas in time windows of interest. Finally, statistical thresholding procedures are used to identify which pairs of cortical areas are truly phase synchronized, yielding the spatial, spectral, and temporal characteristics of inter-areal phase synchronized networks.

The preprocessing of raw MEG/EEG sensor-space data involves both visual data inspection and several noise reduction techniques. Raw data are visually inspected to remove bad channels (sensors with excessive noise or reoccurring artifacts) and to mark bad data segments, such as time periods with increased environmental noise, head movement artifacts, or large-amplitude facial or neck muscle artifacts. MEG and EEG data are also contaminated by both environmental and participant noise that cannot be removed by simple manual inspection. Although MEG scanners are set up in shielded rooms designed to minimize noise and interference from other sources of magnetic fields, it is unavoidable that some extracranial environmental noise will be present in the raw signal. Using signal separation techniques such as temporal extension of signal space separation (tSSS) (Taulu et al. 2005), the presence of this type of noise in the data can be minimized. Also, participants themselves contribute continuous non-cortical noise to the MEG and EEG recordings, most often in the form of cardiac artifacts as well as eye blinks or movements. Using independent component analysis (ICA) (Bell and Sejnowski 1995), electro-oculography (EOG), and electrocardiography (ECG) measured concurrently with MEG/EEG, data components resulting from these interferences can be identified and removed.

2.1.1 Filtering for the Extraction of Narrowband Oscillations from Broadband Signals

Filtering is necessary to extract the oscillatory components of a signal for different frequency bands. Classical methods for converting a time-domain signal into the frequency domain, such as the Fourier transform, are, however, suboptimal here. These methods assume stationary signals, cannot detect temporal interactions (Li et al. 2007), and yield fixed bin-sized frequency scaling. In contrast, analyses of task modulations of neuronal oscillations require techniques that yield estimates of instantaneous amplitude and phase values of the signals, most often from a time–frequency transform of the original signal (Bruns 2004). Using such time-resolved spectral analysis, a time-dependent spectrum $s(t,f)$ can be computed from a time series of interest $s(t)$ where t is time and f is frequency. This time–frequency representation is complex-valued and consists, for each time point, of an instantaneous amplitude $A(t,f)$ and an instantaneous phase $\theta\,(t,f)$:

$$S(t,f) = A(t,f)e^{i\theta(t,f)}$$

Such complex valued time–frequency representations can be obtained using wavelet-based filtering. The time-domain signal $s(t)$ is convolved with a series or family of filter kernels, wavelets $w(t,f_0)$, that cover the frequency range of interest. For each center frequency f_0, the wavelet is defined as the product between a complex-valued oscillation at the frequency of interest and a bell-shaped, real-valued envelope: $w(t,\,f_0) = A\cdot\exp(-t^2/2\sigma_t{}^2\cdot 2)\cdot\exp(2i\pi f_0 t)$ where $\sigma_t = m/2\pi f_0$ is the frequency domain standard deviation. The convolution $S(t,f_0) = s(t) \times w(t,f_0)$ gives a complex vector $S(t,f_0)$, the angle of which is the phase of the signal s in a frequency band with a center frequency of f_0. The parameter m determines the effective number of oscillation cycles used to estimate signal amplitude and phase and therefore represents the compromise between time and frequency resolutions.

2.1.2 Source Reconstruction

While the magnetic fields generated by known sources can be estimated accurately from known current sources through forward modeling, estimation of the location and strengths of current sources in MEG/EEG data is an ill-posed inverse problem with no unique solutions. Nevertheless, inverse modeling can produce good estimates of those sources through the use of constraints such as minimization of total current and modeling of source dipoles on individual cortical surfaces obtained from MRI scans (Palva et al. 2010; Palva and Palva 2012).

Before solving the inverse problem, a forward model must be constructed that gives the distribution of currents and magnetic fields created by known sources in the head. For this, volume conduction models of the head are created assuming a spherical model or spherical harmonics (Mosher et al. 1999), which should be integrated with individual anatomical information obtained with MRI. For accurate modeling, co-registration of MEG/EEG and MRI should be as accurate as possible; subjects' head movements should be as small as possible (Whalen et al. 2008; Gross et al. 2013).

The two most common approaches to inverse modeling are the Beamformer method (Van Veen et al. 1997) and minimum norm estimates (MNE) (Hamalainen and Sarvas 1989; Lin et al. 2006).

MNEs yield time series of 6000–8000 sources, "vertices," covering the cortical surface. Considering that MEG/EEG recordings have only two to three hundreds of sensors and even fewer degrees of freedom, these sources are highly redundant. Thus, to decrease redundancy and improve signal-to-noise ratio (SNR), as well as to analyze MEG/EEG data in a form that is directly comparable with MRI studies, the MNE vertex time series can be collapsed into time series of a few hundreds of cortical areas. These "cortical parcels" can be obtained either by computing a weighted average of the vertex time series (Palva et al. 2010, 2011) or by using the time series of the vertex with maximum power (Hillebrand et al. 2012).

2.1.3 Parcellations

Anatomical parcellations, such as Desikan-Killiany and Destrieux, are derived from brain atlases of cortical gyral and sulcal structure revealed in MRI structural imaging (Dale et al. 1999; Fischl et al. 1999, 2002, 2004). As finer resolutions and/or more balanced parcel sizes are commonly needed, parcels from these atlases can be subdivided further (Cammoun et al. 2012; Hagmann et al. 2008; Palva et al. 2010, 2011). To accurately localize parcels on individual brains, structural scans can be recorded from all subjects with MRI. Software such as

FreeSurfer (http://surfer.nmr.mgh.harvard.edu) can then be used for volumetric segmentation, surface reconstruction, flattening, parcellation, and neuroanatomical labeling of individual brains.

2.1.4 Fidelity-Optimized Source Solution Collapse Operators

One approach to maximize the source reconstruction accuracy is to use sparse fidelity-optimized collapse operators for collapsing the source vertex time series into parcel time series. Simulations are used to select for each parcel the MNE reconstructed vertex time series that is thought to best represent the true parcel time series. Simulated time series for each parcel are forward- and inverse modeled to compute "fidelity," a measure of how accurately an MNE vertex time series represents the original time series. Only the vertices with the highest fidelity are used to compute a parcel's time series as fidelity-weighed average. The enhanced time series reconstruction has been shown to improve accuracy of subsequent analyses of both local dynamics and large-scale interaction mapping while decreasing computational load (Korhonen et al. 2014; Fig. 2).

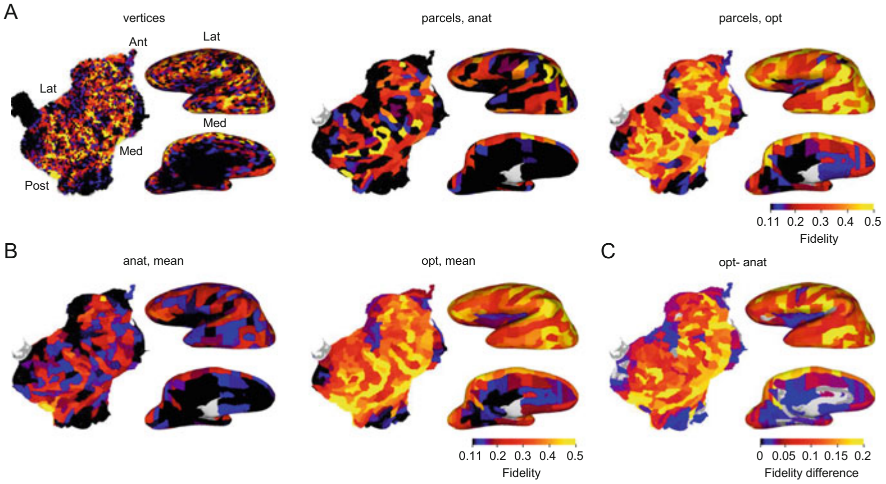

Fig. 2 The optimization of inverse collapse weighting operator increases the fidelity of all parcels, especially on the lateral surface. Adapted from Korhonen et al. (2014). (**a**) The vertex and parcel fidelities of inverse solutions collapsed with standard anatomical and fidelity-optimized weighting operators for one representative subject. Low fidelity ($f < 0.11$) parcels are colored black. (**b**) Grand-average parcel fidelity for anatomical and fidelity-optimized weighting operators. The color scale is similarly as in **a**, and the group level low-fidelity parcels are identified on the anatomical map (*bottom panel*). (**c**) Significant parcel fidelity differences between inverse solutions collapsed with the different operators (opt–anat; $p < 0.001$, uncorrected, paired t-test across 13 subjects, parcels without a significant change uncolored)

3 Interaction Metrics, Solutions to the Linear Mixing Problem, and Residual Challenges

To quantify the connections between signal pairs, various interaction metrics exist that can be estimated from either the amplitude or the phase of signals' time series.

3.1 Amplitude Correlations

The correlations between the amplitude envelopes can be assessed with the Pearson correlation coefficient (CC). CC will, however, yield inflated values in the presence of linear mixing. To estimate amplitude correlations in a manner insensitive to linear mixing, the narrowband time series are orthogonalized for each pair of cortical parcels or electrode contacts, using linear regression algorithm (Brookes et al. 2012), and the orthogonalized correlation coefficient (oCC) is computed for the amplitude envelopes of the orthogonalized time series:

$$\mathrm{CC} = \frac{1}{2}\left(\mathrm{corr}\left(A_X, A_{Y\left|_X\right.}\right) + \mathrm{corr}\left(A_{X\left|_Y\right.}, A_Y\right)\right) \tag{2}$$

where A_X, A_Y and $A_{X\left|_Y\right.}$, $A_{Y\left|_X\right.}$ are the amplitude envelopes of the original and orthogonalized time series, respectively.

The narrowband time series X and Y can be orthogonalized as follows:

$$Y_{\left|_X\right.} = Y - \beta X = Y - \left[\left(XX^T\right)^{-1} XX^T\right] X \tag{3}$$

and analogously for $X_{\left|_Y\right.}$.

3.2 Phase Locking and Phase Lag Index

Phase locking between two sources is statistically indicated by a nonrandom phase or phase-difference distribution. The most common index is the phase locking value (PLV) that is given by means of the complex phases θ_i (Lachaux et al. 1999; Sinkkonen et al. 1995).

$$\mathrm{PLV} = \frac{1}{N_t}\left|\sum e^{i(\theta_1-\theta_2)}\right|$$

where N_t is the number of samples pooled across trials and/or time and i is the imaginary unit.

PLV is 1 for perfect coupling (delta-function phase distribution) and approaches 0 for a uniform phase distribution when $N_t \to \infty$. If samples are independent and the marginal phase distributions are uniform, the no-interaction null hypothesis is characterized by a uniform distribution and the Rayleigh test can be applied. When samples are pooled across time, and are not independent, and/or when the underlying process is not sinusoidal (see Nikulin et al. 2007), statistical testing needs to be carried out with surrogate data. Further, the PLV is sample-size biased, and hence sample sizes always need to be equalized across conditions. It is also helpful to define the complex PLV:

$$\mathrm{cPLV} = \frac{1}{N_t}\left[\sum e^{i(\theta_1-\theta_2)}\right]$$

so that $\mathrm{PLV} = |\mathrm{cPLV}|$. While PLV is equally sensitive to coupling at all phase differences, it is also sensitive to inflation of the coupling estimates by linear mixing. The imaginary part of the cPLV is only sensitive to non-zero phase differences, and, thus, imaginary PLV ($\mathrm{iPLV} = |\mathrm{im}(\mathrm{cPLV})|$ can be used to estimate phase coupling in a manner insensitive to linear mixing.

An alternative approach to quantifying phase relationships relies on quantifying the asymmetry of the distribution of phase differences. For non-phase-coupled time series, the distribution of phase differences Φ would be flat, so any deviation from a flat distribution can be taken as evidence of phase synchronization. From this, the phase lag index (PLI) is derived: $\mathrm{PLI} = |\langle sign(\Phi)\rangle|$, where $\langle\ \rangle$ denotes the expectation value (Stam et al. 2007; Stam and van Straaten 2012).

4 Effects of Linear Mixing on Estimates of Phase and Amplitude Correlations

In MEG/EEG sensor space, interaction analyses can be confounded by signal mixing, source amplitude changes, and other issues (Gross et al. 2013; Palva and Palva 2012; Schoffelen and Gross 2009). Identification of the correct anatomical sources is crucial for appropriate interpretations of the results because even nearby cortical regions may play very different functional roles. In connectivity analysis, signal mixing gives rise to two confounders: artificial and spurious connections. Unfortunately, these terms have been used with various definitions in the literature. We will use here the definition from Palva et al. (Palva and Palva 2012): artificial connections are a direct result of the source-space signal spread caused by linear signal mixing.

The reconstructed signal in a given cortical parcel is contaminated by signals emanating from its neighboring parcels, giving rise to an increase in zero-lag phase differences, and thus zero-lag synchrony, in the absence of any true interactions. These are termed false positives of the first order. Spurious connections, or false positives of the second order, are "false" interactions created by the concurrent presence of a true interaction and linear mixing. Since the reconstructed time series of parcels close to the truly connected parcels are contaminated by signals that are truly phase synchronized, these parcels will appear to also be phase synchronized. In contrast to artificial connections, spurious connections are only present between parcels close to true interactions and neither limited to nearby parcels nor to zero-lag phase differences.

4.1 Influence of Linear Mixing on Interaction Metrics

In contrast to true neuronal interactions that often involve a conduction-delay-related phase lag, artificial connections are characterized by zero-lag phase differences. As a consequence, choosing a metric that is not sensitive to zero-lag phase differences such as iPLV or PLI for phase coupling or oCC for amplitude correlations will suppress the effects of artificial linear mixing. This is, however, achieved at the cost of missing also any true phase interactions whose lag is zero or $\pm\pi$. On the other hand, spurious interactions can have any phase lag and are therefore not generally discarded by such metrics.

In both amplitude- and phase-based analyses, measures have been developed that are insensitive to the direct effects of signal mixing (Brookes et al. 2012; Hipp et al. 2012). While the correlation coefficient (CC) reveals artificial connections caused by linear mixing, as can be seen for simulated data (Fig. 3a), orthogonalization of the real-valued signals $x(t)$ and $y(t)$ before the estimation of their amplitude envelopes and their correlation removes linear dependencies. This orthogonalized correlation coefficient (oCC) therefore does not yield artificial correlations between neighboring sensors arising directly from source spread (Fig. 3c), although it will still pick up long-range spurious connections. Further, it can been shown that the values of these measures are also sensitive to the value of phase difference when phase correlations are present (Fig. 3b, d).

Similar to the CC, the PLV is sensitive to artificial connections (Fig. 3e) and biased by phase differences when signal mixing is strong (Fig. 3f).

Metrics which ignore the real part of the complex phase differences, such as the iPLV (the imaginary part of complex PLV) and the weighted phase lag index [wPLI, (Vinck et al. 2011)], are therefore insensitive to direct effects of linear mixing while revealing phase-lagged interactions (Fig. 3g, i). However, not only are these insensitive to true interactions at 0 or $\pm\pi$ phase lag but also their value is dependent on the phase difference per se in addition to the strength of the interaction (Fig. 3h, j).

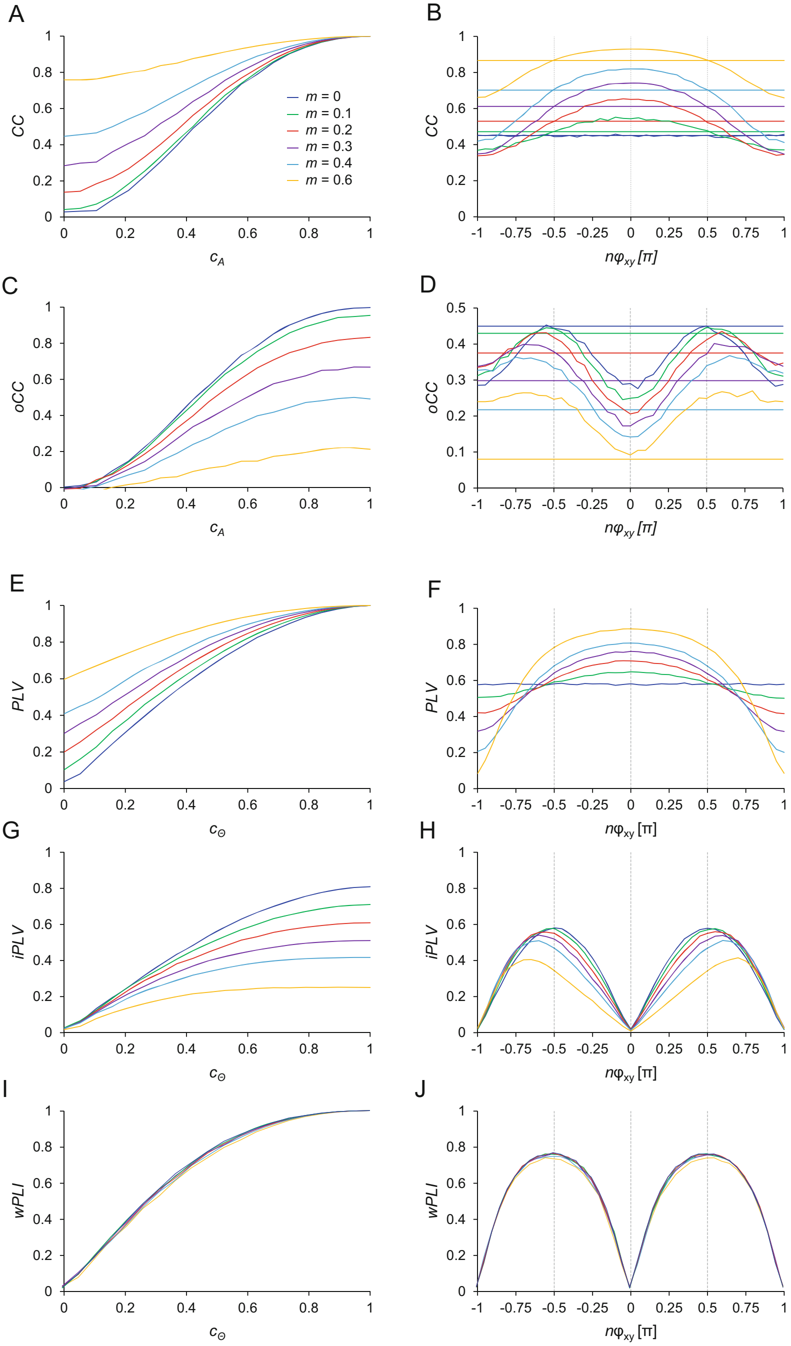

Fig. 3 Interaction metrics are affected by coupling strength, phase difference, and linear mixing. (**a**) Correlation coefficient (CC) as a function of amplitude coupling strength c_A in the absence of phase correlations (phase coupling $c_\Theta = 0$, phase difference $n\phi_{xy} = 0$). CC increases with linear mixing m, leading to false positives. (**b**) CC between the signals as a function of phase difference $n\phi_{xy}$, for $c_\Theta = 0.4$. The horizontal lines visualize the mean CC obtained at $c_\Theta = 0$. In the presence

Ultimately, all interaction measures are sensitive to linear mixing effects, albeit in different manners. While iPLV, wPLI, and oCC do not report artificial connections, they are still sensitive to spurious connections and to the value of phase differences. Therefore, one should not expect optimal results solely from choosing a good interaction measure.

4.2 Interaction of Phase and Amplitude Dynamics

It has been shown that in the analysis of pairwise interactions between signals containing noise, amplitude and phase dynamics influence each other (Daffertshofer and van Wijk 2011; Schoffelen and Gross 2009). In real signals, noise levels change over time, resulting in a fluctuating signal-to-noise ratio (SNR). Not only does this imply that lower noise levels will result in higher measured phase synchrony but also that synchrony estimates will increase when the SNR of the sources is correlated. There can even be cases in which a decrease in true connectivity coinciding with an increase in SNR leads to an increase in measured connectivity (Schoffelen and Gross 2009). Further, as mentioned in the last paragraph, simulations show that as a result of signal mixing, phase coupling also influences amplitude correlations.

When phase differences are small, signal mixing increases amplitude correlations measured with the correlation coefficient CC, whereas when signals are close to anti-phase, signal mixing reduces CC. The orthogonalized correlation coefficient oCC may be further biased by phase effects because the orthogonalization process uses the real part of the signals, which contains both amplitude and phase information.

Spontaneous and stimulus-induced changes in the amplitudes of ongoing activity influence (1) the signal-to-noise ratio of signals from a given source in relation to environmental and sensor noise and (2) the balance in the mixing of signals from multiple concurrent sources. Both effects influence the accuracy of phase (and amplitude) computations and therefore bias interaction estimates.

◀

Fig. 3 (continued) of phase coupling, CC is biased by $n\phi_{xy}$. (**c**) oCC as a function of amplitude coupling strength c_A in the absence of phase correlations ($c_\Theta = 0$, $n\phi_{xy} = 0$). oCC decreases with linear mixing and does not report false positives. (**d**) oCC as a function of $n\phi_{xy}$, for $c_\Theta = 0.4$. Like CC, oCC is biased by $n\phi_{xy}$, but in a different manner. (**e**) PLV as a function of phase coupling strength c_Θ for different linear mixing strengths m. PLV increases with mixing, especially at low or zero coupling, leading to false positives. Here, $n\phi_{xy} = -0.3$. (**f**) PLV as a function of normalized phase difference $n\phi_{xy}$ for different strengths m of linear mixing and for $c_\Theta = 0.4$. PLV is greatly affected by the phase difference when signal mixing is strong. (**g**) iPLV as a function of c_Θ for $n\phi_{xy} = -0.3$. iPLV decreases with linear mixing and does not report false positives. (**h**) iPLV as a function of $n\phi_{xy}$ for $c_\Theta = 0.4$. The strength of iPLV depends highly on phase difference and is biased towards large phase differences; iPLV is 0 for integer values of $n\phi_{xy}$. (**i**) wPLI as a function of c_Θ for $n\phi_{xy} = -0.3$. *wPLI* is unaffected by linear mixing and does not report false positives. (**j**) wPLI as a function of $n\phi_{xy}$ for $c_\Theta = 0.4$. Like iPLV, wPLI depends highly on phase difference

5 All-to-All Connectivity Mapping

Connectivity studies have traditionally focused on analyzing a limited set of interactions between selected regions of interest (ROIs). While this approach has the advantage of limiting computational complexity, it is not without drawbacks. First, relevant interactions between ROIs not included in the analysis will be missed, giving the initial ROI choice a decisive role in the final results. Furthermore, using the same data for ROI selection and connectivity analyses leads to circular analyses and in turn to invalid statistical inference (Ioannidis 2005; Kriegeskorte et al. 2009). In contrast, all-to-all connectivity mapping explores interactions between all possible pairs of cortical parcels. By avoiding selection bias, it ensures that the strongest interactions will be identified regardless of their anatomical location, although it leads to increased computational costs and multiple comparisons, which should be corrected for.

5.1 Statistical Analysis and Thresholding

In all-to-all connectivity matrices, every interaction will have a non-zero value. For network analysis, it is however preferable to have a sparse matrix with only the most relevant connections. One simple way to obtain such a sparse matrix is to discard all connections with values under a chosen threshold. However, it is preferable to estimate the task-related significance of connections and keep only those passing a particular statistical test, for example indexing significant increases in synchrony compared to a chosen baseline. Afterwards, a threshold (or several, see next paragraph) can still be applied to the resulting connectivity matrix to further reduce the number of connections.

5.2 Graph Theory and Networks

Graph theory can be used to characterize synchrony networks, quantifying properties of vertices (parcels), edges (interactions), and whole graphs. Brain connectivity graphs have high clustering, short average path lengths, dense intramodular connectivity, and sparse intermodular connections (Bullmore and Sporns 2009) that are the hallmarks of small-world networks (Watts 2004) These small-world networks are associated with high local and global efficiency in information transmission as well as facilitated parallel processing within hierarchically organized modules (Bullmore and Sporns 2009). Not only can graph properties be modulated by task demands and differ between frequency bands but they also can be significantly different between pathological vs. healthy participants, for example, in schizophrenia (Bassett et al. 2008, 2011; Micheloyannis et al. 2006; Siebenhühner et al. 2013).

Graph metrics are, however, biased by connection density, which is artificially increased by spurious connections (Antiqueira et al. 2010; van Wijk Bernadette et al. 2010). An approach to account for this could be to analyze graph metrics at different density levels which can be obtained by thresholding edges at a range of values of the interaction metric (Bassett et al. 2011; Siebenhühner et al. 2013). This is less problematic for vertex centrality measures such as degree and betweenness centrality that can be used to identify hubs that are highly connected and/or important "relay stations" for information transfer. Modularity analyses may be used to identify subsystems or modules of vertices that are densely connected among each other and work together to fulfill particular cognitive functions.

5.3 Alternatives to All-to-All Connectivity Mapping

An alternative to inverse modeling of the data and then computing pairwise interactions between all reconstructed sources is to use a multivariate (MVAR) approach. Here, an independent component analysis is performed on the sensor-space signals, and an MVAR model is fitted to the components. The residuals of the fitted MVAR model contain true interactions between brain regions and are largely unaffected by signal mixing (Brookes et al. 2012).

6 Using Edge Bundling to Identify True Interactions in the Presence of Signal Mixing

As detailed above, regardless of source reconstruction approach or chosen interaction metric, signal mixing in M/EEG data results in the detection of synchronization between cortical areas that are not truly connected. In this section, we will illustrate how these false positives arise and how edge bundling methods can be used to detect the underlying true interactions. As mentioned in earlier text, artificial interactions are first order, zero-phase lag, false positives directly caused by volume conduction and linear mixing (Drakesmith et al. 2013; Palva and Palva 2012). When an interaction metric sensitive to zero-phase lag interactions, such as PLV, is used to estimate pairwise interactions, the resulting all-to-all connectivity graphs will contain artificial interactions as edges connecting neighboring sources in areas where mixing is significant (Fig. 4a). Interaction metrics insensitive to zero-phase lag interactions, such as iPLV, will not report these (Fig. 4b), albeit at the cost of also discarding any true zero-phase lag and anti-phase interactions.

Spurious interactions are second-order false positives indirectly caused by linear mixing. Spurious interactions arise from the signal spread of truly connected sources to their neighboring sources, which in turn leads to false positive observations of synchronization between such neighbors, or between these neighbors and one of the truly connected sources (Fig. 4a and b). Because two true interacting

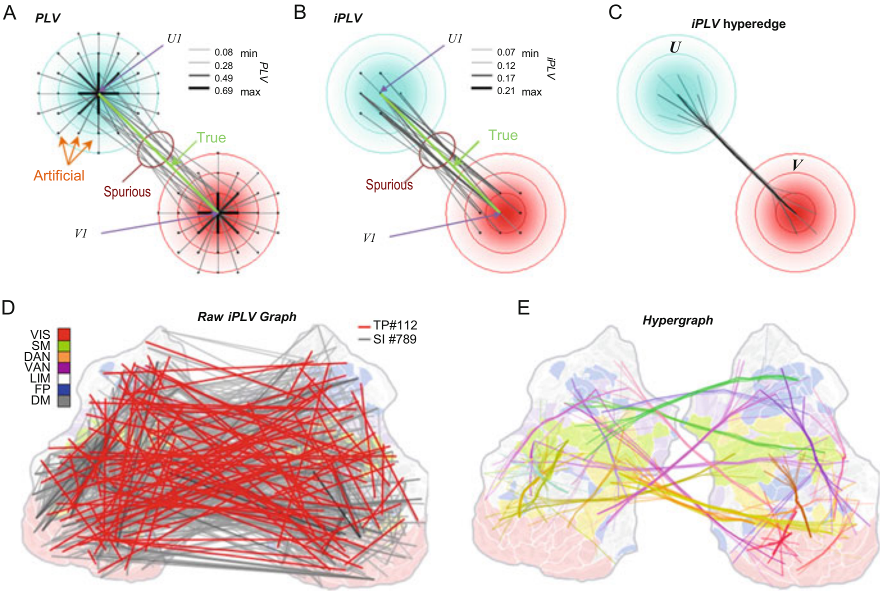

Fig. 4 Using iPLV and edge bundling to detect true positives among artificial and spurious connections. On a grid toy model, one true interaction (coupling = 0.9) was simulated between two sources U_1 and V_1 (the centers of the concentric circles), while the rest of sources were uncorrelated. Linear mixing, i.e., magnetic field spread from true sources, was simulated as a 2D Gaussian function and its strength is indicated by color gradient. (**a**) Phase interaction between all source pairs was estimated with the phase locking value (PLV). Both artificial and spurious connections are reported by PLV. Signal mixing directly causes zero-phase lag artificial connections between a true source and its neighbors. Additionally, it indirectly causes non-zero-phase lag spurious connections between true sources and another source's neighbors or between neighbors of the true sources. (**b**) Using iPLV, the imaginary part of complex PLV, artificial connections are not reported because iPLV is insensitive to zero-phase lag interactions. However, spurious connections, which can have non-zero phase lag, are still observed. (**c**) Hyperedge bundling: an edge representing a true interaction and the edges representing its neighboring spurious connections can be bundled into a hyperedge connecting regions U and V. (**d**) On a realistic cortical system, 200 edges connecting randomly chosen nodes were simulated and estimated with iPLV (the ground truth graph has uniform degree distribution $K = 1$). Significant edges were overlaid on a flattened cortical map. The resulting graph contains 901 significant edges, of which 112 are true positives (*red*), and has average path length = 4.5 and efficiency = 0.22. The color code of the regions indicates cortical subsystems identified with fMRI-based FC network analysis (Yeo et al. 2011). (**e**) The graph in **d** is transformed into a hypergraph where raw edges were all bundled into hyperedges, and only hyperedges that contain at least five raw edges are shown

neuronal processes can have non-zero-phase lag, the same is true for spurious interactions.

Simulations using zero-phase lag insensitive interaction metrics show that a single simulated true interaction can be mirrored into 10–100 of spurious interactions in source-reconstructed cortical networks. Such a large number of false positives severely confound the neurophysiological interpretability of the graphs and distorts any network metrics based on the topology of the connectivity network.

We have examined an approach to minimize the impact of spurious interactions using graph and hypergraph theoretical tools. First, we denote a cortical connectivity network as a "raw" graph wherein brain regions or parcels are nodes and significant interactions are raw edges (Newman 2003; Rubinov and Sporns 2010). We argue that by transforming a "raw" graph into a hypergraph, in which the mixing effect is estimated and raw edges are bundled into hyperedges, it is possible to identify true interactions with high reliability. In such a hypergraph, a true cortical interaction between parcels U_1 and V_1 and the spurious interactions involving neighboring parcels to U_1 and V_1 would be represented as a hyperedge between regions U and V (Fig. 4c). These regions U and V would be centered on U_1 and V_1, respectively.

This hyperedge bundling solution provides a much improved estimate of the true underlying neuronal connectivity graph as well as an enhanced visualization that represents the extent of field spread of the sources. The implementation of hyperedge bundling requires: (1) a linear mixing function $f_{\mathrm{mix}}(u_i,v_j)$ that quantifies the amount of signal mixing between all pairs of brain region and (2) a sparse pairwise interaction matrix as raw graph G_{raw} with n edges resulting from statistical analysis and/or thresholding. The linear mixing function can be obtained through a similar process as described in Sect. 3 for fidelity estimation, in which simulated time series are forward and inverse modeled.

In the bundling procedure, first, an edge-to-edge adjacency matrix EA_{ij} is constructed using $f_{\mathrm{mix}}(u_i,v_j)$ and G_{raw}. EA_{ij} is an $n \times n$ matrix that describes the adjacency between all edge pairs in signal mixing, i.e., the closer two edges are in mixing, the more likely they are to reflect the same underlying true interaction(s). Next, a hierarchical clustering algorithm is applied to EA_{ij} so that the resulting raw edge clusters become hyperedges, in which all raw edges are close to each other in signal mixing but far away from the raw edges assigned to other hyperedges.

Further, one can remove small hyperedges whose number of constituent raw edges is below a threshold. These hyperedges are more likely to represent false positives, although a small fraction of true positives may also be lost in the process. This can be seen in simulated data, where this approach can convert a raw graph of 900 edges, of which the vast majority are false positives, into a hypergraph of a few dozen hyperedges (Fig. 4d, e). Hyperedge bundling hence appears to be a promising solution to the problem of spurious edges and can theoretically be applied to graphs obtained with any interaction metric and source reconstruction method.

References

Antiqueira L, Rodrigues FA, van Wijk BCM, Costa LF, Daffertshofer A (2010) Estimating complex cortical networks via surface recordings—a critical note. Neuroimage 53:439–449

Bassett DS, Bullmore E, Verchinski BA, Mattay VS, Weinberger DR, Meyer-Lindenberg A (2008) Hierarchical organization of human cortical networks in health and schizophrenia. J Neurosci 28:9239–9248

Bassett DS, Nelson BG, Mueller BA, Camchong J, Lim KO (2011) Altered resting state complexity in schizophrenia. Neuroimage 59:2196–2207

Bell AJ, Sejnowski TJ (1995) An information-maximization approach to blind separation and blind deconvolution. Neural Comput 7:1129–1159

Brookes MJ, Woolrich MW, Barnes GR (2012) Measuring functional connectivity in MEG: a multivariate approach insensitive to linear source leakage. Neuroimage 63:910–920

Bruns A (2004) Fourier-, hilbert- and wavelet-based signal analysis: are they really different approaches? J Neurosci Methods 137:321–332

Bullmore E, Sporns O (2009) Complex brain networks: graph theoretical analysis of structural and functional systems. Nat Rev Neurosci 10:186–198

Buzsaki G, Draguhn A (2004) Neuronal oscillations in cortical networks. Science 304:1926–1929

Cammoun L, Gigandet X, Meskaldji D, Thiran JP, Sporns O, Do KQ, Maeder P, Meuli R, Hagmann P (2012) Mapping the human connectome at multiple scales with diffusion spectrum MRI. J Neurosci Methods 203:386–397

Daffertshofer A, van Wijk BCM (2011) On the influence of amplitude on the connectivity between phases. Front Neuroinform 5:6

Dale AM, Fischl B, Sereno MI (1999) Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage 9:179–194

Drakesmith M, El-Deredy W, Welbourne S (2013) Reconstructing coherent networks from electroencephalography and magnetoencephalography with reduced contamination from volume conduction or magnetic field spread. PLoS One 8, e81553

Fischl B, Sereno MI, Dale AM (1999) Cortical surface-based analysis. II: inflation, flattening, and a surface-based coordinate system. Neuroimage 9:195–207

Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, van der Kouwe A, Killiany R, Kennedy D, Klaveness S, Montillo A, Makris N, Rosen B, Dale AM (2002) Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron 33:341–355

Fischl B, van der Kouwe A, Destrieux C, Halgren E, Segonne F, Salat DH, Busa E, Seidman LJ, Goldstein J, Kennedy D, Caviness V, Makris N, Rosen B, Dale AM (2004) Automatically parcellating the human cerebral cortex. Cereb Cortex 14:11–22

Fries P (2015) Rhythms for cognition: communication through coherence. Neuron 88:220–235

Gross J, Baillet S, Barnes GR, Henson RN, Hillebrand A, Jensen O, Jerbi K, Litvak V, Maess B, Oostenveld R, Parkkonen L, Taylor JR, van Wassenhove V, Wibral M, Schoffelen JM (2013) Good practice for conducting and reporting MEG research. Neuroimage 65:349–363

Hagmann P, Cammoun L, Gigandet X, Meuli R, Honey CJ, Wedeen VJ, Sporns O (2008) Mapping the structural core of human cerebral cortex. PLoS Biol 6, e159

Hamalainen MS, Sarvas J (1989) Realistic conductivity geometry model of the human head for interpretation of neuromagnetic data. IEEE Trans Biomed Eng 36:165–171

Hillebrand A, Barnes GR, Bosboom JL, Berendse HW, Stam CJ (2012) Frequency-dependent functional connectivity within resting-state networks: an atlas-based MEG beamformer solution. Neuroimage 59:3909–3921

Hipp JF, Hawellek DJ, Corbetta M, Siegel M, Engel AK (2012) Large-scale cortical correlation structure of spontaneous oscillatory activity. Nat Neurosci 15(6):884–890

Ioannidis JP (2005) Why most published research findings are false. PLoS Med 2, e124

Korhonen O, Palva S, Palva JM (2014) Sparse weightings for collapsing inverse solutions to cortical parcellations optimize M/EEG source reconstruction accuracy. J Neurosci Methods 226C:147–160

Kriegeskorte N, Simmons WK, Bellgowan PS, Baker CI (2009) Circular analysis in systems neuroscience: the dangers of double dipping. Nat Neurosci 12:535–540

Lachaux JP, Rodriguez E, Martinerie J, Varela FJ (1999) Measuring phase synchrony in brain signals. Hum Brain Mapp 8:194–208

Li X, Yao X, Fox J, Jefferys JG (2007) Interaction dynamics of neuronal oscillations analysed using wavelet transforms. J Neurosci Methods 160:178–185

Lin FH, Witzel T, Ahlfors SP, Stufflebeam SM, Belliveau JW, Hamalainen MS (2006) Assessing and improving the spatial accuracy in MEG source localization by depth-weighted minimum-norm estimates. Neuroimage 31:160–171

Micheloyannis S, Pachou E, Stam CJ, Breakspear M, Bitsios P, Vourkas M, Erimaki S, Zervakis M (2006) Small-world networks and disturbed functional connectivity in schizophrenia. Schizophr Res 87:60–66

Mosher JC, Leahy RM, Lewis PS (1999) EEG and MEG: forward solutions for inverse methods. IEEE Trans Biomed Eng 46:245–259

Newman M (2003) The structure and function of complex networks. SIAM Rev 45:167–256

Nikulin VV, Linkenkaer-Hansen K, Nolte G, Lemm S, Muller KR, Ilmoniemi RJ, Curio G (2007) A novel mechanism for evoked responses in the human brain. Eur J Neurosci 25:3146–3154

Palva JM, Palva S, Kaila K (2005) Phase synchrony among neuronal oscillations in the human cortex. J Neurosci 25:3962–3972

Palva S, Palva JM (2012) Discovering oscillatory interaction networks with M/EEG: challenges and breakthroughs. Trends Cogn Sci 16:219–230

Palva JM, Monto S, Kulashekhar S, Palva S (2010) Neuronal synchrony reveals working memory networks and predicts individual memory capacity. Proc Natl Acad Sci USA 107:7580–7585

Palva S, Kulashekhar S, Hamalainen M, Palva JM (2011) Localization of cortical phase and amplitude dynamics during visual working memory encoding and retention. J Neurosci 31: 5013–5025

Rubinov M, Sporns O (2010) Complex network measures of brain connectivity: uses and interpretations. Neuroimage 52:1059–1069

Schoffelen JM, Gross J (2009) Source connectivity analysis with MEG and EEG. Hum Brain Mapp 30:1857–1865

Sharon D, Hamalainen MS, Tootell RB, Halgren E, Belliveau JW (2007) The advantage of combining MEG and EEG: comparison to fMRI in focally stimulated visual cortex. Neuroimage 36:1225–1235

Siebenhühner F, Weiss SA, Coppola R, Weinberger DR, Bassett DS (2013) Intra- and inter-frequency brain network structure in health and schizophrenia. PLoS One 8, e72351

Singer W (1999) Neuronal synchrony: a versatile code for the definition of relations? Neuron 24(49–65):111–125

Singer W (2009) Distributed processing and temporal codes in neuronal networks. Cogn Neurodyn 3:189–196

Sinkkonen J, Tiitinen H, Naatanen R (1995) Gabor filters: an informative way for analysing event-related brain activity. J Neurosci Methods 56:99–104

Stam CJ, van Straaten ECW (2012) Go with the flow: use of a directed phase lag index (dPLI) to characterize patterns of phase relations in a large-scale model of brain dynamics. Neuroimage 62:1415–1428

Stam CJ, Nolte G, Daffertshofer A (2007) Phase lag index: assessment of functional connectivity from multi channel EEG and MEG with diminished bias from common sources. Hum Brain Mapp 28:1178–1193

Taulu S, Simola J, Kajola M (2005) Applications of the signal space separation method. IEEE Trans Signal Process 53:3359–3372

Van Veen BD, van Drongelen W, Yuchtman M, Suzuki A (1997) Localization of brain electrical activity via linearly constrained minimum variance spatial filtering. IEEE Trans Biomed Eng 44:867–880

van Wijk Bernadette CM, Stam CJ, Daffertshofer A (2010) Comparing brain networks of different size and connectivity density using graph theory. PLoS One 5, e13701

Vinck M, Oostenveld R, van Wingerden M, Battaglia F, Pennartz CM (2011) An improved index of phase-synchronization for electrophysiological data in the presence of volume-conduction, noise and sample-size bias. Neuroimage 55:1548–1565

Yeo BT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, Roffman JL, Smoller JW, Zollei L, Polimeni JR, Fischl B, Liu H, Buckner RL (2011) The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J Neurophysiol 106: 1125–1165

Watts DJ (2004) Small worlds. Princeton University Press, Princeton, NJ

Whalen C, Maclin EL, Fabiani M, Gratton G (2008) Validation of a method for coregistering scalp recording locations with 3D structural MR images. Hum Brain Mapp 29:1288–1301

Dynamical Network States as Predisposition of Perception

Nicholas A. Peatfield, Dawoon Choi, and Nathan Weisz

1 Introduction

One example of an area where the concepts of multimodal oscillation-based connectivity theory can be applied to is consciousness research. Within this chapter, we will outline a specific question that regards the broad framework of the neural correlates of consciousness (NCC; Crick and Koch 2003). Here, NCC does not refer to the phenomenological state of consciousness, but the measures/states that correlate with the particulars of consciousness (e.g., seen vs. unseen). This chapter will not go into depth about the philosophical debates that are ongoing in consciousness research, instead, it will focus initially on two main theories of consciousness, and then outline the "Windows to Consciousness" [Win2Con; (Weisz et al. 2014)] framework. It is within this experimental framework where we present our evidence that consciousness and NCC encompass connectivity dynamics. Specifically, the theory assigns the connectivity pattern of the brain before the event to be a critical determinant of the conscious experience of that event. The experimental evidence presented will primarily focus on the working term of "conscious access" which is the state in which participants report the observation of the stimulus (i.e., seen vs. unseen). Towards the conclusion, we will provide some evidence of how preestablished connectivity patterns prior to stimulus onset also matters for the "conscious content" (e.g., seen house vs. seen face).

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S. Palva (ed.), *Multimodal Oscillation-based Connectivity Theory*,
DOI 10.1007/978-3-319-32265-0_2

The question of NCC has been approached by some of the world's best scientists, and although much progress has been made, there remain some nuances that need to be addressed. One of the shortcomings of NCC studies is the limited epochs of analysis investigated in addressing the question of consciousness. With the classic approach being tied heavily to the event-related averaging in neurophysiology, we now have a strong grasp of the correlations between consciousness and poststimulus effects. Within, we will give a short introduction to the current understanding of the poststimulus NCC, in particular, focusing on the global workspace (GW) theory of consciousness (Baars 2002) and later present an outline of the "gating-by-inhibition" prestimulus effects (Mazaheri and Jensen 2008).

Due to the measurement limitations within fMRI, the research on the timing of the conscious experience is sparser when measured using fMRI. To provide a scope of temporally finer aspects of consciousness research, this chapter will focus mainly on the electro- and magnetoencephalography measures of consciousness and make inferences about the sources based on our knowledge gleamed from fMRI.

2 Stimulus-Evoked Activity and Local–Global Connectivity

Using masking paradigms, for example, the attentional-blink task, researchers have examined the differences in evoked responses between visible and invisible stimuli—a measure of conscious access. A seminal piece by Sergent and colleagues (2005) recorded EEG during the attentional-blink task and contrasted the activation to an identical stimulus that was either seen or unseen in the task. The critical finding here was that during the early components (P1:96 ms and N1:180 ms), there was no difference in the response or the topography (both residing primarily in occipital cortices) for the contrast of seen vs. unseen, whereas in the later components (N2:275 ms; P3a:436 ms; and P3b:576 ms), there was a marked difference in both the level of response and the topography, with the seen stimulus showing amplified activity in the parietal/temporal/frontal topographies. This finding was used as an evidence towards one of the prominent models of consciousness that Dehaene and Changeux (2011) put forward. One of the main components of the model proposed by Dehaene and Changeux (2011) is the notion that for conscious experience to be manifested there needs to be a "global workspace" (GW) activation, that is, a top-down recurrent, reentrant, or resonant connectivity state that drives the state of the brain to a coherent form of subjective consciousness (Dehaene et al. 2003). The model predicts [a progressive model derived from Baars (1988) GW model] a variety of neural states: sustained activity in the primary sensory areas (V1, A1, S1); an amplification of perceptual processing; correlations across distant regions; joint parietal, frontal, and cingulate activation; the P300 waveform; and gamma-band oscillations. Furthermore, in concurrence with the bottom-up activation and top-down processes, an "ignition" of brain-wide neural assembly induces a state of coherent activity involving many neurons distributed. The relation between the ignited states to the conscious states lies in the core idea behind the GW that the heavily interconnected brain state allows the active coherent brain state to distribute its contents to a number of other brain processes, allowing for information to be globally available. Such global availability of information is the subjective experience of a conscious state. Major areas including the prefrontal cortex, anterior cingulate, and related areas are postulated to form the global workspace (Dehaene et al. 2006; Baars 2002).

Evidence for this model is shown in a variety of experimental paradigms, such as the backward masking (Dehaene et al. 2001) and attentional blink (Dehaene et al. 2003) in the visual domain. Furthermore, evidence has been shown also in nonhuman primates. Using a figure-ground display, Supèr et al. (2001) demonstrated that during trials where the figure was present but unseen, there was a modulation difference in macaque V1 late in processing (>100 ms) suggesting once again that the reentrant processes drove perception and, thus, conscious access within macaque monkeys. These findings were further corroborated with MEG using frequency domain analysis in the beta band power (Gross et al. 2004) where the contrast showed increased power predominately in the frontal and parietal cortices during conscious perception as well as increased beta phase synchrony.

3 Prestimulus Effects and Phase

There is a vast array of evidence that suggest that different neural oscillatory dynamics is present before stimulus onset, which subsequently influence the perception of the upcoming stimulus. In particular, the effects within the alpha range (8–12 Hz) and the low-beta range (12–20 Hz) have been correlated with conscious access. Increased low-frequency oscillatory activity is associated with the inhibition of the respective brain region resulting in decreased stimulus processing (Haegens et al. 2011; Jensen and Mazaheri 2010; Keil et al. 2014). Although the inhibitory role of the alpha rhythm in the visual domain has been consistently shown in the classical alpha range (8–12 Hz), the frequency range can differ from the classical alpha band in other sensory modalities (Bernasconi et al. 2011; Chen et al. 2008; Hari and Salmelin 1997; Keil et al. 2014; Siegel et al. 2008).

The low-oscillatory inhibitory effect has been formalized in a variety of working theories. Take, for example, the alpha gating-by-inhibition theory (Jensen and Mazaheri 2010), which postulates that effective brain states are driven not by coupling but by the strong and ubiquitous alpha oscillatory inhibition. This inhibition blocks irrelevant pathways in the network, which conversely guides the network into a preferential state. Inhibitory effects of alpha power can also be seen within the conscious access domain. In a study by Van Dijk et al. (2008), the authors contrasted "hit" vs. "miss" MEG responses and indeed showed that prestimulus alpha power correlated with the subjective report of a visual task. Specifically, the heightened inhibitory alpha was correlated prior to the miss condition in the early visual and parietal areas, and this heightened alpha activity reduced the likelihood of stimulus perception. This task was very robust as it showed a lateralized effect, which clearly demonstrates a local (in this case, the visual areas) blocking of the network state.

Prestimulus alpha also alters as a function of visual excitability as shown by a single pulse transcranial magnetic stimulation (TMS) to the occipital region during EEG recording (Romei et al. 2008). The authors examined how prestimulus period predicted the report of the phosphenes as evoked by TMS. Following from other studies, they replicated that a low power prestimulus low oscillation (alpha band) determined perception. Specifically, the same intensity TMS pulse evoked a "yes" report vs. a "no"' report depending on whether there was lower alpha activity in the visual cortex at the time of the stimulation, or not.

Not only the power but also the phase of the low-frequency ongoing oscillations has been shown to influence the perceptual fate during the upcoming task. Cyclic variation of phase occurs at a much faster timescale than changes in power. Further, phase could represent a variability in excitability independent of overall power. Thus, studying phase effects in conjunction to power is advantageous over studying power effects alone. The literature shows evidence for both entrainments of phase to stimulus (Lakatos et al. 2008) and stimulus perception correlated to optimal phases (Busch et al. 2009). One EEG study in humans demonstrated that the phase ~7 Hz oscillation just prior to stimulus onset are aligned differently between conditions in which subjects report the target to be seen and unseen, thereby suggesting that the phase of ongoing alpha oscillation influences perception (Busch et al. 2009).

A number of studies reported prestimulus low-oscillatory effects to occur in the primary sensory domain, for instance, tasks using illusory percept (Romei et al. 2008) and NT stimuli (Van Dijk et al. 2008) report alpha phasic effects in the early visual area. Yet, others report a fronto-central effect of alpha phase (Busch et al. 2009). For the case of conscious access, the theory goes as follows: low-frequency oscillation is a signature of inhibition that reflects a dampening of local excitation within a given area. In other words, the presence of high alpha dampens the subjective experience of the upcoming stimulus, thus increasing the likelihood that this stimulus will not be perceived.

3.1 Converging the Windows to Consciousness

These two previous sections have presented opposing predictions of conscious access. Although the alpha inhibition hypothesis has been predominantly postulated in the attentional theories, it also must be taken within the context of conscious access (although consciousness and attention most likely rely on discrete neural mechanisms; Dehaene et al. 2001; Supèr et al. 2001). A more dynamic model seems to be evidenced in a number of findings. Take, for example, that in a follow-up study to the figure-ground effects in macaques (Supèr et al. 2001), the internal state of the early visual cortex before stimulus processing has been shown to predict the report of the figure (Super et al. 2003). The authors suggested that this could be present due to neural activity strength and functional connectivity. However, this evidence was limited by the methodology and not much else.

Together, the prestimulus local early inhibition–excitation model of alpha and the local–global late recurrent GW model can be fused to form a new working framework of consciousness. This framework, the Win2Con, stipulates a dynamical network state before stimulus onset, which is the required state for full conscious access. The model constructs a variety of hypotheses about the brain state in both the domains of connectivity and oscillatory power. It does not aim to disprove either alpha inhibition or GW, but proposes an overarching explanatory plug.

3.2 Windows to Consciousness: The Evidence

The first experimental evidence for the Win2Con theory was outlined in Weisz et al. (2014; see also Ruhnau et al. 2014) in a near-threshold somatosensory study. The authors extended the analysis of the prestimulus state beyond examining only the alpha-power effects and critically analyzed the connectivity state of the brain state that determined stimulus perception. In particular, the study focused on global and local graph-theoretical models in addition to functional connectivity differences.

Global network properties (the state of a network as a whole) were first assessed for differences in prestimulus small-worldness between trials where participants felt the stimulus (Hit) and trials where they did not (Miss). A small-world network is seen as a plausible network for neural assemblies (Humphries et al. 2006), and it is characterized by two properties. (1) Dense interconnectivity within small groups of nodes: two common neighbors of one node are more likely to be neighbors of each other than two nodes selected at random. Note that if the nodes exist in physical space, for example, people or neurons, then the nodes of a highly interconnected group will tend to be physically close in space. (2) The average shortest path length is small: to connect any two nodes only a small number of intermediate nodes are typically traversed due to long-range links between the small groups of nodes. Although these properties seem finite, the brain state fluctuates and the network state, which in this case is defined by oscillatory coherence, can depend on ongoing activity. With this in mind, Weisz et al. (2014) demonstrated that this measure of small-worldness differed between Hit and Miss specifically at 17 Hz in which there was an increase in the measure for Misses. Taken together, the two characteristic properties of small-worldness suggest that there was either an increase in dense interconnectivity or a decrease in the average shortest path length, or both. To ascertain the contribution of the properties of small-world networks to the differences observed, Weisz et al. (2014) further used three global measures: global clustering, distance, and efficiency. The clustering measures the dense interconnectivity and revealed that the network states before misses were more clustered than hits. There was no difference in distance, but in efficiency, there was an indication of shorter path lengths for hits. This last point critically diverged the two network states that defined the conscious access; misses were in local integration state (closed windows) and hits were in a global integration state (open window). These findings cumulatively gave a resounding idea that ratified a component of the Win2Con framework by demonstrating that an open state of the network before stimulus onset was important in the participants' ability to consciously access the sensation of touch.

The framework gained further empirical evidence in the auditory modality (Leske et al. 2015). Within this study, the authors interrogated the prestimulus brain state that predisposed participants to perceive an NT auditory signal. Once again the prestimulus effects in power were observed; however, as is critical with the framework, the network state was also examined. With essential nodes within the auditory system (the left auditory cortex) showing a network state of enhanced node degrees and betweenness centrality. Interestingly, when the authors stratified the trials to equal out the power effects they were still able to robustly observe the network effects that they describe. Thus suggesting an independent state of connectivity from that of the state of local power (i.e., local excitatory modulations).

With the two studies in mind, and, in particular, the last, it would seem prudent to reassess the local excitatory role in the prestimulus period and its role in the NCC. However, independent of that point, which needs further experimentation, the connectivity state prior to stimulus seems to necessitate the observers' conscious access and thus can be defined as a constituent of the NCC (Fig. 1).

3.3 Windows to Consciousness: The Future

Within this chapter so far, we have highlighted the empirical evidence for the Win2Con theory. However, future efforts must be made to question other relevant features of consciousness and ratify the correlative results with more causal approaches. The features of consciousness that need to be probed next move beyond the mere hit and miss reports, and we must interrogate the brain states that invoke differing states of conscious content. One avenue that could be fruitful in this endeavor is exploiting stimulus with bistable properties; indeed, we have recently demonstrated a case for the prestimulus functional connectivity state that predicted the reported percept of a vase or a pair of houses in the Rubin Vase illusion (Peatfield et al. Under Review). This evidence could be supported by other forms of bistable stimulus, for example, binocular rivalry (Blake et al. 2014), or varieties of binocular rivalry like continuous flash suppression (Tsuchiya and Koch 2005).

Another approach would be to use neural stimulation methods to directly influence the brain state. While TMS is a plausible option, with its relatively precise spatial accuracy, it does come with problems such as the impulse-like stimulation form, the difficulty of creating a sham condition, and technical difficulties in combined acquisition (these are solved but still not nontrivial). Recently,

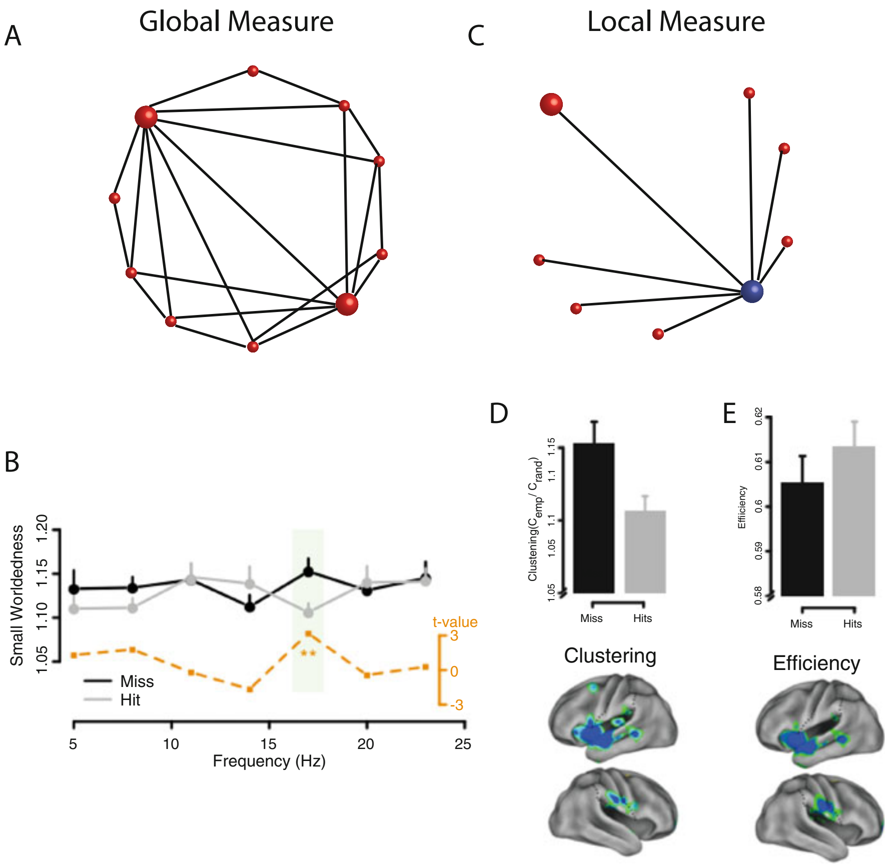

Fig. 1 (**a**) An example of a small-world graph as the global measure; here you define the networks whole aspect. (**b**) An example of a local measure. Here, this node is defined purely by its individual attributes. For example, note the different path lengths and the number of connections. (**c**) This graph taken from Weisz et al. (2014) shows how the difference between miss at hits peaked at around 17 Hz for the measure of small-worldness. This being a global measure, both **d** and **e** show how to interrogate the effect of this effect on the local graph measures. **d** highlights how the clustering measure was lower for hits than misses; whereas, **e** shows how there was increased state of efficiency for hits than misses

oscillatory forms of transcranial electrical stimulation, in particular transcranial alternating current stimulation (tACS), have enjoyed an impressive comeback to neuroscience (Herrmann et al. 2013). In combination with the possibility to assess the neurostimulation effects even at the actual stimulation frequency using MEG (Neuling et al. 2015), this enables powerful approaches to scrutinize the causal relevance of prestimulus brain states. A series of NT experiments using “single” and “dual” site tACS is currently underway in our laboratory.

References

Baars BJ (1988) A cognitive theory of consciousness. Cambridge University Press, Cambridge

Baars BJ (2002) The conscious access hypothesis: origins and recent evidence. Trends Cognit Sci 6(1):47–52. doi:10.1016/S1364-6613(00)01819-2

Bernasconi F, Manuel AL, Murray MM, Spierer L (2011) Pre-stimulus beta oscillations within left posterior sylvian regions impact auditory temporal order judgment accuracy. Int J Psychophysiol 79(2):244–248. doi:10.1016/j.ijpsycho.2010.10.017

Blake R, Brascamp J, Heeger DJ (2014) Can binocular rivalry reveal neural correlates of consciousness? Philos Trans R Soc Lond B Biol Sci 369(1641), 20130211. doi:10.1098/rstb.2013.0211

Busch NA, Dubois J, VanRullen R (2009) The phase of ongoing EEG oscillations predicts visual perception. J Neurosci 29(24):7869–7876. doi:10.1523/JNEUROSCI.0113-09.2009

Chen ACN, Feng W, Zhao H, Yin Y, Wang P (2008) EEG default mode network in the human brain: spectral regional field powers. Neuroimage 41(2):561–574. doi:10.1016/j.neuroimage.2007.12.064

Crick F, Koch C (2003) A framework for consciousness. Nat Neurosci 6(2):119–126. doi:10.1038/nn0203-119

Dehaene S, Changeux JP (2011) Experimental and theoretical approaches to conscious processing. Neuron 70(2):200–227. doi:10.1016/j.neuron.2011.03.018

Dehaene S, Naccache L, Cohen L, Bihan DL, Mangin JF, Poline JB, Rivière D (2001) Cerebral mechanisms of word masking and unconscious repetition priming. Nat Neurosci 4(7):752–758. doi:10.1038/89551

Dehaene S, Sergent C, Changeux J-P (2003) A neuronal network model linking subjective reports and objective physiological data during conscious perception. Proc Natl Acad Sci USA 100(14):8520–8525. doi:10.1073/pnas.1332574100

Dehaene S, Changeux JP, Naccache L, Sackur J, Sergent C (2006) Conscious, preconscious, and subliminal processing: a testable taxonomy. Trends Cogn Sci 10(5):204–211. doi:10.1016/j.tics.2006.03.007

Gross J, Schmitz F, Schnitzler I, Kessler K, Shapiro K, Hommel B, Schnitzler A (2004) Modulation of longrange neural synchrony reflects temporal limitations of visual attention in humans. Proc Natl Acad Sci USA 101(35):13050–13055. doi:10.1073/pnas.0400266101

Haegens S, Nácher V, Luna R, Romo R, Jensen O (2011) α-Oscillations in the monkey sensorimotor network influence discrimination performance by rhythmical inhibition of neuronal spiking. Proc Natl Acad Sci USA 108(48):19377–19382. doi:10.1073/pnas.1117190108

Hari R, Salmelin R (1997) Human cortical oscillations: a neuromagnetic view through the skull. Trends Neurosci 20(1):44–49. doi:10.1016/S0166-2236(96)10065-5

Herrmann CS, Rach S, Neuling T, Strüber D (2013) Transcranial alternating current stimulation: a review of the underlying mechanisms and modulation of cognitive processes. Front Hum Neurosci 7:1–13. doi:10.3389/fnhum.2013.00279

Humphries MD, Gurney K, Prescott TJ (2006) The brainstem reticular formation is a small-world, not scale-free, network. Proc Biol Sci R Soc 273(1585):503–511. doi:10.1098/rspb.2005.3354

Jensen O, Mazaheri A (2010) Shaping functional architecture by oscillatory alpha activity: gating by inhibition. Front Hum Neurosci 4:186. doi:10.3389/fnhum.2010.00186

Keil J, Müller N, Hartmann T, Weisz N (2014) Prestimulus beta power and phase synchrony influence the sound-induced flash illusion. Cereb Cortex 24(5):1278–1288. doi:10.1093/cercor/bhs409

Lakatos P, Karmos G, Mehta AD, Ulbert I, Schroeder CE (2008) Entrainment of neuronal oscillations as a mechanism of attentional selection. Science 320(5872):110–113. doi:10.1126/science.1154735

Leske S, Ruhnau P, Frey J, Lithari C, Müller N, Hartmann T, Weisz N (2015) Prestimulus network integration of auditory cortex predisposes near-threshold perception independently of local excitability. Cereb Cortex 25(12):4898–4907. doi:10.1093/cercor/bhv212

Mazaheri A, Jensen O (2008) Asymmetric amplitude modulations of brain oscillations generate slow evoked responses. J Neurosci 28(31):7781–7787. doi:10.1523/JNEUROSCI.1631-08.2008

Neuling T, Ruhnau P, Fuscà M, Demarchi G, Herrmann CS, Weisz N (2015) Friends, not foes: magnetoencephalography as a tool to uncover brain dynamics during transcranial alternating current stimulation. Neuroimage 118:406–413. doi:10.1016/j.neuroimage.2015.06.026

Romei V, Brodbeck V, Michel C, Amedi A, Pascual-Leone A, Thut G (2008) Spontaneous fluctuations in posterior alpha-band EEG activity reflect variability in excitability of human visual areas. Cereb Cortex 18(9):2010–2018. doi:10.1093/cercor/bhm229

Ruhnau P, Hauswald A, Weisz N (2014) Investigating ongoing brain oscillations and their influence on conscious perception—network states and the window to consciousness. Front Psychol 5:1230. doi:10.3389/fpsyg.2014.01230

Sergent C, Baillet S, Dehaene S (2005) Timing of the brain events underlying access to consciousness during the attentional blink. Nat Neurosci 8(10):1391–1400. doi:10.1038/nn1549

Siegel M, Donner TH, Oostenveld R, Fries P, Engel AK (2008) Neuronal synchronization along the dorsal visual pathway reflects the focus of spatial attention. Neuron 60(4):709–719. doi:10.1016/j.neuron.2008.09.010

Supèr H, Spekreijse H, Lamme VA (2001) Two distinct modes of sensory processing observed in monkey primary visual cortex (V1). Nat Neurosci 4(3):304–310. doi:10.1038/85170

Super H, van der Togt C, Spekreijse H, Lamme VAF (2003) Internal state of monkey primary visual cortex (V1) predicts figure-ground perception. J Neurosci 23(8):3407–3414, Retrieved from http://www.jneurosci.org/content/23/8/3407.full

Tsuchiya N, Koch C (2005) Continuous flash suppression reduces negative afterimages. Nat Neurosci 8(8):1096–1101. doi:10.1167/4.8.61

Van Dijk H, Schoffelen JM, Oostenveld R, Jensen O (2008) Prestimulus oscillatory activity in the alpha band predicts visual discrimination ability. J Neurosci 28(8):1816–1823. doi:10.1523/JNEUROSCI.1853-07.2008

Weisz N, Wühle A, Monittola G, Demarchi G, Frey J, Popov T, Braun C (2014) Prestimulus oscillatory power and connectivity patterns predispose conscious somatosensory perception. Proc Natl Acad Sci USA 111(4):E417–E425. doi:10.1073/pnas.1317267111

Neuronal Synchronization, Attention Orienting, and Primary Consciousness

Lawrence M. Ward

1 Introduction

How does the brain implement cognitive processes such as perception, attention, memory, decision-making, and consciousness? Part of the answer is specialization of function in particular regions. In some cases, a single brain area is critical to the performance of a specific perceptual or cognitive function. It is well known, for example, that the right fusiform gyrus appears to be particularly important in face-specific visual processing (e.g., Kanwisher 2006), and the superior temporal sulcus, an analogous part of the auditory system, performs an analogous role in voice-specific processing (Belin et al. 2000), although clearly these regions also perform other functions. Similarly, the left fusiform gyrus seems to be especially important for reading (Bedo et al. 2014; Dehaene and Cohen 2011). Complex cognitive processes involved in attention, memory, reading, and consciousness, however, appear to require the coordinated activity of at least several of these specialized regions. For example, several frontal and posterior brain regions have been said to perform separate specific functions during the implementation of attention orienting (e.g., Corbetta and Shulman 2002; Corbetta et al. 2008; Wright and Ward 2008; Fig. 1). Moreover, such specialized regions, including those appearing to perform a single function alone, must interact with other regions to receive the information they are acting upon and to send processed information to other areas including back to the sending area. Strikingly, such specialized areas often (always?) exhibit different functions depending on the particular subset of other regions with which they are functionally interacting (e.g., McIntosh 2000; Pessoa 2014). Finally, because cognitive tasks vary dramatically over timescales of

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S. Palva (ed.), *Multimodal Oscillation-based Connectivity Theory*,
DOI 10.1007/978-3-319-32265-0_3

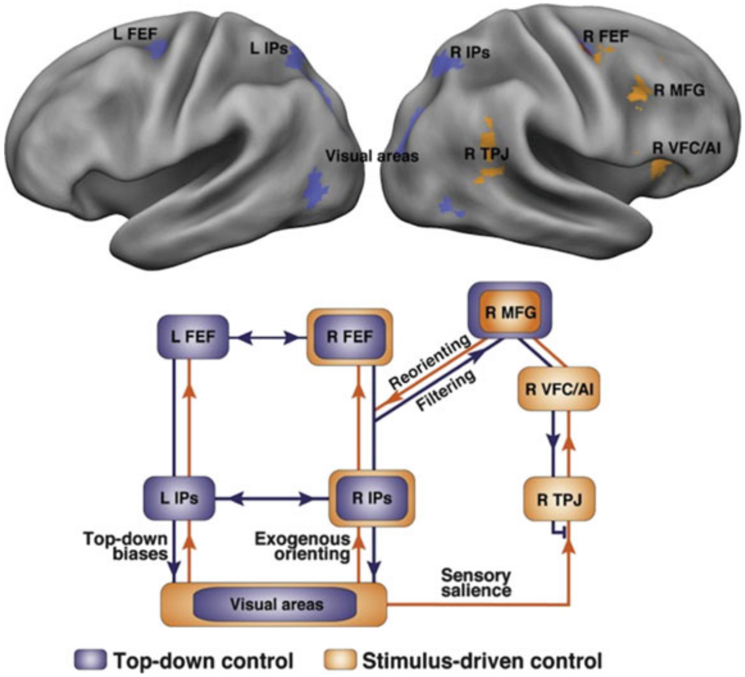

Fig. 1 Some brain areas involved in reorienting attention. *L,* left; *R*, right; *FEF*, frontal eye fields; *IPs*, intraparietal sulcus; *MFG*, middle frontal gyrus; *TPJ*, temporo-parietal junction; *VFC/AI*, ventral frontal cortex/anterior insula. Reprinted with permission from Corbetta et al. (2008)

hundreds of milliseconds to a few seconds, the functionally relevant regional networks must form and dissolve over these short timescales, which are too short to accommodate mechanisms such as synaptic modification via spike-timing dependent plasticity or long-term potentiation. It has been suggested that oscillatory, or rhythmic, synchronization of neural activity provides a mechanism whereby networks of functionally specialized brain regions could be integrated and function transiently on such timescales (Varela et al. 2001). This chapter describes some experiments that begin to uncover how these networks of brain regions are integrated in the implementation of endogenous attention orienting and of switching between conscious percepts in binocular rivalry.

A general theory of functional integration of brain regions via oscillatory neural synchronization requires that at least the following mechanisms be specified. First, the relevant brain networks must be described. Second, their order of activation (or causal order, in the sense of Granger causality at least) and/or recurrent or resonant processing modes must be determined. Third, the mechanism(s) of how oscillatory rhythms are achieved in the brain must be described. Fourth, the mechanism(s) by which synchrony (phase locking) is attained and that by which it is broken (phase scattering) must be described. Fifth, the effects of oscillatory synchronization on information exchange must be described. Although it is at present impossible to describe all of these, or even a small subset of them, completely for any particular cognitive process, I will indicate here a sketch of how such a theory would appear in general, in order to contextualize the specific mechanisms described in what follows.

fMRI, among other techniques, is illuminating at least part of the functional anatomy of the brain. Although a few functional networks have been identified, there is still a paucity of information about them, including the necessary areas that are common to both baseline and experimental tasks, and especially their subcortical components, which seldom appear in published reports. Two such incomplete networks are described briefly in what follows: one involves attention orienting and the other involves consciousness.

How are these networks activated or suppressed? An important general theory has it that population-coded activity of neurons in one brain area is transmitted via more or less hardwired neural pathways to neurons in other areas to which it is connected, including of course back to the initiating areas from the connected areas (reentrant processing) (e.g., Rolls and Treves 2011). But is the wiring always so specific that activity in a particular group of neurons can activate only a particular group of other neurons? This seems to be the case in early sensory areas and in some subcortical areas. But neural connectivity within and between other cortical areas, particularly in the so-called association areas of cortex, and also ascending systems of connections from subcortical areas to the cortex, seems to be more general or diffuse (e.g., Jones 2001). In the case of such diffuse connections, a subsidiary selective mechanism is necessary to communicate information and control signals from relevant neurons in one brain area to those in another area that are involved in the same functional network. Synchronization at particular oscillatory frequencies is one mechanism that has been proposed to transiently and, at specifically required moments, functionally connect groups of neurons engaged in implementing a particular cognitive process (e.g., Bastos et al. 2015; Fries 2005; Varela et al. 2001).

Most networks involve recurrent processing, and some will display adaptive resonance between hierarchically arranged processing stages (Grossberg 2000). In others, a feed-forward sweep will be identifiable in specific experimental situations, and neural synchrony should appear between the relevant brain regions in a specific time order (e.g., Lamme and Roelfsema 2000). A compelling example of this process recorded by EEG is the feed-forward sweep initiated by electrical stimulation of the esophagus: from sensory reception, to thalamus, to primary and secondary sensory cortex, and finally to various association areas (Drewes et al. 2006). In this study, significant coherence of the EEG estimated from neural sources followed exactly the time course of the feed-forward sweep.

Oscillatory rhythms are ubiquitous in the brain (Buzsáki 2006). There are several ways in which groups of neurons can generate these oscillatory rhythms. Most appear to involve reciprocal excitatory or inhibitory connections between groups of spiking neurons (e.g., Buzsáki and Wang 2012; Wilson and Cowan 1972). One prominent suggestion is that such groups of interconnected neurons act as resonant filters. That is, the synaptic efficacies and time constants characteristic of these neurons are such that only a relatively narrow frequency band of their broadband noisy input appears in their output spike rate, thus generating oscillations predominantly at that frequency (Kang et al. 2010). This mechanism operates even when the spiking of the individual neurons is fairly sparse and does not reliably follow the generated narrow-band oscillation (Brunel and Hakim 1999). Mathematical analysis of this model shows that it can account for the bursts of increased power at particular oscillatory frequencies (e.g., gamma at 30–50 Hz) that appear in the local field potential recorded both from electrodes in the brain and on the scalp (Greenwood et al. 2015).

There are also several mechanisms by which oscillatory neural synchronization can be attained. One important mechanism involves sending bursts of spikes to all neurons in a downstream population that is to be synchronized (e.g., Fries 2005, but see Buzsáki and Schomberg 2015). This is easily accomplished by the upstream neurons if they themselves are synchronized because they tend to fire the most spikes at the peaks of their own oscillatory cycles. Some brain areas spontaneously generate synchronized oscillatory activity, for example, the hippocampus generates a synchronized theta (4–8 Hz) rhythm through the same kinds of excitatory–inhibitory interactions that generate the oscillations in the first place (Buzsáki 2006). Cortico-thalamic interactions also generate synchronized activity in both cortex and thalamus, possibly through the actions of special neurons in the thalamus called “matrix” cells (Jones 2001). Any of these mechanisms might be involved in particular cases, although timing considerations might determine which is used for particular cognitive tasks. Sending simultaneous spikes is the fastest mechanism and might be required for long-distance synchronization, although it is known from models that local synchronization in an interconnected oscillating population of relaxation oscillators can be achieved within one or a few cycles (Somers and Kopell 1993). At present, measurements of long-range synchronization do not suffice to determine the mechanism in any specific case (Buzsáki and Schomberg 2015).

Finally, Salinas and Sejnowski (2001) have begun to describe the ways in which neural synchrony can affect the flow of neural information. In particular, they have described the way in which correlated neural input can affect downstream activity. It is not simple: input correlations can act as a switch, can enhance gain, can change overall firing rates, and can change correlations in the target population. Any of these effects could be important for the communication of information in the brain. Moreover, Fries (2005) has argued, based on experiments by Azouz and Gray (2000) and Volgushev et al. (1998), that interactions between communicating neural groups are most effective when bursts of impulses from one group reach the dendrites or somas of the other group during the most receptive period of their subthreshold oscillations. Bastos et al. (2015) extended this argument to include delays arising from synaptic interactions among hierarchically organized brain regions. Thus, oscillatory synchronization between interacting groups of neurons could be important for effective communication in the brain, even between hard-wired and invariably connected neurons.

It should be noted that synchronization is not the only way in which oscillating populations of neurons can transmit and receive neurally encoded information. Multiplexing in oscillatory populations of neurons can achieve information transmission in much the same way that AM and FM radio signals work (e.g., Akam and Kullman 2014). In this case, the oscillatory rhythms can serve as carriers of the modulations that constitute the information. Complementarily, oscillating populations at the receiving end can then decode the information and either perform further computations or pass it along to additional brain areas. In this view, changes in synchronization associated with information processing could either be a signature of a special type of multiplexing or could be related to an entirely different mechanism of information exchange.

The brain networks involved in attention and consciousness are closely related, involving both frontal and parietal regions in addition to sensory and subcortical regions. The cognitive processes themselves are also closely related, although there is no agreement as to the exact nature of the relationship. It is possible that attending to a perceptual object creates a representation of that object in consciousness, a position that seems to be reinforced by experiments in change blindness, inattentional blindness and deafness, and so forth (e.g., Simons and Rensink 2005). Alternatively, it is possible that we are aware of much more than we can report, and attention merely determines what we can report (e.g., Lamme 2003). The two might be completely different processes, as argued by Koch and Tsuchiya (2006), or consciousness might arise from the processes controlling attention, as suggested by Taylor (2007). Regardless of which view ultimately prevails, it is clear that both processes require integrated activity in several brain areas and that the primary object of both processes changes frequently, on a timescale of hundreds of milliseconds, requiring corresponding changes in the supporting neural network on the same timescale. In what follows, I will review some experimental work that provides evidence concerning the dynamic organization of the neural networks responsible for implementing these two complex cognitive processes. Consistent with other models (e.g., Gregoriou et al. 2015; Niebur et al. 2002; Srinivasan et al. 1999), I will argue that oscillatory synchronization of neuronal oscillations both within and between brain regions is an important mechanism mediating formation of, and communication within, these neural networks.

2 Neural Synchronization and Attention

Ward (2003) among others reviewed data suggesting that increases in local alpha power (indexing intra-regional synchronization) in a particular brain region are associated with active suppression of information processing, whereas increases in local gamma power in the same region are associated with active information processing. Ward (2003) also raised the question of whether decreases in local alpha power were necessary for perceptual binding to occur via a mechanism of increased gamma-band synchronization. These ideas suggest a reciprocal relationship between intra-regional synchronization in the alpha and gamma bands: when one is high or increasing, the other should be low or decreasing. A related question also arises: is the relationship between these two frequency bands the same for intra-regional (local power) and interregional synchronization? If not, how are intra-regional and interregional synchronizations coordinated? Must local conditions in each of two brain regions be in a certain state for interregional synchronization between them to occur? Also, there are some data that imply that both intra-regional (e.g., Canolty et al. 2006; Canolty and Knight 2010) and interregional synchronizations in the gamma band (Sects. 2.2, 3) are modulated by theta oscillations, perhaps being maximum at a preferred theta phase (but see Aru et al. 2015, for caveats). How do theta phase and alpha power interact to regulate gamma synchronization, both locally and interregionally? Here, I review several experiments from the laboratories of myself and my collaborators that address these questions in the context of attention orienting (see Wright and Ward 2008, for a review of attention orienting in general). Gregoriou et al. (2015) review many other studies suggesting that oscillatory synchronization is an important mechanism for attentional selection and integration.

2.1 Interregional Gamma-Band Synchronization Implements Attention-Relevant Communication

Doesburg et al. (2008) reported an experiment designed to test the hypothesis that gamma-band synchronization is involved in spatial attention orienting. Subjects were required to orient their attention to a small box on one side or the other of the visual field in preparation for a target stimulus that appeared either in the indicated box or the other box with equal probability from 1000 ms to 1200 ms after cue onset. If the target appeared in the indicated box (half the time, randomly) and was a "+" (half the time, randomly), they were to respond by pressing a button, otherwise they did not respond. EEG was recorded during the entire experiment, and the resulting time series were then divided into epochs time locked to cue onset so that the period between cue onset and target onset could be studied. In order to measure synchronization, the Laplacian transform was taken on the broadband time series, creating time series of scalp current density values that represented the activity of shallow brain sources near each electrode, thus negating to some extent the effects of volume conduction of the EEG signal from deeper and far away sources. These signals were then filtered into narrow bands, and the analytic signal was computed for a subset of 19 evenly spaced electrodes (see Doesburg and Ward 2009 and Ward and Doesburg 2009 for detailed descriptions of this approach and a comparison with others). Phase locking value was then computed from the differences of the instantaneous phases of each pair of electrodes across all of the epochs available after artifact rejection for each time point in various frequency bands. We considered changes in phase locking to be significant if the observed normalized (re - pre-cue mean and standard deviation) PLV lay outside the 97.5th or 2.5th percentiles of a surrogate distribution obtained by randomly shuffling the epochs and recomputing the normalized PLV 200 times. Figure 2 shows the results of this

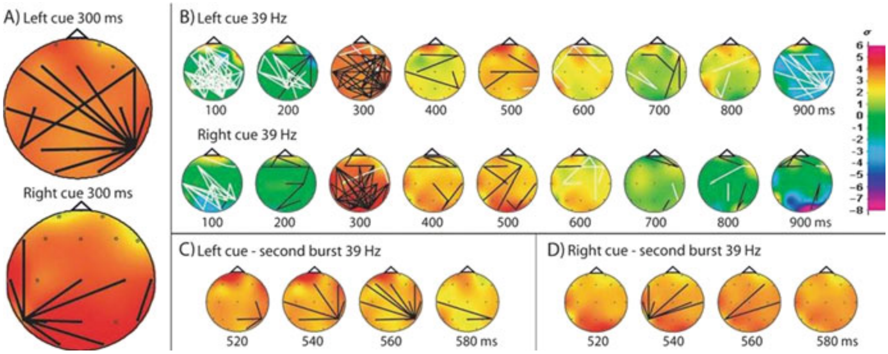

Fig. 2 (**a**) Lateralized bursts of gamma-band synchronization (*black lines*) between scalp current density at an electrode over visual cortex and that at other, distant, electrodes occur about 300 ms after a spatial attention-directing cue. (**b**) More detailed time line reveals desynchronization (*white lines*) at around 100 ms after the cue. (**c**, **d**) Even more detailed time line reveals a second burst of lateralized synchronization around 540–560 ms post-cue onset. Reprinted from Doesburg et al. (2008) with permission from Oxford University Press

analysis for 39 Hz (actually about 37–41 Hz because of the filter bandwidth). Results for nearby frequencies from about 35–45 Hz were similar.

At the same time as the burst of increased long-distance gamma-band synchronization, local gamma power in the occipital lobes increased and local alpha power at that location decreased dramatically. Doesburg et al. (2008) interpreted this pattern of coordinated changes in local and long-distance synchronization to indicate the establishment of a network of interacting brain regions that would effect the reorienting of attention from the cue location to the location of the impending target. These results also confirmed the hypothesis that changes in local alpha and gamma power would be reciprocal and extended this to long-distance gamma-band synchronization. Subsequent to these changes, local alpha power increased again and gamma power decreased. Interestingly, beginning at around 800 ms post-cue onset, the increase in alpha power was greater ipsilateral to the cued location than contralateral to that location, replicating the data of Worden et al. (2000) and leading to the conclusion that the local alpha power increase was associated with readying the brain to respond to a target in the cued location by suppressing the brain region responsible for initial target processing at the uncued location.

Although the results of Doesburg et al. (2008) are intriguing, they rely on inferences about synchronization between brain regions based on changes in synchronization between electrodes rather than on changes in synchronization measured directly between brain regions. A few studies have demonstrated that it is possible to measure synchronization directly between brain regions from outside the head (e.g., Cosmelli et al. 2004; Gross et al. 2004; Supp et al. 2007). Each of these studies used a different, somewhat customized approach to locating brain sources, however, and these are not readily available. Accordingly, we developed our own approach in several studies. It involves using a beamformer spatial filter applied to the EEG recordings to discover the brain regions that are active during a cognitive task, and then using a source montage (Scherg et al. 2002) with dipoles located in those active regions to generate broadband signals that account for the observed scalp topography (see Green and McDonald 2009, for a detailed description of this technique). These broadband signals are then filtered into narrow bands for synchronization analysis as described earlier.

We used this technique in a study of auditory attention orienting designed to confirm and amplify the results of Doesburg et al. (2008) (Green et al. 2011; Doesburg et al. 2012). It was based on an earlier successful use of the beamformer approach to study the sequence of EEG-recorded regional brain activation in a visual attention orienting task resembling that used by Doesburg et al. (Green and McDonald 2008). In our experiment, subjects reoriented their attention from central fixation to the location (left or right) of a subsequent auditory target stimulus based on an auditory cue. On some trials, the (neutral) cue indicated that they should not reorient attention but should stay focused on the fixation location. We analyzed the EEG recordings between cue onset and target onset on the attention-shift trials with the recordings from the neutral trials subtracted out in order to focus on attention-shift-related brain activity. The beamformer was used to find bilateral sources of activity in the theta-frequency band (4–7 Hz), which had been previously found by Green and McDonald (2008) to be commensurate with other EEG and fMRI studies of attention reorienting (see Sect. 1). Figure 3 shows an illustrative summary of our results. Notice that the brain regions indicated as active are highly similar to those

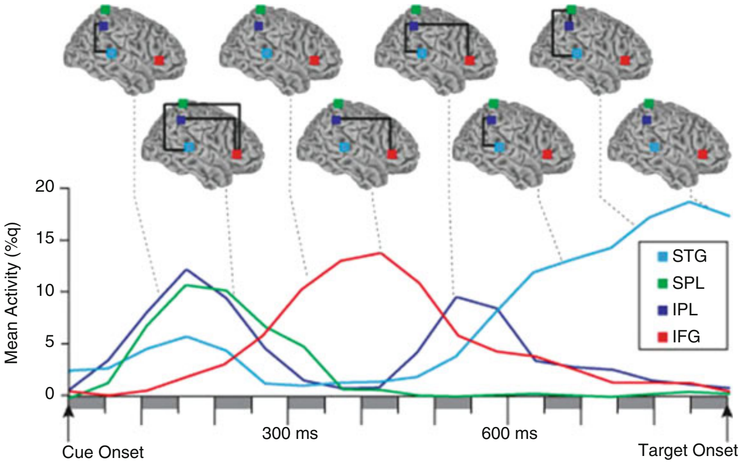

Fig. 3 Bottom: *Colored lines* (color code in box) represent activation of theta-band beamformer sources from cue onset until target onset (based on Green et al. 2011). *Top*: Representation of brain regions (*colored squares*) on right side of brain that was active according to the colored lines at bottom. *Black lines* connecting brain regions indicate significant increases in gamma band phase locking during the 50-ms time interval indicated by a *gray bar* on timescale at bottom (based on Doesburg et al. 2012). *STG*, superior temporal gyrus (audition); *SPL*, superior parietal lobule; *IPL*, inferior parietal lobule; *IFG*, inferior frontal gyrus

described by Corbetta et al. (2008) as involved in the attention reorienting networks based on fMRI data (Fig. 1).

It can be seen from Fig. 3 (bottom) that after the cue (0–100 ms) was presented, neural activity in the theta band arose first in posterior regions of the brain responsible for audition (superior temporal gyrus, STG) and in those associated with attention reorienting (superior parietal lobule, SPL, and inferior parietal lobule, IPL; 100–200 ms). Then, as theta-band activity in those areas declined, activity in the inferior frontal gyrus (IFG) increased (200–350 ms), until the IFG alone was active (350–450 ms). The posterior areas again became active as IFG activity declined (450–650 ms), followed by a continuing increase in STG activity until target presentation. These brain areas and their theta-band activation sequence are nearly identical to those found by Green and McDonald (2008) for a visual cue–visual target attention reorienting task, indicating that we are addressing a supramodal attention reorienting network (Green et al. 2011). This activation sequence is consistent with the following processing progression: first the cue causes shift-specific activation of STG, and then shift-specific activation of posterior brain regions responsible for attention reorienting occurs, indicating the need for a shift of attention. These regions in turn give way to activity in IFG that interprets the cue in terms of where attention must be shifted. Then this information is conveyed to the posterior regions that initiate the shift, which in turn ready the auditory cortex for the upcoming target presentation.

In addition, the peak voxels of the sources uncovered by the beamformer analysis were used as the loci of dipoles in a source montage, whose broadband signals were filtered and analyzed as described above, concentrating on gamma-band phase locking (Doesburg et al. 2012) and theta–gamma cross-frequency coupling. Gamma band phase locking was considered to be significant within a 50-ms time bin only if the observed normalized PLV was outside 97.5th or 2.5th percentiles of the surrogate distribution bilaterally for the same three or more successive time points at least once in a given bin. The top part of Fig. 3 illustrates that phase locking in the gamma band between the active brain regions followed fairly closely the progression of activations from posterior to frontal to posterior again. Phase locking between active posterior regions increased first, followed by increases between SPL and IPL and IFG. For a period, no phase locking increases were seen, but then IFG locked with IPL again and IPL and SPL locked with each other and with STG. Finally, no phase locking was observed just before target onset. We conjectured that this pattern of phase locking among a subset of brain regions active in a specific sequence during reorienting of attention indicates that gamma-band synchronization could be the mechanism by which distant brain regions coordinate their activity so as to communicate information or control signals relevant to the accomplishment of a cognitive task (cf. Gregoriou et al. 2015). This conjecture is supported by the fact that there is significant coupling between the gamma-band PLV and the amplitude and the phase of the theta oscillations occurring in the various neural sources, although this finding is somewhat stronger within posterior areas than between posterior and frontal regions (Doesburg et al. 2012).

Although this experiment cannot be compared directly with that of Doesburg et al. (2008) because of a variety of differences in task and timing, the involvement of gamma-band synchronization is similar. This study, however, shows more directly that interregional gamma-band synchronization seems to be indexing communication among active brain areas, whereas activation in the theta band in specific brain regions seems to be associated with processing stages. Interestingly, in this study there was no significant relationship between intraregional activity in the gamma band and interregional synchronization, although gamma amplitude was relatively high in the posterior regions early in the cue–target interval as found by Doesburg et al. (2008). Gamma amplitude in the various regions did bear some relationship to theta-band activation, however, for IPL and IFG, although it waxed and waned in an irregular pattern for SPL and STG (Doesburg et al. 2012).

2.2 Alpha-Band (9–14 Hz) Synchronization Maintains the Attention Network

The results just discussed indicate that interregional gamma-band synchronization is likely to be associated with communication between brain regions involved in reorienting attention. But these synchronizations are short lived and only occur at particular points in the sequence of attention-related processing. Moreover, theta-band activations also are relatively short lived and time-point specific. What mechanism might be responsible for maintaining the biased readiness characteristic of orienting attention to a specific location in space? In a replication of the Doesburg et al. (2008) study using the magnetoencephalograph, Doesburg and Ward (2007) discovered that lateralized synchronization between occipital sensors and other distant sensors in the alpha band persisted over much of the cue–target interval. They proposed, consistent with other recent evidence (e.g., Palva and Palva 2007; von Stein and Sarnthein 2000), that long-distance alpha-band synchronization maintains selective attention at a particular spatial locus. A beamformer analysis of these same data enabled Doesburg et al. (2007) to specify that the long-distance synchronization was occurring between occipital and parietal cortical loci at the same time that local alpha power was lateralized in the opposite direction.

We reanalysed the data of Green and McDonald (2008) using the approach I described earlier to test this hypothesis more directly (Doesburg et al. 2009a). Green and McDonald's (2008) experiment was very similar to the experiment of Green et al. (2011), except that the cues and targets were visual stimuli rather than auditory stimuli. On some trials, subjects had to shift their attention from fixation to a cued location and on others a neutral cue indicated that they were to maintain their attention at fixation. Neutral trial data were subtracted from shift trial data in order to reveal attention-shift related activity during the cue–target interval. As Green and McDonald (2008) had already reported a beamformer analysis of theta-band regions active during their visual attention reorienting task, we created a source

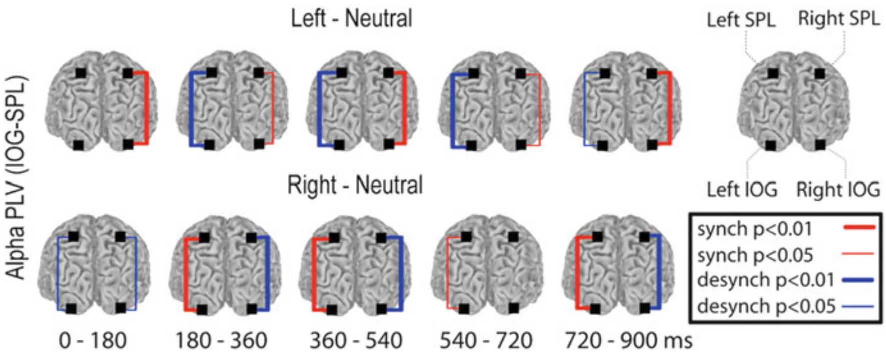

Fig. 4 Increases in synchronization, relative to the pre-cue baseline and for indicated time intervals, between inferior occipital gyrus (IOG) and superior parietal lobule (SPL) in the alpha band (8–12 Hz) during the cue–target interval are indicated by *red lines* connecting the *black squares* located at those brain regions. Decreases in synchronization are indicated by *blue lines*. Results are shown separately for shift-left and shift-right trials. Note the opposite lateralization of the synchronization patterns and also that this trend is evident over nearly the entire cue–target interval. Reprinted from Doesburg et al. (2009a) with permission from Elsevier

montage with dipoles located in those active regions. This is preferable to trying to locate sources active in the alpha band, as these are likely to be regions where processing is being suppressed. We then extracted the broadband signals from the source montage and analyzed them for local and long-distance synchrony as described earlier. In this analysis, we focused on the relationship between sources in occipital and parietal cortices (IOG, SPL, and IPL), as these are the regions most likely to reflect maintenance of attention over longer periods of time. A summary of our findings is shown in Fig. 4.

Whereas reciprocal lateralized changes in synchronization between IOG and SPL were evident during the entire cue–target interval (Fig. 4), only increased synchronization between IOG and IPL in both hemispheres was observed (not shown). Thus, IPL–IOG synchronization seems to represent a more general readiness to respond, whereas SPL–IOG synchronization couples visual areas specific to the attended target location and desynchronization decouples areas specific to other locations. Importantly, and in replication of many previous results, local alpha amplitude in the occipital cortex ipsilateral to a cued location was much higher than that contralateral to a cued location over much of the cue–target interval. Thus, local and long-distance synchronization seems to play different roles in attention reorienting: increases in local alpha amplitude suppress processing in regions receiving input from unattended locations, whereas increases in long-distance alpha phase locking link regions receiving input from attended locations.

This perspective was confirmed by additional MEG data from the same paradigm used by Doesburg et al. (2008). We analyzed these data for effective connectivity using narrow-band transfer entropy (NBTE) to measure Granger-like causal interactions between brain loci involved in orienting visual attention to the cued location (Doesburg et al. 2016). For these data, we employed an event-related beamformer to localize brain regions during time periods after cue presentation during which evoked activity was greatest. We then measured NBTE between the time series of alpha-band activations from these regions for plausible lags of 30–50 ms. NBTE measures the additional information that can be predicted in a time series of interest by using a second time series. Granger causality is inferred because the predictive part of the second time series is lagged with respect to the predicted part of the time series of interest. We also used a wavelet analysis to measure the relative power in the alpha band in occipital cortex during the cue–target interval. Figure 5 shows a summary of some of these results. Around 500–700 ms after cue presentation, there was significantly lateralized NBTE in the alpha band between frontal and parietal brain regions and occipital cortex. That is, when the cue indicated that attention was to be oriented to the left side of visual space, top-down NBTE was greater on that side of the brain. At this same time, relative alpha power was also greater in occipital cortex on the same side as the greater NBTE, possibly indicating that the NBTE was indexing a control signal

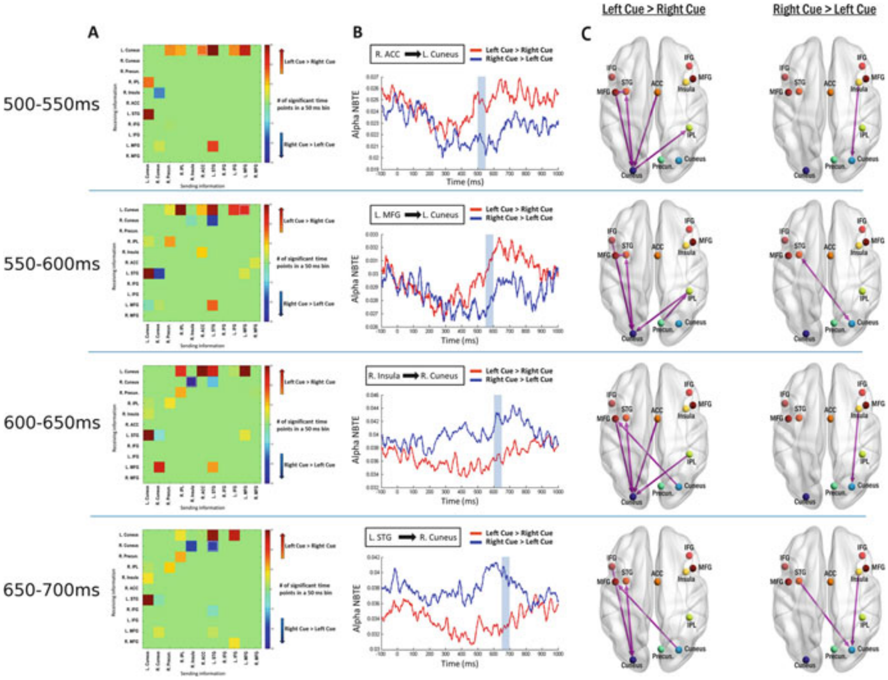

Fig. 5 Summary of significant NBTE between indicated brain regions in relevant time intervals (**a**) and illustration of mean NBTE data in specific cells outlined in *white* (**b**) in the matrices of **a**. Shaded areas in **b** indicate the relevant time bin in **a**. These data were used to construct (**c**). *Arrows* indicate time periods in the cue–target interval during which higher levels of information flow in the alpha band were observed for the indicated cue condition (see **a**). Reprinted from Doesburg et al. (2015) with permission

eliciting an increase in alpha power on the side of the brain contralateral to the side that would be analyzing the expected target.

3 Neural Synchronization, Binocular Rivalry, and Primary Consciousness

Binocular rivalry is one of the most used and one of the most informative paradigms within which to study primary phenomenal consciousness. When incompatible images, such as gratings with differently colored stripes that are at right angles to each other, are presented continuously to the left and right eyes, respectively, rather than amalgamating the separate images, the visual system presents them alternately and (mostly) randomly to awareness (Fig. 6). That is, phenomenal consciousness of the two patterns alternates, with first one and then the other dominating. Quite often one of the two images is suppressed altogether, although both are present continuously on the retina and the brain continues to respond to both of them. Because this rivalry occurs in conscious perceptual experience, and can be reported upon by pressing a button to indicate which percept is presently dominant, it is ideal for studying the neural correlates of consciousness in the absence of stimulus variation. Importantly, because the indication of the perceptual switch can be nonverbal, binocular rivalry can be studied in any animal with two eyes that can make a discriminative response, making possible invasive neurobiological studies. The presumption is that the neural correlates of the perceptual switches are plausible candidates for the neural correlates of primary perceptual awareness.

One of the earliest and most influential studies investigating the neural correlates of perceptual switching in binocular rivalry was that of Logothetis and Schall (1989). They trained a monkey to indicate in which direction it perceived gratings, presented separately to each eye through a stereoscope, to be drifting by making a saccade to the left or to the right. The direction of perception was also checked by optokinetic nystagmus, which correlates well with perceived direction of movement. Some trials contained gratings moving in both directions, different in the two eyes, and were thus rivalrous. In these cases, the direction of the monkey's eye movement and optokinetic nystagmus reflected the perceived dominant grating. Activity of neurons in area MT (contains directionally movement sensitive neurons) reflected the direction of motion when the gratings were the same in the two eyes, being greater for the preferred direction of movement. Although some neurons responded only when their preferred direction of movement was present on the retina, others responded to their preferred direction only when it was perceived, even when the two eyes were rivalrous. In these latter cases, the neurons were silent on those trials when the rivalrous stimulus was perceived to move in the non-preferred direction, even though the preferred motion stimulus was present in the suppressed eye. The activities of these neurons, thus, are candidates for neural correlates of perceptual awareness.

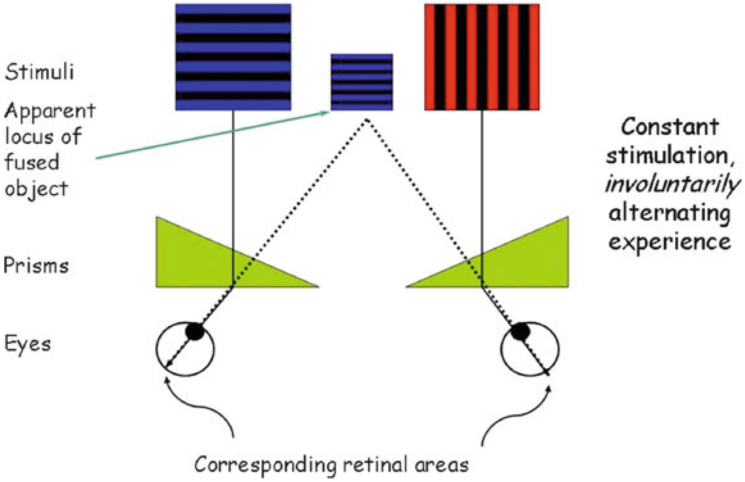

Fig. 6 The paradigm of binocular rivalry illustrating one possible percept (*horizontal blue stripes*). Note that rivalry is dynamic and the switching of percepts occurs at random under most conditions, often following a gamma probability distribution

Using a similar design in which the direction of perception was indicated by optokinetic nystagmus, Fries et al. (1997) demonstrated increased gamma-band neural synchrony for seen vs suppressed gratings in cat visual cortex. They found that this synchronization, rather than activity of the neurons per se, was the important correlate of which stimulus the cats were perceiving. In the same time frame, Srinivasan et al. (1999) demonstrated greater brain-wide MEG coherence at the driven frequency of the perceived flickering grating (of the type shown in Fig. 6) than of the non-perceived grating during binocular rivalry in humans. They also promulgated the dynamic core theory in which primary consciousness arises from a synchronously oscillating core of neural activity that both integrates information from a variety of brain regions and also differentiates the current conscious state from other possible states (Tononi and Edelman 1998). In an elegant MEG study, Cosmelli et al. (2004) demonstrated, also in humans, that consciousness of a 5 Hz oscillating stimulus presented to one eye during binocular rivalry (the other eye received a non-oscillating face stimulus) took place only when there was increased phase locking between the diverse brain areas responding to that stimulus. The local brain regions responding to the 5 Hz stimulus were still active when face was seen, but they were not significantly phase locked with each other during these periods. Thus, it seems that synchronously oscillating brain regions are closely associated with consciousness of an oscillating stimulus during binocular rivalry.

While intriguing, the human studies are limited in generality to stimuli flickering at relatively slow rates. Doesburg et al. (2005) extended the conclusions of Fries et al. (1997) to non-flickering stimuli and the gamma band by demonstrating that endogenous gamma-band synchrony between diverse EEG electrodes was increased around the time of the perceptual switch between images during binocular rivalry in humans. Their study also utilized gratings similar to those in Fig. 6 and data analyses similar to those described for attention reorienting. Their analyses were limited to scalp electrodes, however, and thus the brain regions participating in the synchronous activity were not identified. Subsequently, we used beamformer on EEG data collected during binocular rivalry to identify brain regions active in the gamma band during switching of perceptual awareness (Doesburg et al. 2009b). In our experiment, subjects again pressed one of two buttons to indicate which of two rivaling images they were seeing (Fig. 7, left side, shows the two images). The beamformer identified the regions shown in Fig. 7, right side, as active in the gamma band during two intervals prior to a button press in stable epochs (700 ms or longer of one dominant percept) relative to a third interval between the two during which gamma-band activity was significantly lower (370–430 ms). A source montage of these regions was used to extract broadband signals, which were then analyzed for changes in phase locking in the same way as described above.

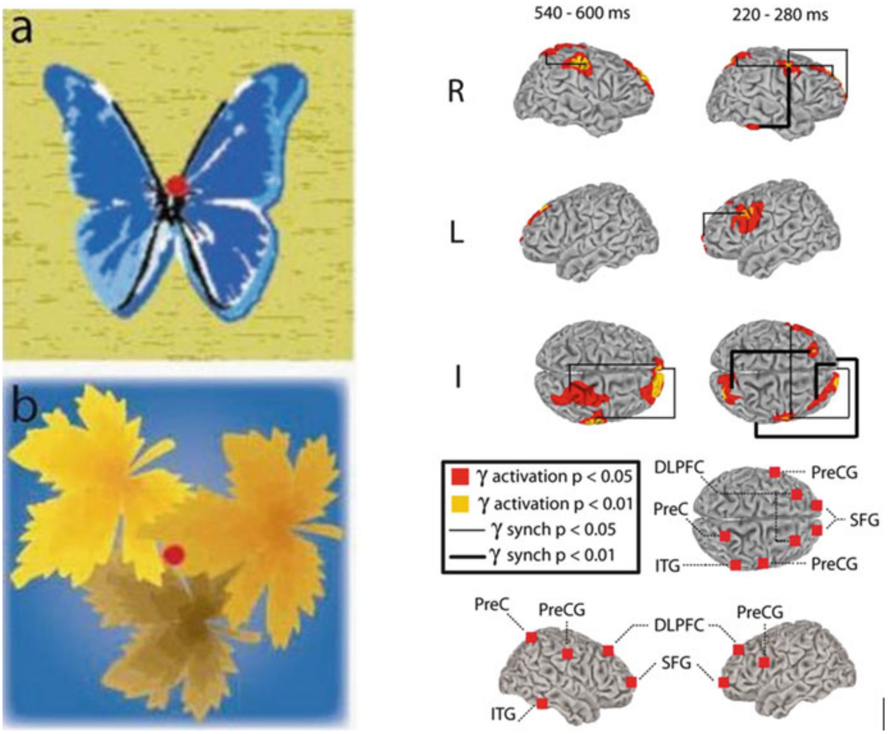

Fig. 7 *Left*: Rivaling images used by Doesburg et al. (2009b). These complex patterns should induce pattern rivalry rather than eye rivalry. *Right*: Brain regions with increased activation in the indicated periods, relative to the baseline period 370–430 ms, before the button press signaling a change in conscious percept. *Black lines* connecting regions indicate significant (by surrogate) increases in phase locking. Reprinted from Doesburg et al. (2009b)

Figure 7, right side, shows the increases in gamma-band synchronization measured in those two time intervals relative to a baseline period between them. Clearly, increased gamma-band synchronization is associated with the change in perceptual consciousness indicated by the button press and is particularly prominent in the period 220–280 ms before the button press, a time interval approximately equal to the time it takes to classify a familiar visual stimulus. Moreover, there was activity in left motor cortex (presumably associated with the right-handed button press) and in right inferior temporal gyrus (implicated in processing of complex visual patterns) in this time period that was not evident in the preceding time period (540–600 ms). This activity indicates that the 220–280 ms period preceding the button press was the temporal locus of the percept change leading to the button press.

Because this analysis revealed changes in synchronization relative to a period of desynchronized gamma-band activity, and based on the overall pattern of waxing and waning of gamma-band activity and gamma-band synchronization over the entire epoch preceding the button press that indicated a change in conscious percept, and also consistent with several previous studies of memory and attention (Ward 2003), we speculated that both intra- and interregional gamma-band synchronization could be modulated by the phase of theta-band oscillations. To check this, we sorted gamma amplitudes by the theta phases in the same brain regions and computed mean gamma amplitudes for each of sixty 0.105-radian-wide bins of theta phase. We did the same thing for the PLVs between regions in the various pairs of active regions and also determined the relationship between theta phases for the regions in each pair. Figure 8 displays some of the results of this analysis. Both gamma amplitude (local synchronization of gamma oscillations) and interregional phase locking in the gamma band were modulated by theta phase. Moreover, theta phases in all of the various region pairs were locked with each other, although they were not in phase, indicating that although there seems to be no single overarching theta-frequency rhythm in the brain, the theta oscillations generated by various functionally distinct regions are relatively tightly phase locked. Theta oscillations do indeed seem to define the rhythm of consciousness, and the gamma-band oscillations modulated by these phase-locked theta rhythms are very good candidates for the neural correlates of primary consciousness, given that they are associated closely with changes in consciousness in the absence of any corresponding stimulus changes.

4 Dynamic Core of Consciousness

The work discussed above deeply implicates synchronized neural activity in the implementation of attention and consciousness. Tononi and Edelman (1998) proposed that consciousness, in particular, is created by a dynamic core of synchronous neural activity that simultaneously integrates diverse information processed by the brain and also differentiates the current conscious state from a myriad of possible

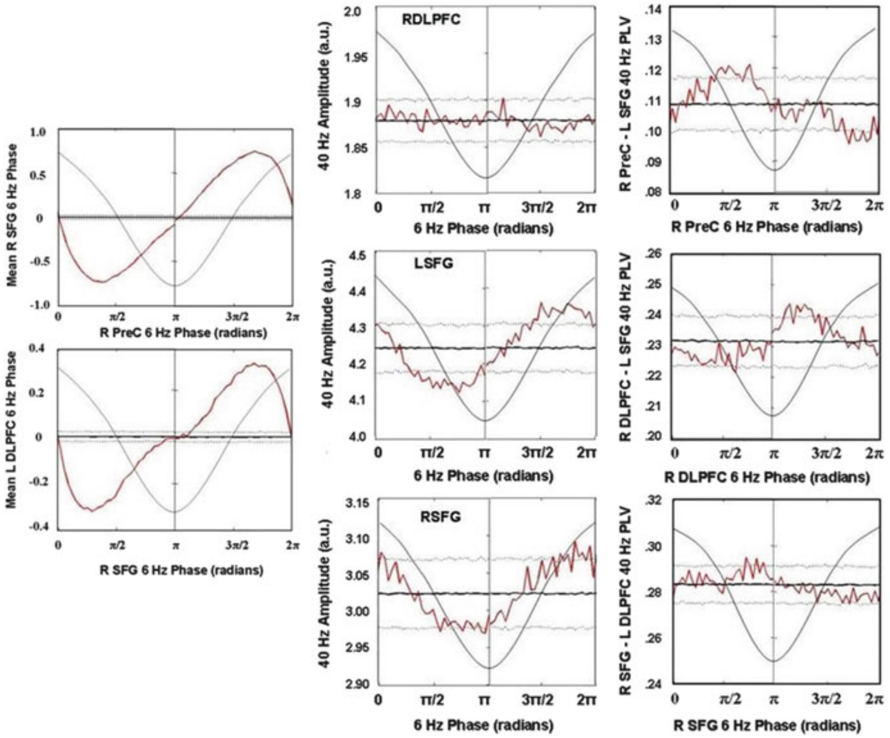

Fig. 8 *Left*: *Red lines* indicate relationship between theta phases in indicated active regions in stable epochs 1000 ms in duration terminated by button press signaling percept switch. *Middle*: *Red lines* indicate relationship between gamma amplitude in indicated region and theta phase in that region. *Right*: *Red lines* indicate relationship between gamma phase locking value (PLV) and theta phase in the indicated regions. In all panels, *thick black lines* indicate the means of the surrogate distributions, and the parallel lines of *light black dots* indicate the 2.5th and 97.5th percentiles of those distributions. Theta phase is relative to a cosine wave, one cycle of which is represented by the *thin black lines*. Reprinted with permission from Doesburg et al. (2009b)

other states. I have proposed also that the thalamus of the brain plays a particularly significant role in the creation, maintenance, and experiential locus of this dynamic core (Ward 2004, 2011). In my theory, the dynamic core is implemented in the higher-order nuclei of the thalamus (which receive no direct sensory input and are dominated by matrix cells; Jones 2001), where the neural activity directly giving rise to primary consciousness takes place as a consequence of their receiving and integrating the results of cortical computations. The dynamic core arises from inhibitory control over the synchronization of the activities of the various higher-order nuclei exerted by the nucleus reticularis, where lateral inhibitory competition among these nuclei takes place. Synchronization among activities in a subset of relevant nuclei willy-nilly synchronizes activity in the cortical areas to which they are closely and reciprocally connected, allowing them to communicate their contents to each other in a global workspace (e.g., Baars 1997; Dehaene and Naccache 2001). This proposal is consistent with evidence and models indicating that the dynamic core is implemented by cortico–thalamic loops (e.g., Lumer et al. 1997; Llinás et al. 1998). This process has a dynamic that is revealed by the pattern of cortical synchronization detailed earlier here and in other work (e.g., Supp et al. 2007).

5 Implications for the Global Workspace

The research and ideas discussed above have several implications for the global workspace model of consciousness (Baars 1997; Dehaene and Naccache 2001). The first is that the dynamic core of consciousness constitutes the global workspace. Its integrative aspect implements communication between various specialized brain regions, allowing the results of their computations to interact and giving rise to a general, context-sensitive understanding of the organism's current situation in the world relative to its current goals. The dynamic core, and thus the global workspace, is established by synchronization between various active processing modules mediated by the thalamic dynamic core. An alternative and possibly less controversial possibility is that the dynamic core is established by mutually inhibitory competition among active brain regions, either directly or mediated by thalamic areas such as the pulvinar nucleus, which contains a salience map, and by parietal and frontal areas, which mediate attentional control, assess value and goal state, and so forth.

What mechanisms are involved in establishing these transient networks of brain regions (processing coalitions)? It is highly plausible that these are established by synchronization of low-frequency oscillations, probably in the theta–alpha range, among a subset of active regions. I discussed evidence of such low-frequency synchronization in two different cognitive processes, attention and switching of conscious percepts in binocular rivalry. Others have discussed similar results (e.g., von Stein and Sarnthein 2000). Higher frequency synchronization, especially in the gamma band, seems to play the role of establishing transient information exchange between processing areas in necessary temporal sequences. Of course, it also probably plays other roles as well. For example, there is evidence that gamma oscillations in the amygdala of the cat can directly drive similar oscillations in the striatum (adjacent to the amygdala), thereby promoting neural plasticity and learning (Popescu et al. 2009). This kind of communication is medium range between functionally and anatomically distinct brain regions that are, nonetheless, nearest neighbors and probably consists of synaptic modulatory input. And as mentioned in Sect. 1, synchronized neural oscillations could also function in information exchange via multiplexing (Akam and Kullman 2014). Thus, there are diverse roles for neural oscillations in the various frequency ranges, and these are probably task dependent.

Acknowledgement This chapter and much of the research described were sponsored by Discovery Grant A9958 from the Natural Sciences and Engineering Research Council (NSERC) of Canada. I thank the coauthors of the various papers emanating from the laboratories of myself and my collaborators whose results I describe here for their vital contributions to this research program.

References

Akam T, Kullman DM (2014) Oscillatory multiplexing of population codes for selective communication in the mammalian brain. Nat Rev Neurosci 15:111–122

Aru J, Aru J, Priesemann V, Wibral M, Lana L, Pipa G, Singer W, Vicente R (2015) Untangling cross-frequency coupling in neuroscience. Curr Opin Neurobiol 31:51–61

Azouz R, Gray CM (2000) Dynamic spike threshold reveals a mechanism for synaptic coincidence detection in cortical neurons in vivo. Proc Natl Acad Sci USA 97:8110–8115

Baars BJ (1997) In the theatre of consciousness. J Conscious Stud 4(4):521–535

Bastos AM, Vezoli J, Fries P (2015) Communication through coherence with inter-areal delays. Curr Opin Neurobiol 31:173–180

Bedo N, Ribary U, Ward LM (2014) Fast dynamics of cortical effective connectivity during word reading. PLoS One 9(2), e88940 (1–13)

Belin P, Zatorre RJ, Lafaille P, Ahad P, Pike B (2000) Voice-selective areas in human auditory cortex. Nature 403:309–312

Brunel N, Hakim V (1999) Fast global oscillations in networks of integrate-and-fire neurons with low firing rates. Neural Comput 11:1621–1671

Buzsáki G (2006) Rhythms of the brain. Oxford University Press, New York

Buzsáki G, Schomberg EW (2015) What does gamma coherence tell us about inter-regional neural communication? Nat Neurosci 18:1–7

Buzsáki G, Wang XJ (2012) Mechanisms of gamma oscillations. Annu Rev Neurosci 35:203–225

Canolty RT, Knight RT (2010) The functional role of cross-frequency coupling. Trends Cogn Sci 14:506–515

Canolty RT, Edwards E, Dalal SS, Soltani M, Nagarajan SS, Kirsch HE, Berger MS, Barbaro NM, Knight RT (2006) High gamma power is phase-locked to theta oscillations in human neocortex. Science 313:1626

Corbetta M, Shulman GL (2002) Control of goal-driven and stimulus-driven attention in the brain. Nat Rev Neurosci 3:201–215

Corbetta M, Patel G, Shulman GL (2008) The reorienting system of the human brain: from environment to theory of mind. Neuron 58:308–324

Cosmelli D, David O, Lachaux JP, Martinerie J, Garnero L et al (2004) Waves of consciousness: ongoing cortical patterns during binocular rivalry. Neuroimage 23:128–140

Dehaene S, Cohen L (2011) The unique role of the visual word form area in reading. Trends Cogn Sci 15:254–262

Dehaene S, Naccache J (2001) Towards a cognitive neuroscience of consciousness: basic evidence and a workspace framework. Cognition 79:1–37

Doesburg SM, Ward LM (2007) Long-distance alpha-band MEG synchronization maintains selective visual attention. Int Congr Ser 1300:551–554

Doesburg SM, Ward LM (2009) Synchronization between sources: emerging methods for understanding large-scale functional networks in the human brain. In: Perez-Velazquez J-L, Wennberg R (eds) Coordinated activity in the brain. Springer, New York, pp 25–42

Doesburg SM, Kitajo K, Ward LM (2005) Increased gamma-band synchrony precedes switching of conscious perceptual objects in binocular rivalry. Neuroreport 2:229–239

Doesburg SM, Herdman A, Ward LM (2007) MEG reveals synchronous neural network for visuospatial attention. Poster presented at CNS Meeting, New York City

Doesburg SM, Roggeveen AB, Kitajo K, Ward LM (2008) Large-scale gamma-band phase synchronization and selective attention. Cereb Cortex 18(2):386–396. doi:10.1093/cercor/bhm073

Doesburg SM, Green JJ, McDonald JJ, Ward LM (2009a) From local inhibition to long-range integration: a functional dissociation of alpha-band synchronization across cortical scales in visuospatial attention. Brain Res 1303C:97–110. doi:10.1016/j.brainres.2009.09.069

Doesburg SM, Green JJ, McDonald JJ, Ward LM (2009b) Rhythms of consciousness: binocular rivalry reveals large-scale oscillatory network dynamics mediating visual perception. PLoS One 7, e6142 (1–14)

Doesburg SM, Green JJ, McDonald JJ, Ward LM (2012) Theta modulation of inter-regional gamma synchronization during auditory attention control. Brain Res 1431:77–85

Doesburg SM, Bedo N, Ward LM (2016) Top-down alpha oscillatory network interactions during visuospatial attention orienting. NeuroImage 132:512–519

Drewes AM, Sami SAK, Dimcevski G, Nielsen KD, Funch-Jensen P, Valeriani M, Arendt-Nielsen L (2006) Cerebral processing of painful oesophageal stimulation: a study based on independent component analysis of the EEG. Gut 55:619–629

Fries P (2005) A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. Trends Cogn Sci 9:474–480

Fries P, Roelfsema PR, Engel AK, Königl P, Singer W (1997) Synchronization of oscillatory responses in visual cortex correlates with perception in interocular rivalry. Proc Natl Acad Sci USA 94:12699–12704

Green JJ, McDonald JJ (2008) Electrical neuroimaging reveals timing of attentional control activity in human brain. PLoS Biol 6(4), e81

Green JJ, McDonald JJ (2009) A practical guide to beamformer source reconstruction for EEG. In: Handy TC (ed) Brain signal analysis: advances in neuroelectric and neuromagnetic methods. The MIT Press, Cambridge, MA, pp 79–98

Green JJ, Doesburg SM, Ward LM, McDonald JJ (2011) Electrical neuroimaging of voluntary audio-spatial attention: evidence for a supramodal attention control network. J Neurosci 31:3560–3564

Greenwood PE, McDonnell MD, Ward LM (2015) Dynamics of gamma bursts in local field potentials. Neural Comput 27:74–103

Gregoriou GG, Paneria S, Sapountzis P (2015) Oscillatory synchrony as a mechanism of attentional processing. Brain Res 1626:165–182

Gross J, Schmitz F, Schnitzler I, Kessler K, Shapiro K et al (2004) Modulation of long-range neural synchrony reflects temporal limitations of visual attention in humans. Proc Natl Acad Sci USA 101:13050–13055

Grossberg S (2000) The complementary brain: unifying brain dynamics and modularity. Trends Cogn Sci 4:233–246

Jones EG (2001) The thalamic matrix and thalamocortical synchrony. Trends Neurosci 24:595–601

Kang K, Shelley M, Henrie JA, Shapley R (2010) LFP spectral peaks in V1 cortex: network resonance and cortico-cortical feedback. J Comput Neurosci 29:495–507

Kanwisher N (2006) What's in a face? Science 311:617–618

Koch C, Tsuchiya N (2006) Attention and consciousness: two distinct brain processes. Trends Cogn Sci 11:16–22

Lamme VAF (2003) Why visual attention and awareness are different. Trends Cogn Sci 7:12–18

Lamme VAF, Roelfsema PR (2000) The distinct modes of vision offered by feedforward and recurrent processing. Trends Neurosci 23:571–579

Llinás R, Ribary U, Contreras D, Pedroarena C (1998) The neuronal basis for consciousness. Philos Trans R Soc London Ser B 353:1841–1849

Logothetis N, Schall JD (1989) Neuronal correlates of subjective visual perception. Science 245:761–763

Lumer ED, Edelman GM, Tononi G (1997) Neural dynamics in a model of the thalamocortical system. I. Layers, loops and the emergence of fast synchronous rhythms. Cereb Cortex 7:207–227

McIntosh AR (2000) Towards a network theory of cognition. Neural Netw 13:861–870

Niebur E, Hsiao SS, Johnson KO (2002) Synchrony: a neuronal mechanism for attentional selection? Curr Opin Neurobiol 12:190–194

Palva S, Palva JM (2007) New vistas for alpha-frequency band oscillations. Trends Neurosci 30:150–158

Pessoa L (2014) Understanding brain networks and brain organization. Phys Life Rev 11:400–435

Popescu AT, Popa D, Paré D (2009) Coherent gamma oscillations couple the amygdala and striatum during learning. Nat Neurosci 12:801–807

Rolls ET, Treves A (2011) The neuronal encoding of information in the brain. Prog Neurobiol 95:448–490

Salinas E, Sejnowski TJ (2001) Correlated neuronal activity and the flow of neural information. Nat Rev Neurosci 2:539–550

Scherg M, Ille N, Bornfleth H, Berg P (2002) Advanced tools for digital EEG review: virtual source montages, whole-head mapping, correlation, and phase analysis. J Clin Neurophysiol 19:91–112

Simons DJ, Rensink RA (2005) Change blindness: past present and future. Trends Cogn Sci 9:16–20

Somers D, Kopell N (1993) Rapid synchrony through fast threshold modulation. Biol Cybern 68:393–407

Srinivasan R, Russell DP, Edelman GM, Tononi G (1999) Increased synchronization of neuromagnetic responses during conscious perception. J Neurosci 19:5435–5448

Supp GG, Schlögl A, Trujillo-Barreto N, Müller M, Gruber T (2007) Directed cortical information flow during human object recognition: analyzing induced EEG gamma-band responses in brain's source space. PLoS One 2(8), e648

Taylor JG (2007) CODAM model: through attention to consciousness. Scholarpedia 2(11):1598

Tononi G, Edelman GM (1998) Consciousness and complexity. Science 282:1846–1851

Varela F, Lachaux JP, Rodriguez E, Martinerie J (2001) The brainweb: phase synchronization and large-scale integration. Nat Rev Neurosci 2:229–239

Volgushev M, Chistiakova M, Singer W (1998) Modification of discharge patterns of neocortical neurons by induced oscillations of the membrane potential. Neuroscience 83:15–25

von Stein A, Sarnthein J (2000) Different frequencies for different scales of cortical integration: from local gamma to long range alpha/theta synchronization. Int J Psychophysiol 38:301–313

Ward LM (2003) Synchronous neural oscillations and cognitive processes. Trends Cogn Sci 17:553–559

Ward LM (2004) Oscillations and synchrony in cognition. In: Jirsa V, Kelso JAS (eds) Coordination dynamics: issues and trends. Springer, New York, pp 217–242

Ward LM (2011) The thalamic dynamic core theory of conscious experience. Conscious Cogn 20:464–486

Ward LM, Doesburg SM (2009) Synchronization analysis in EEG and MEG. In: Handy TC (ed) Brain signal analysis: advances in neuroelectric and neuromagnetic methods. MIT Press, Cambridge, MA, pp 171–204

Wilson HR, Cowan JD (1972) Excitatory and inhibitory interactions in localized populations of model neurons. Biophys J 12:1–24

Worden MS, Foxe JJ, Wang N, Simpson GV (2000) Anticipatory biasing of visuospatial attention indexed by retinotopically specific α-band electroencephalography increases over occipital cortex. J Neurosci 20(63):1–6

Wright RD, Ward LM (2008) Orienting of attention. Oxford University Press, New York

The Role of Local and Large-Scale Neuronal Synchronization in Human Cognition

Satu Palva and J. Matias Palva

1 Inter-Areal Synchronization Coordinates Anatomically Distributed Processing in Local Neuronal Networks

Human perceptual, cognitive, and motor functions are based on neuronal activity distributed across many brain areas. For example, in the visual modality, neuronal feature representations of peripheral sensory information are constructed in a simple-to-complex manner in a network of visual cortex areas with both parallel and hierarchical organization. Primary sensory cortices process simple sensory information, and the progressively higher-level sensory and associative cortices construct higher-level object representations and analyze their identities (Grill-Spector and Malach 2004; Leaver and Rauschecker 2010; Rauschecker and Scott 2009; Riesenhuber and Poggio 2002). Like sensory processing, also core cognitive functions such as attention, working memory (WM), and awareness arise from distributed neuronal activity. These functions largely emerge in a network comprising posterior parietal cortex (PPC), temporal cortex (TC), and prefrontal cortex (PFC) (Corbetta and Shulman 2002; Kastner and Ungerleider 2000; Marois et al. 2004; Prabhakaran et al. 2000; Todd and Marois 2004).

For identifying the systems-level mechanisms underlying human cognitive functions, the crucial challenge is to understand what mechanisms coordinate the communication and integration of the neuronal processing in the distributed cortical networks and among the set of task-relevant brain structures. Because neurons effectively respond to temporally coincident spikes, synchronization endows a neuronal assembly an advantage over a less coherent pool neurons in the competition of engaging their postsynaptic targets (Singer 1999, 2009). Neuronal

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S. Palva (ed.), *Multimodal Oscillation-based Connectivity Theory*,
DOI 10.1007/978-3-319-32265-0_4

synchronization, i.e., millisecond-range spike-time correlations, may hence be a mechanism for the integration of anatomically distributed processing, e.g., for the binding of sensory features (Konig et al. 1996; Singer 1999). Moreover, neuronal synchronization is often accompanied by neuronal oscillations and because oscillations directly indicate rhythmic neuronal excitability fluctuations (Pastor et al. 2002; Schroeder and Lakatos 2009), spiking responses to presynaptic inputs and synchronization are facilitated during the high-excitability phases of neuronal oscillations compared to their low-excitability phases. Coupling of neuronal oscillations with an optimal phase difference thus promotes communication between the assemblies, while the opposite phase difference suppresses it (Fries 2015).

A number of studies from cat and monkey visual cortices have shown that stimulus-related neuronal activity is synchronized in the gamma-frequency band (30–80 Hz) when the stimulus features are in line with Gestalt binding criteria, such as continuity, similarity, colinearity, and common motion and hence when stimulus is likely to signify a coherent sensory object (Singer 1999). Invasive local field potential (LFP) and multiunit (MUA) recordings from invasive animal physiology also show that the strength of gamma-band synchronization is positively correlated with attentional (Bosman et al. 2012; Buschman and Miller 2007; Womelsdorf et al. 2007) and working memory (WM) (Buschman et al. 2011; Salazar et al. 2012; Siegel et al. 2009) task demands. Hence, inter-areal synchronization appears to play a functional role in perception and cognition, which is in line with the hypothesis that synchronization underlies the integration and coordination of distributed neuronal processing.

1.1 Challenges in the Analyses of Synchrony from Noninvasive MEG/EEG Data

In both humans and animal models, invasive recordings yield only a sparse coverage of the task-relevant brain areas and are hence limited in the completeness of the information they yield. Human cognitive operations appear invariably to emerge from collective neuronal activity in widely distributed large-scale networks. To assess whether neuronal synchronization coordinates the scattered neuronal processing underlying perceptual, attentional, and WM functions in humans, network synchronization must be measured noninvasively. Electro- and magnetoencephalography (EEG and MEG) can be acquired during cognitive tasks and yield millisecond-accurate electrophysiological signals from cortical sources. As an engineering or mathematical challenge, the estimation of synchronization per se is straightforward and synchronization among EEG or MEG sensors has indeed been observed in a number of studies addressing the neuronal correlates of sensory awareness (Melloni et al. 2007; Rodriguez et al. 1999), attention (Doesburg et al. 2009), and WM (Freunberger et al. 2008; Kitzbichler et al. 2011; Sauseng et al. 2005). Large-scale synchronization also characterizes higher-level cognitive operations such as mental arithmetic with numbers maintained in WM (Palva et al. 2005a). These studies are thus supportive of the notion that synchronization plays a role in the coordination of distributed neuronal processing also in humans. However, sensor-to-sensor interaction analyses are greatly confounded by volume conduction and signal mixing and by many other factors such as changes in source amplitudes or topographies [see (Palva and Palva 2012; Schoffelen and Gross 2009) and Siebenhühner et al. (2016)]. Hence, the utility of sensor–sensor interaction analyses is, at most, very limited in the study of cortical synchronized networks (Palva and Palva 2012 and Siebenhühner et al. 2016). Crucially, sensor-level analyses shed no light on the anatomical structures wherefrom the synchronized oscillations originate and hence leave their functional significance in task performance unclear. To overcome these issues, both local and inter-areal synchronization in EEG and MEG recordings must be estimated from source-localized data. Several methods such as beamformers (Gross et al. 2001), low resolution electromagnetic tomography (LORETA) (Pascual-Marqui et al. 2011), and minimum-norm estimation (MNE) (Hamalainen and Ilmoniemi 1994; Lin et al. 2006) have been developed for source reconstruction. Indeed, a large body of source reconstruction-based MEG studies have shown that the amplitudes of local cortical oscillations, which reflect synchronization in the local neuronal populations, are correlated with attention (Händel et al. 2011; Rouhinen et al. 2013; Zumer et al. 2014), perception (Haegens et al. 2011; Hirvonen and Palva 2016), and WM (Bonnefond and Jensen 2012; Honkanen et al. 2015; Palva et al. 2011; Roux et al. 2012) and hence with many distinct cognitive functions.

2 Does Local Synchrony Reflect Sensory Perception?

In line with invasive animal data, EEG sensor-level analyses have shown that stimulus-induced gamma oscillations characterize processing of visual stimuli (Tallon-Baudry et al. 1996, 1997) and that early gamma oscillations that are phase locked to the stimulus onset reflect sensory representations for well-known auditory stimuli such as speech (Palva et al. 2002) and chords (Pallesen et al. 2015). Hence, in humans, the early evoked gamma oscillations could reflect memory matching of sensory stimuli to feed-forward templates (Cooper et al. 2006) and initial processing of sensory information.

From neuronal signals, in addition to oscillation amplitudes, also phase locking to stimulus onset can be measured. Phase locking reflects how well signal is temporally aligned with stimulus onset across trials. Interestingly, we have found that both oscillation amplitude and phase locking to stimulus onset are stronger for chords in musicians compared to nonmusicians (Pallesen et al. 2015). Interestingly, this effect in phase locking was much more robust than that in oscillation amplitudes showing that specifically temporal precision of neuronal activities imposed by neuronal oscillations is facilitated by musical training. These data demonstrate that phase locking of band-limited neuronal oscillations to stimulus onset carries out important computational functions in cognitive task processing, which are also prone to experience-dependent plastic modulations.

Furthermore, sustained phase locking of ongoing neuronal activity to somatosensory stimulus and a transient increase in the strength of oscillation amplitudes predicted also whether weak stimuli presented at the threshold of detection were consciously perceived (Hirvonen and Palva 2016; Palva et al. 2005b) (Fig. 1a–b). Importantly, the phase locking and transient amplitude increases were most robust and sustained from the stimulus onset to the behavioral response in the alpha (8–12 Hz)-frequency band and observed in lateral prefrontal cortex (LPFC), posterior parietal cortex (PPC), as well as in the middle and anterior cingulate structures (Fig. 1c–d), which have in prior functional magnetic resonance imaging (fMRI) studies been found to be positively correlated with conscious sensory perception (Bar et al. 2001; Grill-Spector et al. 2000; Hesselmann and Malach 2011; Hesselmann et al. 2011; Kouider et al. 2007; Polonsky et al. 2000; Sadaghiani et al. 2009, 2010; Tong et al. 1998). These data thus reveal that, similarly to studies in animal models, oscillatory dynamics are correlated with perception. In addition, it is clear that in the human brains, the correlations of oscillatory activities with behavioral performance are concurrently observed in multiple frequency bands.

3 Oscillation Amplitudes in Many Frequencies Are Correlated With Performance in Attention and Memory Tasks

Attention and WM are core cognitive functions that select behaviorally relevant information from amongst irrelevant information and maintain it online for further usage. We have investigated the role of local synchronization, i.e., oscillation amplitude dynamics in coordinating multi-object visual attention and multi-object visual WM demands by using concurrent MEG and EEG recordings (M/EEG) and source localization. Both visual WM and attention have a limited capacity between two and five objects (Cowan 2001; Luck and Vogel 1997, 2013; Zhang and Luck 2008), although some studies suggest that this capacity is dependent on the complexity of objects (Xu and Chun 2006; Xu and Chun 2009). Several theoretical frameworks have been advanced to explain the systems-level neuronal mechanisms determining the individual capacity limitations of these functions as well as on the intertwined relationship of attention and WM (Chun 2011; Cowan 2001; Drew et al. 2012; Luck and Vogel 2013; Tsubomi et al. 2013). We have investigated the role of local and large-scale synchronization in these distinct functions.

In the multi-object visual attention study, the subjects were attending one to four visual objects that were moving around the visual scene. In one of the conditions, subjects were attending all objects in the screen (General attention task) and in the other, only subset of objects while ignoring the others (Selective attention task). From source-localized MEG data, we investigated the correlation of oscillation

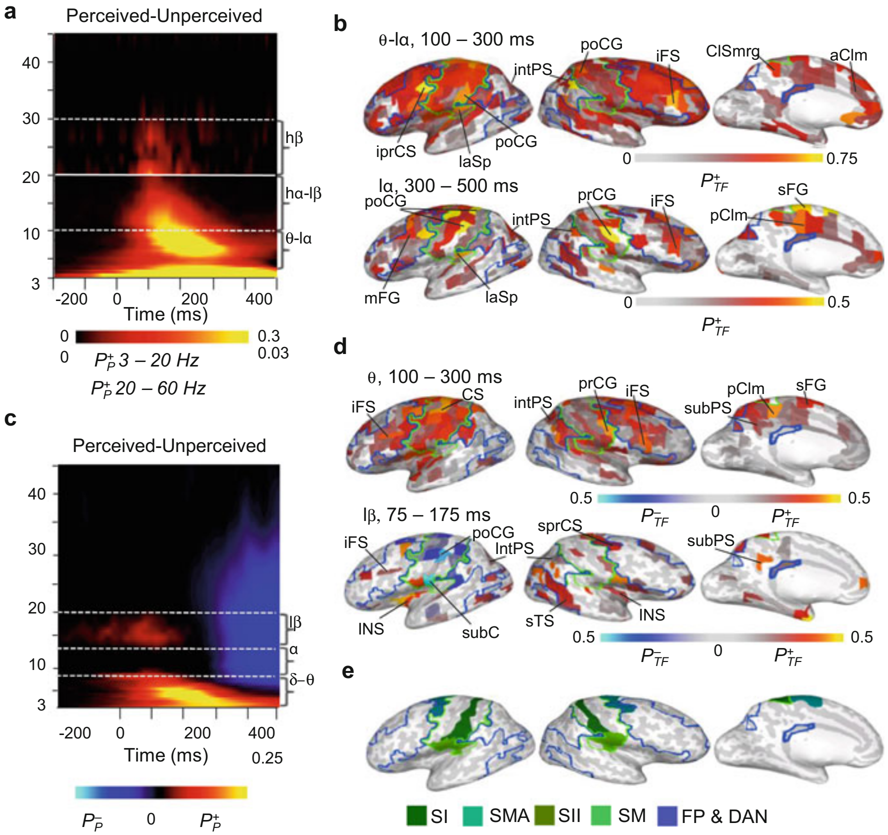

Fig. 1 Conscious somatosensory perception is predicted by strong and stimulus-locked oscillations. (**a**) Time–frequency representation (TFR) shows that neuronal oscillations are more phase locked to perceived than unperceived somatosensory stimuli in all frequency bands between 3 and 30 Hz. Only in the alpha (α, 8–12 Hz) band, phase locking is sustained until behavioral responses at around 400 ms suggesting that alpha-band phase locking is a crucial component of somatosensory perception. (**b**) Phase locking in the theta and/or low alpha bands ($\theta - \mathrm{l}\alpha$, $\mathrm{l}\alpha$) is observed in the somatomotor system (SM) as well as in areas of lateral prefrontal and parietal cortices that belong to fronto-parietal (FP) and dorsal attention (DA) systems. (**c**) TFR of oscillation amplitude modulations shows that perception of weak somatosensory stimuli is correlated with an early increase of theta (θ) and low-beta ($\mathrm{l} - \beta$) band oscillations and a subsequent wide-band amplitude suppression. (**d**) Theta-band amplitude increase is visible in the SM system and in some parcels of the lateral prefrontal and parietal cortices. Although, beta-band amplitude increase is observed in the same brain systems, it is present only in few parcels. (**e**) Template brain defining different brain systems: *SI*, primary somatosensory area; *SII*, secondary somatosensory area; *SM*, somatomotor system; *FP&DAN*, fronto-parietal & dorsal attention network. Modified from ref (Hirvonen and Palva 2016)

amplitudes with the attentional load. These data revealed that the strength of gamma oscillations is increased as a function of attended objects similarly in both conditions and that these load-effects were positively correlated with individual

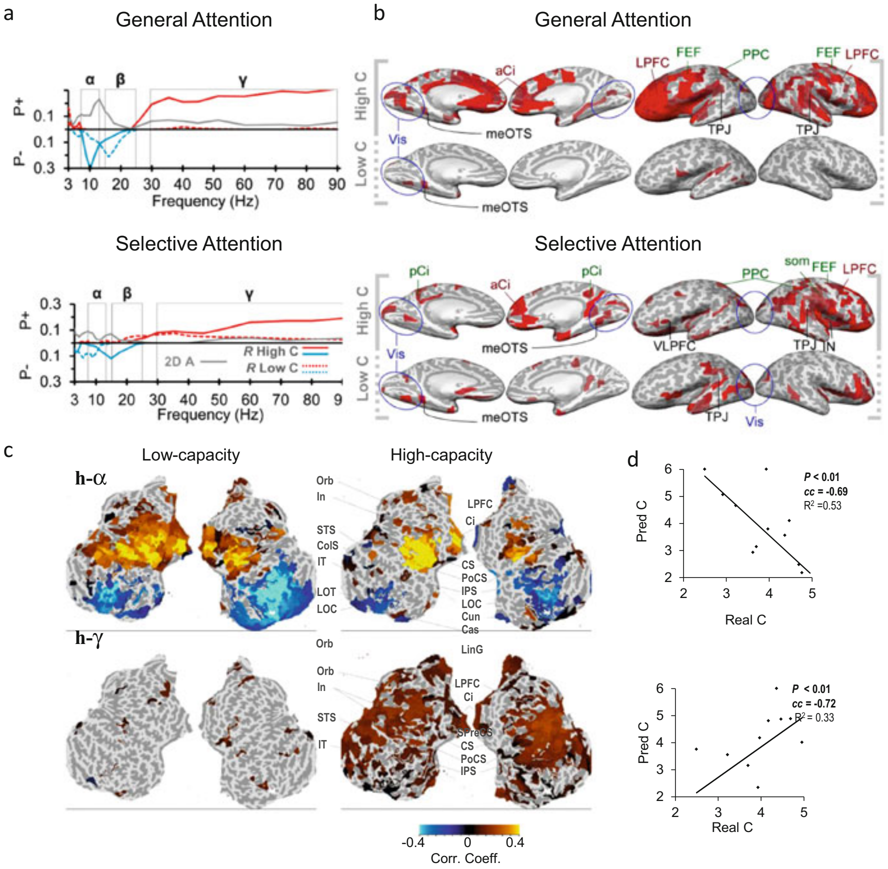

Fig. 2 Visual attention and visual working memory are correlated with enhanced stimulus-induced oscillations in fronto-parietal and visual systems. (**a**) Graphs display a proportion of brain areas in which oscillation amplitudes are positively (P+) or negative (P–) modulated by attentional load as a function of frequency (Hz). Both General attention and Selective attention tasks are associated with load-dependently strengthened gamma oscillations. (**b**) Load-dependent strengthening of gamma oscillations is observed in the frontal, parietal and visual cortical areas. This increase is more wide-spread in the General attention than in the Selective attention task. (**c**) During visual working memory (WM) task, oscillation amplitudes are load-dependently strengthened during the retention period. High-alpha (*h–α*) oscillations are load-dependently strengthened in frontal cortex and sensorimotor areas more in subjects who have low visual WM capacity than in subjects with high capacity. Conversely, high-gamma (*h–γ*) oscillations are strengthened more in subjects with high capacity. Oscillations are displayed on an inflated and flattened cortical surface. (**d**) The load-dependent increase in high *α* and high *γ* band amplitude predicts individual WM capacity limitations. Real WM capacity is displayed in *x*-axis and that predicted by oscillation amplitudes in the *y*-axis. Modified from refs (Palva et al. 2011; Rouhinen et al. 2013)

capacity limitations of visual attention (Fig. 2a) (Rouhinen et al. 2013). The localization of the load dependency of gamma oscillations revealed a network of active areas in the visual cortex but even more so also in frontal and posterior parietal areas that are known to coordinate attention to sensory objects (Corbetta and Shulman 2002; Kastner and Ungerleider 2000) (Fig. 2b). Importantly, this effect was much more pronounced in the General attention task than in the Selective attention task, wherein the effects were more confined. Importantly, subjects with high attentional capacity had much larger load-dependent recruitment of gamma oscillations compared to those with low capacity (Fig. 2b). These findings thus provide evidence for the view of local gamma oscillations coordinating neuronal processing to support attentional functions in task-relevant cortical areas.

We have also used multi-object WM task that was very similar to that of visual attention task, but in which subjects memorized the colors and positions of one to six visual objects. Also, in this case, we analyzed oscillation amplitude modulations from source-localized MEG data. Interestingly, however, local oscillations not only in the gamma- but also in alpha- (8–14 Hz) and beta (14–30 Hz)-frequency bands were load dependently strengthened by the VWM task performance (Palva et al. 2011) (Fig. 2b). Load-dependent modulations in all frequency bands were observed in the frontal cortex but in the beta and gamma bands load-dependent modulations were also observed in visual cortical areas. Yet, similarly to the visual attention task, only the amplitudes of gamma oscillations but not those of other frequencies were positively correlated with individual VWM capacity limits (Fig. 2c). In contrast, also the amplitude of alpha oscillations was correlated with VWM capacity but with an inverse relationship. Subjects with low VWM capacity, hence, recruited more load-dependent alpha oscillations than subjects with high capacity, suggesting that alpha oscillations underlie the recruitment of attentional resources.

Hence, in both visual attention and WM tasks, local gamma oscillations appear to underlie the maintenance of visual information in visual cortical regions. This view is supported by observations of the strength of local gamma oscillations during VWM maintenance being correlated with the maintenance of feature-specific information and specifically increased for such visual objects which require the representation of combinations of features, such as color and location, which are processed in separate functional areas (Honkanen et al. 2015; Tallon-Baudry et al. 1998) (Fig. 3). These data together are also in line with LFP data and support the idea that local gamma synchronization underlies the construction or maintenance of feature-integrated sensory object representations in WM and in the focus of attention.

Visual WM and attention tasks show, however, oscillation amplitude modulations also in lower frequencies. The amplitude of alpha oscillations is strengthened during the performance of both visual (Bonnefond and Jensen 2012; Honkanen et al. 2015; Palva et al. 2011; Park et al. 2014) and auditory (Haegens et al. 2010) WM task. Source localization has revealed that these positive modulations take place in the parietal and frontal cortical areas, while the amplitude of alpha oscillations is suppressed in sensory areas. Taken that the frontal and parietal cortices underlie the attentional and executive control of WM (Linden et al. 2003; Mohr et al. 2006; Munk et al. 2002; Pessoa et al. 2002; Prabhakaran et al. 2000; Rowe et al. 2000; Sakai et al. 2002), the amplitude modulations in these regions likely reflect the attentional control of memorized sensory information.

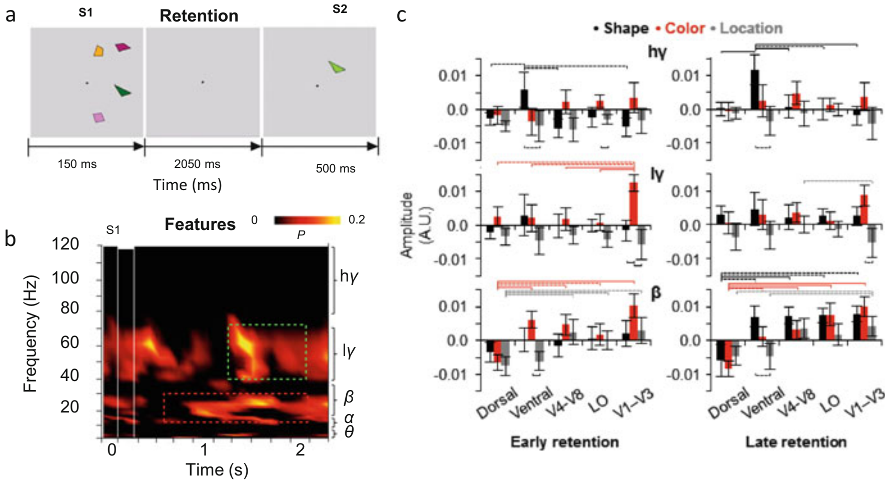

Fig. 3 Gamma oscillation amplitudes are correlated with the features maintained in VWM. (**a**) An example of the visual WM task in which subjects memorized either shape, location, color, or conjunction of color and location information of complex visual objects with geometrical shapes. (**b**) TFR of oscillation amplitudes shows the correlation between the strength of oscillation amplitudes and the maintenance of distinct features and reveals that beta- and gamma-band amplitudes are correlated with the maintenance of distinct features. (**c**) For the maintenance of shape information, high-γ oscillations are strengthened in visual ventral stream areas, while the maintenance of color information is associated with increased β and γ oscillations in early visual areas V1–V3. Modified from ref (Honkanen et al. 2015)

In visual attention tasks, the amplitude of alpha oscillations is also decreased in sensory areas processing the attended sensory information (Lange et al. 2013; Romei et al. 2008; Rouhinen et al. 2013; Thut et al. 2006; Worden et al. 2000). This amplitude decrease in sensory areas is thought to reflect enhanced neuronal excitability that is necessary for efficient information processing. In contrast to WM tasks, the alpha amplitude is not increased in the frontal cortical areas in attention task (Rouhinen et al. 2013), demonstrating that the neuronal oscillations may carry distinct functional roles in attentional control of sensory information in attention and WM. Taken together, these studies reveal functionally significant local synchronization in both alpha- and gamma-frequency bands in perception, attention, and WM functions.

4 Inter-areal Synchronization is Correlated with Task Performance in Humans

In addition to local measure of synchronization reflected in oscillation amplitudes, during the past decade, a growing number of studies have addressed inter-areal synchronization, i.e., phase correlations of neuronal oscillations among brain regions by using MEG or EEG and source modeling. Several studies have estimated the interactions among ~2–9 cortical regions of interest (ROIs) and observed enhanced inter-areal synchrony to correlate with the execution of perceptual and attentional tasks (Gross et al. 2004; Kujala et al. 2007; Kveraga et al. 2011; Lou et al. 2010; Siegel et al. 2008). Gross and colleagues revealed beta-band (14–30 Hz) inter-areal synchronization to be correlated with attention in an attention-blink paradigm where visual stimuli were presented at a rapid rate and the subjects' task was to detect target letters presented randomly in the stimulus stream (Gross et al. 2004). Also gamma-band synchronization between frontal and parietal regions of interest has been observed to be correlated with spatial visual attention (Siegel et al. 2008), which is in line with prior observations of a relationship between gamma synchrony and the allocation of spatial attention in monkey LFP recordings (Bosman et al. 2012; Buschman and Miller 2007; Womelsdorf et al. 2007). MEG studies using source reconstruction have also reported alpha- and beta-band inter-areal synchronization to be correlated with behavioral contextual associations (Kveraga et al. 2011) and sensorimotor integration (Pollok et al. 2005, 2009). A recent study also revealed that alpha-band synchronization between the inferior frontal gyrus and somatosensory areas was enhanced for somatosensory stimuli that were to be ignored, which suggested that the role of long-range alpha-band synchrony is to inhibit the processing of to be ignored somatosensory stimuli (Sacchet et al. 2015).

However, ROI-based studies do not reveal whether the observed synchronization is a robust component in task processing or whether synchronization among other frequency bands or between other brain areas than that were investigated could show significant task-relevant modulations. Specifically, the contribution of artifactual and spurious synchronization (see chapter "Measuring Large-Scale Synchronization with Human MEG and EEG: Challenges and Solutions") confounds ROI-based synchrony analyses. In contrast to ROI-based analyses of synchronization, data-driven analyses of synchrony mapping all interregional interactions are much less confounded by these issues. However, only a handful of studies (see Palva and Palva 2012), so far, have used the data-driven approach for assessing inter-areal synchronization. One of the first attempts to map all-to-all inter-areal synchrony was made by David and colleagues, who used MNE-based source modeling and data-driven analyses together with a visual task (David et al. 2002). Later, Kujala and colleagues revealed large-scale cortical networks during reading (Kujala et al. 2007) and showed that reading is associated with enhanced coherence in a network comprising of the cerebellum, PFC, temporal cortical regions, and orbital structures, while comprehension strengthened coherence among cerebellar and temporal regions.

Our study mapped cortex-wide networks of inter-areal synchronization using a novel data-driven all-to-all analysis of source-reconstructed MEG data. We characterized statistically significant inter-areal connections of synchrony and represented these data as undirected graphs where cortical areas were the vertices and interactions the edges (Bullmore and Sporns 2009; Rubinov and Sporns 2009). We observed that prominent load-dependent inter-areal synchronization in alpha

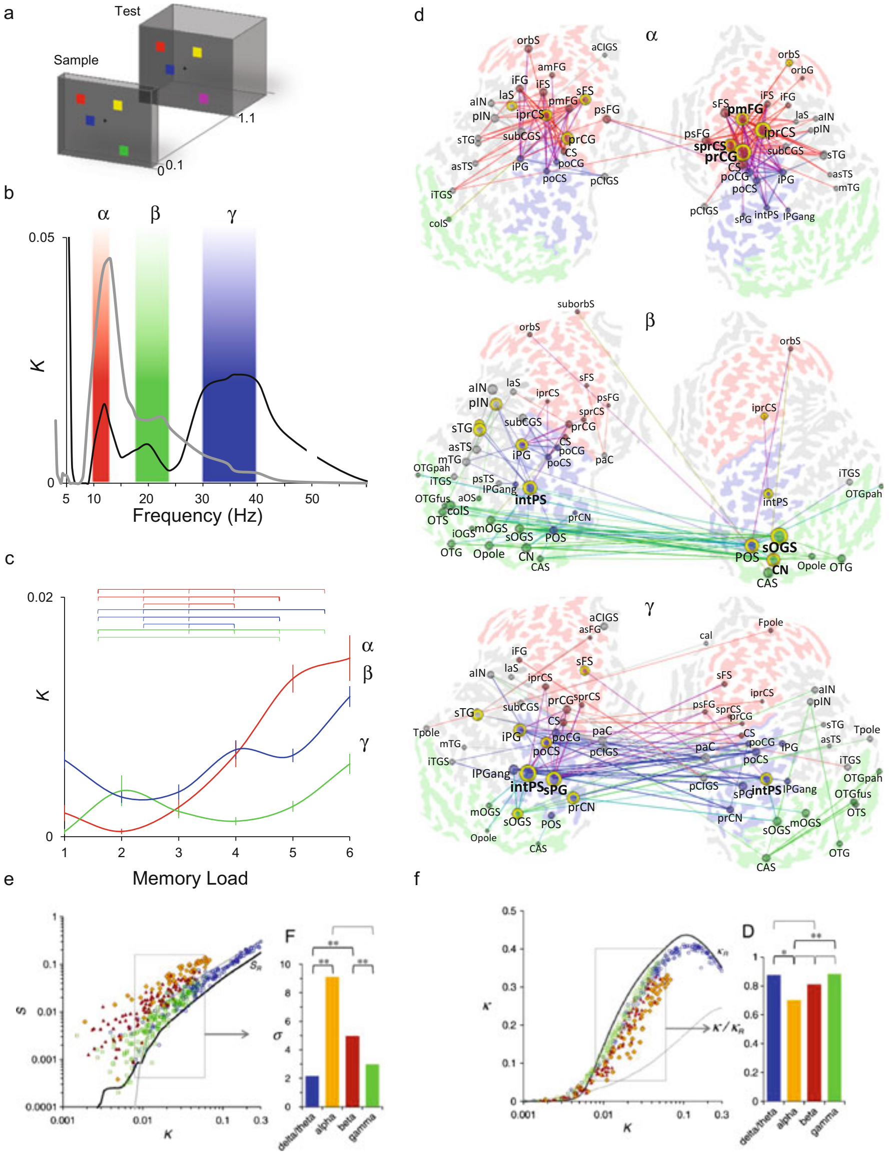

Fig. 4 Visual working memory maintenance is associated with concurrent alpha-, beta-, and gamma-band synchronization in distinct cortical networks. (**a**) An example of the visual WM task. (**b**) Inter-areal synchrony is concurrently observed in alpha, beta, and gamma bands during visual WM retention period. Frequency is displayed on an *x*-axis and connection density *K* that is the proportion of synchronized connections from all possible connections in the *y*-axis. (**c**) Memory load-dependent increase of synchrony during the WM retention period. (**d**) Graphs displaying *α*-, *β*-, and *γ*-band networks show that these networks are localized into distinct cortical structures. Graphs are displayed in inflated and flattened cortical surface. Color of the surface indicates different cortical parts: *green* = occipital cortex, *blue* = parietal cortex, *red* = frontal cortex, *gray* = other regions. (**e**) Small-worldness (*S*) is larger for alpha-band network compared to those of other frequencies. (**f**) Global efficiency (*K*) is smaller in the alpha band compared to other frequency bands. Modified from refs (Palva et al. 2010a, b)

(8–14 Hz), beta (14–30 Hz), and gamma bands characterized the visual WM retention period (Palva et al. 2010a, b) (Fig. 4a). These results were in line with analyses of oscillation amplitudes and suggested that beta- and gamma-band synchronization among visual regions could indeed underlie the maintenance of object representations, i.e., the contents of WM, while the strengthened synchrony concurrently in alpha, beta, and gamma bands among fronto-parietal regions would be well positioned to support the coordination of attention and the "context" of WM. As central evidence for large-scale synchronization to be functionally significant, we found that interindividual variability in the VWM capacity was predicted by the strength of alpha- and beta-band phase synchronization in networks having the bilateral intraparietal sulci as most central hubs (Fig. 4b). This finding fits prior fMRI studies well because the intraparietal sulci are central in mediating visual attention (Kastner and Ungerleider 2000; Reynolds and Chelazzi 2004) and, importantly, observed in prior fMRI studies to be key areas in limiting the VWM capacity (Todd and Marois 2004). These data, therefore, showed that phase synchrony in large-scale networks is a behaviorally relevant phenomenon and could conceivably regulate the collective neuronal processing in visual and frontal regions to support WM functions. Our recent data show that concurrent synchrony in alpha-, beta-, and gamma-frequency bands characterizes also sustained multi-object attention (unpublished observations). Hence, similar large-scale patterns of synchronization may underlie the coordination of attention and WM and their interaction with sensory systems.

5 The Topology of Synchronized Cortical Networks

Not only the specific anatomical areas connected in synchronized networks but also their topology is thought to be important factor in understanding how network synchronization can efficiently mediate the integration and coordination of neuronal processing. The topological structure of synchronized networks can be characterized with graph theoretical network metrics (Bullmore and Sporns 2009) that yield quantitative insight into the network properties at three levels: edges, vertices, and the entire graph. At the edge and vertex levels, network metrics can be used to extract topologically important information from a bulk of connectivity data. Vertex centrality measures, such as degree and betweenness centrality, reveal which nodes are most important for network integrity in terms of having many connections or being a waypoint for many of the shortest paths in the graph, respectively. At the graph level, several metrics can be used to characterize the efficiency of information transmission within the graph. Brain connectivity graphs have dense intra-modular connectivity and less inter-modular connections, which leads to high clustering and short average-path lengths (Bullmore and Sporns 2009) that are the hallmarks of a small-world organization (Watts and Strogatz 1998) which is, in turn, associated with high local and global efficiency in information transmission as well as facilitated parallel processing within hierarchically organized modules (Bassett and Bullmore 2006; Bullmore and Sporns 2009).

Several studies have used signal-space MEG/EEG connectivity analyses to explore the graph properties of inter-areal networks during task execution (Achard et al. 2008; Bassett et al. 2006, 2008, 2009; Kitzbichler et al. 2011; Micheloyannis et al. 2009; Stam 2004) but since the sensor-level synchrony estimates are severely confounded by signal mixing, the level at which these data reflect the real cerebral graph properties remains unknown (Antiqueira et al. 2010). We used M/EEG to assess the topological properties of network synchrony during visual WM retention. We observed that networks in theta, alpha, beta, and gamma bands have memory load-dependent truncated power-law degree distributions, small-worldness, efficiency, and clustering (Palva et al. 2010a, b). Even nearby frequency bands can hence exhibit very different kinds of topologies in task-induced networks (Fig. 4c). Topological properties have also been assessed for resting-state MEG networks (de Pasquale et al. 2015; Rutter et al. 2013), which also exhibit truncated power-law degree distributions but with several shared network hubs across frequencies (Rutter et al. 2013). These results together suggest that task performance changes the network topology, which can be correlated with the efficiency of information processing. These studies pave the way for understanding how global network properties are related to information processing in the brain and changed by task execution. Further studies are, however, needed to reveal the role of network properties in human cognition and behavior.

6 Conclusions

In the past decade, several source reconstruction methods have been advanced to estimate the amplitude and phase dynamics of local cortical oscillations and their roles in cognitive processes. These studies have consistently revealed multiple functional roles for local alpha-, beta-, and gamma-frequency band oscillations in perception and action, but also that the local phase dynamics shape both the pre- and poststimulus neuronal processing. Advancements in recent data-analysis approaches have also begun to elucidate the putative roles of large-scale inter-areal synchronization in human perception, action, and cognition. In comparison to fMRI-based functional connectivity analyses, MEG network synchrony analyses have the potential to reveal a brain dynamic connectome that is much more complex and information rich because of the time and frequency dimensions available in MEG and EEG data. However, future studies are required to reveal both the anatomical and topological network structures of synchronized cortical networks and hence their role in cortical information processing.

References

Achard S, Bassett DS, Meyer-Lindenberg A, Bullmore E (2008) Fractal connectivity of long-memory networks. Phys Rev E Stat Nonlin Soft Matter Phys 77:036104

Antiqueira L, Rodrigues FA, van Wijk BCM, Costa LF, Daffertshofer A (2010) Estimating complex cortical networks via surface recordings—a critical note. Neuroimage 53:439–449

Bar M, Tootell RB, Schacter DL, Greve DN, Fischl B, Mendola JD, Rosen BR, Dale AM (2001) Cortical mechanisms specific to explicit visual object recognition. Neuron 29:529–535

Bassett DS, Bullmore E (2006) Small-world brain networks. Neuroscientist 12:512–523

Bassett DS, Meyer-Lindenberg A, Achard S, Duke T, Bullmore E (2006) Adaptive reconfiguration of fractal small-world human brain functional networks. Proc Natl Acad Sci USA 103:19518–19523

Bassett DS, Bullmore E, Verchinski BA, Mattay VS, Weinberger DR, Meyer-Lindenberg A (2008) Hierarchical organization of human cortical networks in health and schizophrenia. J Neurosci 28:9239–9248

Bassett DS, Bullmore ET, Meyer-Lindenberg A, Apud JA, Weinberger DR, Coppola R (2009) Cognitive fitness of cost-efficient brain functional networks. Proc Natl Acad Sci USA 106 (28):11747–11752

Bonnefond M, Jensen O (2012) Alpha oscillations serve to protect working memory maintenance against anticipated distracters. Curr Biol 22:1969–1974

Bosman CA, Schoffelen JM, Brunet N, Oostenveld R, Bastos AM, Womelsdorf T, Rubehn B, Stieglitz T, De Weerd P, Fries P (2012) Attentional stimulus selection through selective synchronization between monkey visual areas. Neuron 75:875–888

Bullmore E, Sporns O (2009) Complex brain networks: graph theoretical analysis of structural and functional systems. Nat Rev Neurosci 10:186–198

Buschman TJ, Miller EK (2007) Top-down versus bottom-up control of attention in the prefrontal and posterior parietal cortices. Science 315:1860–1862

Buschman TJ, Siegel M, Roy JE, Miller EK (2011) Neural substrates of cognitive capacity limitations. Proc Natl Acad Sci USA 108:11252–11255

Chun MM (2011) Visual working memory as visual attention sustained internally over time. Neuropsychologia 49:1407–1409

Cooper NR, Burgess AP, Croft RJ, Gruzelier JH (2006) Investigating evoked and induced electroencephalogram activity in task-related alpha power increases during an internally directed attention task. Neuroreport 17:205–208

Corbetta M, Shulman GL (2002) Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 3:201–215

Cowan N (2001) The magical number 4 in short-term memory: a reconsideration of mental storage capacity. Behav Brain Sci 24:87–114, discussion 114-85

David O, Garnero L, Cosmelli D, Varela FJ (2002) Estimation of neural dynamics from MEG/EEG cortical current density maps: application to the reconstruction of large-scale cortical synchrony. IEEE Trans Biomed Eng 49:975–987

de Pasquale F, Della Penna S, Sporns O, Romani GL, Corbetta M (2015) A dynamic core network and global efficiency in the resting human brain. Cereb Cortex (in press)

Doesburg SM, Green JJ, McDonald JJ, Ward LM (2009) From local inhibition to long-range integration: a functional dissociation of alpha-band synchronization across cortical scales in visuospatial attention. Brain Res 1303:97–110

Drew T, Horowitz TS, Wolfe JM, Vogel EK (2012) Neural measures of dynamic changes in attentive tracking load. J Cogn Neurosci 24:440–450

Freunberger R, Klimesch W, Griesmayr B, Sauseng P, Gruber W (2008) Alpha phase coupling reflects object recognition. Neuroimage 42:928–935

Fries P (2015) Rhythms for cognition: communication through coherence. Neuron 88:220–235

Grill-Spector K, Malach R (2004) The human visual cortex. Annu Rev Neurosci 27:649–677

Grill-Spector K, Kushnir T, Hendler T, Malach R (2000) The dynamics of object-selective activation correlate with recognition performance in humans. Nat Neurosci 3:837–843

Gross J, Kujala J, Hamalainen M, Timmermann L, Schnitzler A, Salmelin R (2001) Dynamic imaging of coherent sources: studying neural interactions in the human brain. Proc Natl Acad Sci USA 98:694–699

Gross J, Schmitz F, Schnitzler I, Kessler K, Shapiro K, Hommel B, Schnitzler A (2004) Modulation of long-range neural synchrony reflects temporal limitations of visual attention in humans. Proc Natl Acad Sci USA 101:13050–13055

Haegens S, Osipova D, Oostenveld R, Jensen O (2010) Somatosensory working memory performance in humans depends on both engagement and disengagement of regions in a distributed network. Hum Brain Mapp 31:26–35

Haegens S, Handel BF, Jensen O (2011) Top-down controlled alpha band activity in somatosensory areas determines behavioral performance in a discrimination task. J Neurosci 31:5197–5204

Hamalainen MS, Ilmoniemi RJ (1994) Interpreting magnetic fields of the brain: minimum norm estimates. Med Biol Eng Comput 32:35–42

Händel BF, Haarmeier T, Jensen O (2011) Alpha oscillations correlate with the successful inhibition of unattended stimuli. J Cogn Neurosci 23:2494–2502

Hesselmann G, Malach R (2011) The link between fMRI-BOLD activation and perceptual awareness is “stream-invariant” in the human visual system. Cereb Cortex 21:2829–2837

Hesselmann G, Hebart M, Malach R (2011) Differential BOLD activity associated with subjective and objective reports during “blindsight” in normal observers. J Neurosci 31:12936–12944

Hirvonen J, Palva S (2016) Cortical localization of phase and amplitude dynamics predicting access to somatosensory awareness. Hum Brain Mapp 37(1):311–326

Honkanen R, Rouhinen S, Wang SH, Palva JM, Palva S (2015) Gamma oscillations underlie the maintenance of feature-specific information and the contents of visual working memory. Cereb Cortex 25:3788–3801

Kastner S, Ungerleider LG (2000) Mechanisms of visual attention in the human cortex. Annu Rev Neurosci 23:315–341

Kitzbichler MG, Henson RN, Smith ML, Nathan PJ, Bullmore ET (2011) Cognitive effort drives workspace configuration of human brain functional networks. J Neurosci 31:8259–8270

Konig P, Engel AK, Singer W (1996) Integrator or coincidence detector? The role of the cortical neuron revisited. Trends Neurosci 19:130–137

Kouider S, Dehaene S, Jobert A, Le Bihan D (2007) Cerebral bases of subliminal and supraliminal priming during reading. Cereb Cortex 17:2019–2029

Kujala J, Pammer K, Cornelissen P, Roebroeck A, Formisano E, Salmelin R (2007) Phase coupling in a cerebro-cerebellar network at 8–13 hz during reading. Cereb Cortex 17:1476–1485

Kveraga K, Ghuman AS, Kassam KS, Aminoff EA, Hamalainen MS, Chaumon M, Bar M (2011) Early onset of neural synchronization in the contextual associations network. Proc Natl Acad Sci USA 108:3389–3394

Lange J, Oostenveld R, Fries P (2013) Reduced occipital alpha power indexes enhanced excitability rather than improved visual perception. J Neurosci 33:3212–3220

Leaver AM, Rauschecker JP (2010) Cortical representation of natural complex sounds: effects of acoustic features and auditory object category. J Neurosci 30:7604–7612

Lin FH, Witzel T, Ahlfors SP, Stufflebeam SM, Belliveau JW, Hamalainen MS (2006) Assessing and improving the spatial accuracy in MEG source localization by depth-weighted minimum-norm estimates. Neuroimage 31:160–171

Linden DE, Bittner RA, Muckli L, Waltz JA, Kriegeskorte N, Goebel R, Singer W, Munk MH (2003) Cortical capacity constraints for visual working memory: dissociation of fMRI load effects in a fronto-parietal network. Neuroimage 20:1518–1530

Lou HC, Gross J, Biermann-Ruben K, Kjaer TW, Schnitzler A (2010) Coherence in consciousness: paralimbic gamma synchrony of self-reference links conscious experiences. Hum Brain Mapp 31:185–192

Luck SJ, Vogel EK (1997) The capacity of visual working memory for features and conjunctions. Nature 390:279–281

Luck SJ, Vogel EK (2013) Visual working memory capacity: from psychophysics and neurobiology to individual differences. Trends Cogn Sci 17:391–400

Marois R, Yi DJ, Chun MM (2004) The neural fate of consciously perceived and missed events in the attentional blink. Neuron 41:465–472

Melloni L, Molina C, Pena M, Torres D, Singer W, Rodriguez E (2007) Synchronization of neural activity across cortical areas correlates with conscious perception. J Neurosci 27:2858–2865

Micheloyannis S, Vourkas M, Tsirka V, Karakonstantaki E, Kanatsouli K, Stam CJ (2009) The influence of ageing on complex brain networks: a graph theoretical analysis. Hum Brain Mapp 30:200–208

Mohr HM, Goebel R, Linden DE (2006) Content- and task-specific dissociations of frontal activity during maintenance and manipulation in visual working memory. J Neurosci 26:4465–4471

Munk MH, Linden DE, Muckli L, Lanfermann H, Zanella FE, Singer W, Goebel R (2002) Distributed cortical systems in visual short-term memory revealed by event-related functional magnetic resonance imaging. Cereb Cortex 12:866–876

Pallesen KJ, Bailey CJ, Brattico E, Gjedde A, Palva JM, Palva S (2015) Experience drives synchronization: the phase and amplitude dynamics of neural oscillations to musical chords are differentially modulated by musical expertise. PLoS One 10, e0134211

Palva S, Palva JM (2012) Discovering oscillatory interaction networks with M/EEG: challenges and breakthroughs. Trends Cogn Sci 16:219–230

Palva S, Palva JM, Shtyrov Y, Kujala T, Ilmoniemi RJ, Kaila K, Naatanen R (2002) Distinct gamma-band evoked responses to speech and non-speech sounds in humans. J Neurosci 22: RC211

Palva JM, Palva S, Kaila K (2005a) Phase synchrony among neuronal oscillations in the human cortex. J Neurosci 25:3962–3972

Palva S, Linkenkaer-Hansen K, Naatanen R, Palva JM (2005b) Early neural correlates of conscious somatosensory perception. J Neurosci 25:5248–5258

Palva JM, Monto S, Kulashekhar S, Palva S (2010a) Neuronal synchrony reveals working memory networks and predicts individual memory capacity. Proc Natl Acad Sci USA 107:7580–7585

Palva S, Monto S, Palva JM (2010b) Graph properties of synchronized cortical networks during visual working memory maintenance. Neuroimage 49:3257–3268

Palva S, Kulashekhar S, Hamalainen M, Palva JM (2011) Localization of cortical phase and amplitude dynamics during visual working memory encoding and retention. J Neurosci 31:5013–5025

Park H, Lee DS, Kang E, Kang H, Hahm J, Kim JS, Chung CK, Jensen O (2014) Blocking of irrelevant memories by posterior alpha activity boosts memory encoding. Hum Brain Mapp 35:3972–3987

Pascual-Marqui RD, Lehmann D, Koukkou M, Kochi K, Anderer P, Saletu B, Tanaka H, Hirata K, John ER, Prichep L, Biscay-Lirio R, Kinoshita T (2011) Assessing interactions in the brain with exact low-resolution electromagnetic tomography. Philos Trans A Math Phys Eng Sci 369:3768–3784

Pastor MA, Artieda J, Arbizu J, Marti-Climent JM, Penuelas I, Masdeu JC (2002) Activation of human cerebral and cerebellar cortex by auditory stimulation at 40 hz. J Neurosci 22:10501–10506

Pessoa L, Gutierrez E, Bandettini P, Ungerleider L (2002) Neural correlates of visual working memory: FMRI amplitude predicts task performance. Neuron 35:975–987

Pollok B, Sudmeyer M, Gross J, Schnitzler A (2005) The oscillatory network of simple repetitive bimanual movements. Brain Res Cogn Brain Res 25:300–311

Pollok B, Krause V, Butz M, Schnitzler A (2009) Modality specific functional interaction in sensorimotor synchronization. Hum Brain Mapp 30:1783–1790

Polonsky A, Blake R, Braun J, Heeger DJ (2000) Neuronal activity in human primary visual cortex correlates with perception during binocular rivalry. Nat Neurosci 3:1153–1159

Prabhakaran V, Narayanan K, Zhao Z, Gabrieli JD (2000) Integration of diverse information in working memory within the frontal lobe. Nat Neurosci 3:85–90

Rauschecker JP, Scott SK (2009) Maps and streams in the auditory cortex: nonhuman primates illuminate human speech processing. Nat Neurosci 12:718–724

Reynolds JH, Chelazzi L (2004) Attentional modulation of visual processing. Annu Rev Neurosci 27:611–647

Riesenhuber M, Poggio T (2002) Neural mechanisms of object recognition. Curr Opin Neurobiol 12:162–168

Rodriguez E, George N, Lachaux JP, Martinerie J, Renault B, Varela FJ (1999) Perception's shadow: long-distance synchronization of human brain activity. Nature 397:430–433

Romei V, Brodbeck V, Michel C, Amedi A, Pascual-Leone A, Thut G (2008) Spontaneous fluctuations in posterior alpha-band EEG activity reflect variability in excitability of human visual areas. Cereb Cortex 18:2010–2018

Rouhinen S, Panula J, Palva JM, Palva S (2013) Load dependence of beta and gamma oscillations predicts individual capacity of visual attention. J Neurosci 33:19023–19033

Roux F, Wibral M, Mohr HM, Singer W, Uhlhaas PJ (2012) Gamma-band activity in human prefrontal cortex codes for the number of relevant items maintained in working memory. J Neurosci 32:12411–12420

Rowe JB, Toni I, Josephs O, Frackowiak RS, Passingham RE (2000) The prefrontal cortex: response selection or maintenance within working memory? Science 288:1656–1660

Rubinov M, Sporns O (2009) Complex network measures of brain connectivity: uses and interpretations. Neuroimage 52(3):1059–1069

Rutter L, Nadar SR, Holroyd T, Carver FW, Apud J, Weinberger DR, Coppola R (2013) Graph theoretical analysis of resting magnetoencephalographic functional connectivity networks. Front Comput Neurosci 7:93

Sacchet MD, LaPlante RA, Wan Q, Pritchett DL, Lee AKC, Hämäläinen M, Moore CI, Kerr CE, Jones SR (2015) Attention drives synchronization of alpha and beta rhythms between right inferior frontal and primary sensory neocortex. J Neurosci 35:2074–2082

Sadaghiani S, Hesselmann G, Kleinschmidt A (2009) Distributed and antagonistic contributions of ongoing activity fluctuations to auditory stimulus detection. J Neurosci 29:13410–13417

Sadaghiani S, Scheeringa R, Lehongre K, Morillon B, Giraud AL, Kleinschmidt A (2010) Intrinsic connectivity networks, alpha oscillations, and tonic alertness: a simultaneous electroencephalography/functional magnetic resonance imaging study. J Neurosci 30:10243–10250

Sakai K, Rowe JB, Passingham RE (2002) Active maintenance in prefrontal area 46 creates distractor-resistant memory. Nat Neurosci 5:479–484

Salazar RF, Dotson NM, Bressler SL, Gray CM (2012) Content-specific fronto-parietal synchronization during visual working memory. Science 338:1097–1100

Sauseng P, Klimesch W, Doppelmayr M, Pecherstorfer T, Freunberger R, Hanslmayr S (2005) EEG alpha synchronization and functional coupling during top-down processing in a working memory task. Hum Brain Mapp 26:148–155

Schoffelen JM, Gross J (2009) Source connectivity analysis with MEG and EEG. Hum Brain Mapp 30:1857–1865

Schroeder CE, Lakatos P (2009) The gamma oscillation: master or slave? Topogr, Brain

Siebenhühner F, Lobier M, Wang SH, Satu P, Matias Palva J (2016) Measuring large-scale synchronization with human MEG and EEG: challenges and solutions. In: Palva S (ed) Multimodal oscillation-based connectivity theory. Springer, Heidelberg

Siegel M, Donner TH, Oostenveld R, Fries P, Engel AK (2008) Neuronal synchronization along the dorsal visual pathway reflects the focus of spatial attention. Neuron 60:709–719

Siegel M, Warden MR, Miller EK (2009) Phase-dependent neuronal coding of objects in short-term memory. Proc Natl Acad Sci USA 106:21341–21346

Singer W (1999) Neuronal synchrony: a versatile code for the definition of relations? Neuron 24 (49–65):111–125

Singer W (2009) Distributed processing and temporal codes in neuronal networks. Cogn Neurodyn 3:189–196

Stam CJ (2004) Functional connectivity patterns of human magnetoencephalographic recordings: a 'small-world' network? Neurosci Lett 355:25–28

Tallon-Baudry C, Bertrand O, Delpuech C, Pernier J (1996) Stimulus specificity of phase-locked and non-phase-locked 40 hz visual responses in human. J Neurosci 16:4240–4249

Tallon-Baudry C, Bertrand O, Delpuech C, Permier J (1997) Oscillatory gamma-band (30–70 Hz) activity induced by a visual search task in humans. J Neurosci 17:722–734

Tallon-Baudry C, Bertrand O, Peronnet F, Pernier J (1998) Induced gamma-band activity during the delay of a visual short-term memory task in humans. J Neurosci 18:4244–4254

Thut G, Nietzel A, Brandt SA, Pascual-Leone A (2006) Alpha-band electroencephalographic activity over occipital cortex indexes visuospatial attention bias and predicts visual target detection. J Neurosci 26:9494–9502

Todd JJ, Marois R (2004) Capacity limit of visual short-term memory in human posterior parietal cortex. Nature 428:751–754

Tong F, Nakayama K, Vaughan JT, Kanwisher N (1998) Binocular rivalry and visual awareness in human extrastriate cortex. Neuron 21:753–759

Tsubomi H, Fukuda K, Watanabe K, Vogel EK (2013) Neural limits to representing objects still within view. J Neurosci 33:8257–8263

Watts DJ, Strogatz SH (1998) Collective dynamics of 'small-world' networks. Nature 393:440–442

Womelsdorf T, Schoffelen J, Oostenveld R, Singer W, Desimone R, Engel AK, Fries P (2007) Modulation of neuronal interactions through neuronal synchronization. Science (New York) 316:1609–1612

Worden MS, Foxe JJ, Wang N, Simpson GV (2000) Anticipatory biasing of visuospatial attention indexed by retinotopically specific alpha-band electroencephalography increases over occipital cortex. J Neurosci 20:RC63

Xu Y, Chun MM (2006) Dissociable neural mechanisms supporting visual short-term memory for objects. Nature 440:91–95

Xu Y, Chun MM (2009) Selecting and perceiving multiple visual objects. Trends Cogn Sci 13:167–174

Zhang W, Luck SJ (2008) Discrete fixed-resolution representations in visual working memory. Nature 453:233–235

Zumer JM, Scheeringa R, Schoffelen JM, Norris DG, Jensen O (2014) Occipital alpha activity during stimulus processing gates the information flow to object-selective cortex. PLoS Biol 12, e1001965

Thalamo-Cortical Interactions and Synchronous Oscillations in MEG Data

Peter J. Uhlhaas and Frédéric Roux

1 Introduction

The thalamus has long been established as a central structure in the afferent pathway that relays inputs from the periphery to the cerebral cortex (Fig. 1a; Sherman and Guillery 2001, 2006). Most of our knowledge on the operations performed by the thalamus is based on studies conducted in the so-called sensory nuclei such as the lateral geniculate nucleus (LGN), which transmits retinal inputs to the primary visual cortex (V1) with a point-to-point correspondence. Similarly, other sensory nuclei, such as the medial geniculate (MGN) and posterior ventral nucleus (VPN), relay acoustic/somatic inputs to corresponding targets in primary auditory/somatosensory cortices (A1/S1). Our current understanding of thalamic function is, thus, largely influenced by the notion that the thalamus acts as a central gateway for ascending peripheral inputs (Sherman and Guillery 2006). More recently, however, several studies have implicated the pulvinar in the modulation of cortical–cortical communication during higher cognitive processes, such as attention and working memory (Wróbel et al. 2007; Saalmann et al. 2012), thereby provoking a renewed interest in the operations performed by different thalamic nuclei.

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S. Palva (ed.), *Multimodal Oscillation-based Connectivity Theory*,
DOI 10.1007/978-3-319-32265-0_5

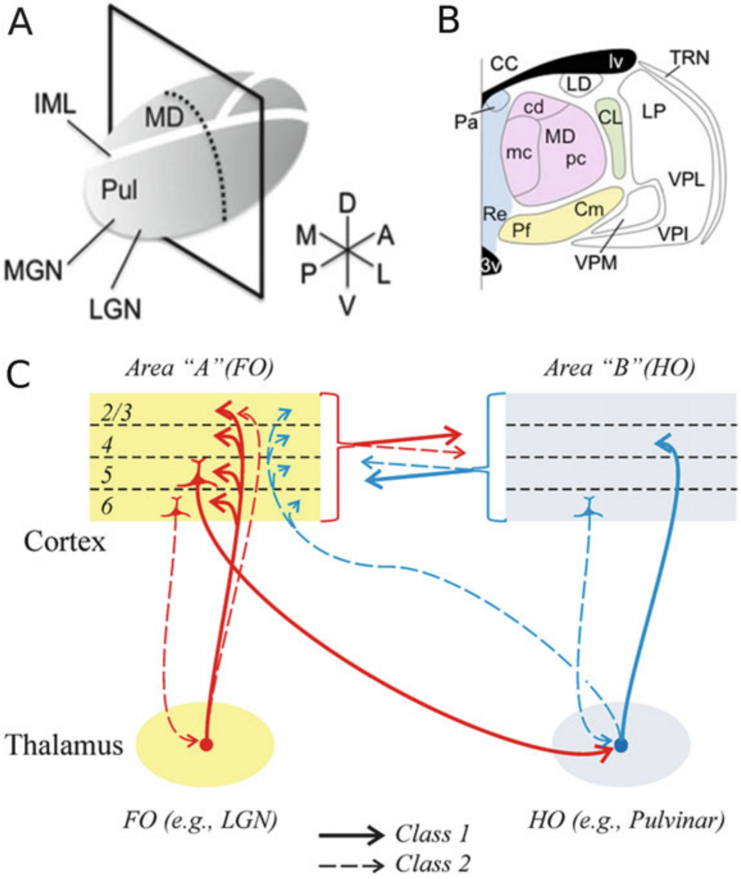

Fig. 1 Anatomy of the thalamus. (**a**) Overview of first-order and higher-order thalamic nuclei including the lateral geniculate nucleus (LGN), the medial geniculate nucleus (MGN), the medial dorsal nucleus (MD), and the pulvinar (Pul). The internal medullary lamina (IML) is composed of myelinated fiber layers that delineate the dorsomedial and ventral nuclei of the thalamus. (**b**) Coronal section of the plane in **a** showing the anterior intralaminar (*green*), posterior intralaminar (*yellow*), MD (*pink*), and midline (*blue*) nuclei [**a**–**b** are adapted from (Saalmann 2014)]. (**c**) Schematic representation of thalamic and cortical pathways in the mouse [**c** is adapted from (Sherman 2012)]. The pulvinar receives inputs from the first-order (FO) brain area "**a**" via corticothalamic projection neurons originating in layer 5 (*red solid line*) and at the same time sends information to the higher-order (HO) brain area "**b**" via thalamo-cortical neurons terminating in layer 4 (*blue solid line*)

A possible role of the pulvinar in modulating cortico-cortical communication is compelling (Saalmann and Kastner 2009; Saalmann and Kastner 2011; Saalmann 2014) because it agrees with anatomical studies suggesting that thalamic nuclei can be subdivided into "first-order" (FO) and "higher-order" (HO) nuclei according to their drivers (Sherman 2007). A consistent characteristic of FO nuclei is that they transmit driving inputs received from subcortical sources to cortical layer 4, thereby forming the basis for the relay of receptive field properties (Sherman and Guillery 2011; Guillery and Sherman 2011). The majority of these nuclei are constituted by the main sensory nuclei (LGN, MGN, VPN). HO nuclei such as the pulvinar, by contrast, receive their driving inputs from layer 5 of one cortical area but send their projections back to layer 1 of a different cortical region (Sherman and Guillery 2001). This nonreciprocal connectivity pattern has been proposed as an indirect trans-thalamic pathway for relaying information between distinct cortical areas (Fig. 1b; Sherman 2012).

Supporting evidence for such an indirect pathway involving the pulvinar has been obtained recently by Saalmann et al. (2012), who demonstrated that synchronous alpha oscillations were involved in relaying pulvinar inputs between two functionally coupled distinct visual areas (V4 and TEO). This effect was modulated by spatial attention, thereby supporting the hypothesis that trans-thalamic routes are involved in cortico-cortical communication during cognitive processing (Saalmann 2014; Sherman and Guillery 2011; Guillery and Sherman 2011; Sherman 2012). Another important observation from the study by Saalmann et al. (2012) showed that the envelope of cortical gamma power in V4 and TEO was coupled to the phase of cortical alpha oscillations. This suggests that synchronous TC alpha oscillations generated in higher-order nuclei could support the emergence of coherent gamma oscillations in cortico-cortical networks (Schmid et al. 2012), thereby providing a thalamic mechanism to regulate cortico-cortical information flow.

Such a mechanism would be in line with the long-standing hypothesis that the thalamus actively regulates cortico-cortical information processing (Crick 1984; Sherman and Koch 1986; Singer 1994) as well as with evidence implicating alpha and gamma oscillations in the routing of information flow in cortico-cortical networks (Fries 2005, 2009; Jensen and Mazaheri 2010; Jensen et al. 2014).

Along these lines, synchronous oscillations could also regulate the efficacy of information transmission in first-order TC circuits. The LGN, for instance, has long been implicated into the generation of synchronized oscillations in the visual cortex at alpha, beta, and gamma frequencies (Lopes da Silva et al. 1980; Ghose and Freeman 1992; von Krosigk et al. 1993; Castelo-Branco et al. 1998; Neuenschwander et al. 2002), thereby suggesting that synchronous oscillations could play a putative role in mediating the transmission of retinal inputs to primary visual areas.

This is supported by recent work demonstrating that geniculo-cortical feedforward processing is mediated by synchronous oscillations at beta frequencies, whereas corticothalamic feedback from V1 to LGN is mediated by synchronous activity in the alpha band (Bastos et al. 2014). Moreover, recent electrophysiological recordings and computational models of LGN activity show that during strong phasic inhibition, spiking of geniculate neurons and pyramidal cells will be phase-coupled with the trough of the alpha cycle, whereas during weaker inhibition, spiking activity will be coupled to the peak of the alpha cycle (Lorincz et al. 2009; Vijayan and Kopell 2012). As a result, alpha-based synchronization of geniculate and cortical responses may lead to a temporal framing of neuronal responses that could modulate the transmission of geniculo-cortical information (Lorincz et al. 2009). This is supported by studies demonstrating that the phase of the alpha cycle modulates neural firing (Haegens et al. 2011), perceptual detection rates (Varela et al. 1981; Dugué et al. 2011), and cerebral blood flow (Scheeringa et al. 2011), thereby suggesting that synchronous alpha-band oscillations exert critical influence on the excitability level of TC networks as well as on neuronal response gains.

2 Subcortical Sources in MEG Data

Current approaches to MEG source reconstruction often rely on distributed source models to estimate the contribution of simultaneously activated neuronal dipoles in different brain regions (Van Veen et al. 1997; Gross et al. 2001; Sekihara et al. 2001). These approaches permit the assessment of functional interactions between multiple sources of brain activity and have been successfully applied to study coherent patterns of cortical oscillatory activity in humans during cognitive processing (Gross et al. 2001; Schoffelen and Gross 2009). One important limitation of these approaches, however, is the fact that the magnetic field strength decays rapidly with increasing distance from the location of the source, and as a result, MEG recordings, therefore, tend to be biased by activity from cortical sources and are less sensitive towards activity in deeper brain structures, such as the thalamus or the brainstem.

Until recently, the possibility of applying source reconstruction techniques to assess directed TC interactions in humans has, therefore, remained largely unexplored. In theory, however, contributions from deeper sources should be detectable in MEG data, given that their fields are strong enough to propagate to the sensor array of MEG-SQUIDs. This hypothesis is supported by several studies that have localized MEG signals in subcortical regions, including the brain stem (Parkkonen et al. 2009), the amygdala (Dumas et al. 2013; Hung et al. 2010), and the hippocampus (Staudigl and Hanslmayr 2013), thereby demonstrating that the activity from subcortical sources can be reconstructed by means of commonly used source modeling techniques.

First evidence supporting that MEG can monitor thalamic sources was reported by Ribary et al. (1991), who were able to demonstrate coherent gamma oscillations between thalamus and cortex in resting-state activity. Subsequent work by Tesche (1996) reported somatosensory-evoked responses in contralateral thalamus that were in line with latencies of similar responses obtained from intracranial recordings in human thalamus. Finally, two studies by Attal and colleagues (Attal and Schwartz 2013; Attal et al. 2007) have implicated thalamic sources in the generation of resting-state alpha oscillations, thereby highlighting the possibility that thalamic sources contribute to a measurable MEG signal during resting state.

In agreement with these findings, a simulation study by Attal et al. (2007) indicated that thalamic fields may achieve up to 21 % (25fT) of the total field strength produced by cortical sources (120fT), adding further evidence to the possibility that thalamic structures may indeed significantly contribute to a measurable MEG signal. Finally, from a biophysical perspective, there is anatomical evidence suggesting that the longitudinal dendritic architecture of the LGN and TRN may contribute to the generation of tangential fields which can be measured with MEG (Yelnik et al. 1984). Whether the cytoarchitecture of the pulvinar is compatible with the generation of tangential fields remains an open question that requires further investigation.

3 Measuring Thalamic–Cortical Interactions in MEG Data

Recent data show that alpha-band rhythms generated in the LGN are linked with the temporal coordination of spiking activity in TC circuits (Lorincz et al. 2009; Vijayan and Kopell 2012), providing important support for the hypothesis that alpha-phase entrainment may regulate cortical spiking activity (Jensen and Mazaheri 2010; Klimesch et al. 2007). Moreover, there is emerging evidence that the pulvinar influences cortical synchrony through rhythmic alpha activity (Saalmann et al. 2012), raising the possibility that synchronous alpha rhythms in TC circuits may contribute to establishing coherent gamma-band oscillations in cortex (Saalmann 2014).

A first step towards testing this hypothesis in humans is to investigate whether thalamic alpha-based entrainment of cortical gamma oscillations is detectable in MEG-recorded brain signals. To investigate this possibility, we have recently recorded resting-state activity in a sample of $n=45$ healthy participants with MEG. We focused on interactions between alpha (8–13 Hz) and broadband gamma (30–70 Hz) activity, as previous work indicates that broadband activity in the gamma frequency range reflects active neuronal processing such as neuronal spiking activity (Rasch et al. 2008; Manning et al. 2009; Whittingstall and Logothetis 2009; Miller 2010; Miller et al. 2010; Buzsáki and Wang 2012) and is modulated by the phase of task related and spontaneous alpha oscillations (Saalmann et al. 2012; Chorlian et al. 2006; Osipova et al. 2008; Cohen et al. 2009; Voytek et al. 2010; Foster and Parvizi 2012; Spaak et al. 2012; Yanagisawa et al. 2012).

Using a whole-brain analysis, as well as a seed region based analysis of phase–amplitude coupling (PAC) at source level, we examined the modulation of neocortical gamma-band activity by the phase of cortical and thalamic alpha oscillations. Consistent with previous work (Saalmann et al. 2012; Chorlian et al. 2006; Osipova

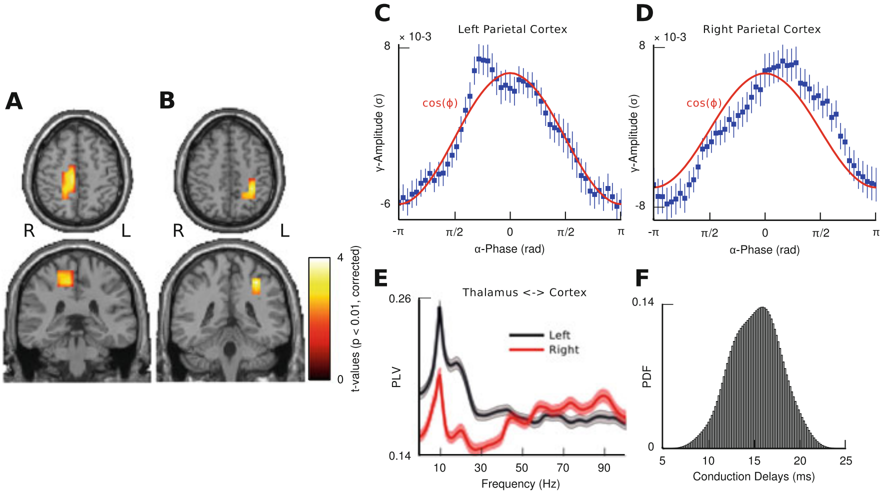

Fig. 2 Thalamo-cortical PAC. (**a**, **b**) Statistical source maps of t-values ($p < 0.01$; dependent t-test; two sided; corrected) for the comparison of thalamo-cortical alpha–gamma PAC with shifted data for seed regions in the left (**a**) and right (**b**) thalamus. (**c**, **d**) Cortical gamma-band amplitude as a function of thalamic alpha phase averaged over grid points in the *left* (**c**) and *right* (**d**) posterior medial parietal cortex. *Error bars* represent SEM, and the *red line* represent the fit of a cosine function ($\cos(\varphi)$) to the data. (**e**, **f**) Same convention as in Figs. 2–3 with the exception that the histograms are based on thalamic alpha-phase estimates. (**g**) Phase synchronization between the thalamus and posterior medial parietal areas in the left (*black*) and right (*red*) hemisphere for frequencies from 1 to 100 Hz. Phase synchronization was measured by means of the phase locking value (PLV). (**h**) PDF of thalamo-cortical conduction delays as measured by TE (mean: 15.8 ms; SD: 2.4 ms)

et al. 2008; Cohen et al. 2009; Voytek et al. 2010; Foster and Parvizi 2012; Spaak et al. 2012), we observed that local gamma-band activity was coupled to the phase of the alpha-band rhythm which was most pronounced over the visual cortex, suggesting that fluctuations of broadband gamma-band activity are linked to the phase of a local source of alpha oscillations. To investigate the contribution of a potential thalamic alpha generator, we carried out a seed region-based analysis of alpha–gamma coupling. This approach consisted of measuring the coupling of brain-wide broadband gamma power in source space with the phase of thalamic alpha oscillations as measured by two virtual electrodes at thalamic coordinates. The results of this approach revealed that TC alpha–gamma coupling became significant in posterior medial parietal cortex where cortical gamma-band activity was greatest at the peak of the thalamic alpha rhythm (Fig. 2). In addition, we tested the physiological validity of our findings using transfer entropy (TE) and addressed the potential contribution of spatial source leakage using a reversed seed-region analysis to control for spurious TC interactions (Fig. 3).

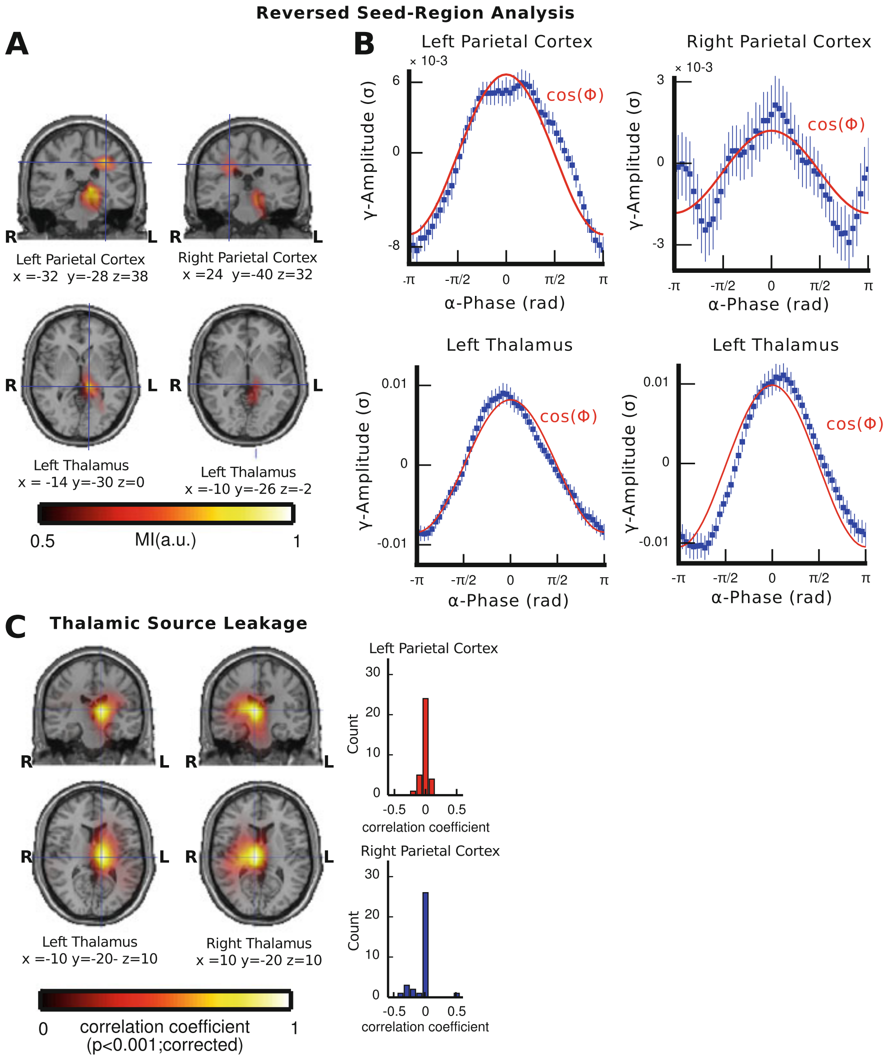

Fig. 3 Reversed-seed region analysis.(**a**) Source maps of normalized MI values for the modulation of 30–70 Hz activity in the left and right posterior medial parietal cortex by the phase of brain-wide alpha oscillations. The amplitude of broadband gamma activity in posterior medial parietal cortex was modulated by the phase of alpha oscillations in the left thalamus as well as in the left and right posterior medial parietal cortex. (**b**) Same convention as in Fig. 4 with the exception that the histograms are based on phase estimates of alpha activity in the left and right parietal cortex (*top panel*) and left thalamus (*bottom panel*). (**c**) Source maps of Pearson correlation coefficients (*r*) for the correlation of spatial filters in the left and right thalamus and spatial filters at brain-wide source locations (*left panel*). *Right panel*: histograms showing the distribution of Pearson correlation coefficients across participants for the correlation of spatial filters in the left and right thalamus and spatial filters in the left and right posterior medial parietal cortex

4 Impact of NMDA-R Hypofunctioning on TC Networks in Resting MEG Data

Further evidence for the possibility to reconstruct TC interactions in MEG data comes from a study in which we examined the impact of NMDA-R receptor antagonist ketamine on resting-state neural oscillations. In the cortex, networks of mutually interacting GABAergic neurons and their glutamatergic inputs are crucially involved in the generation of high-frequency oscillations. In the thalamus, NMDA-R contributes to the excitatory potentials evoked at corticothalamic synapses in both the reticular (de Curtis et al. 1989; Golshani and Jones 1999) and relay neurons (Hu et al. 1989; Golshani et al. 1998; Scharfman et al. 1990; Deschênes and Hu 1990; Turner and Salt 1998; Kao and Coulter 1997). Moreover, there is evidence to suggest that NMDA-R contributes to oscillatory activity in TC pathways, in particular at lower frequencies (Jacobsen et al. 2001).

NMDA receptors' number and functionality have been critically implicated in the pathophysiology of ScZ (Moghaddam and Javitt 2012; Kirov et al. 2012) and abnormalities in glutamatergic transmission and are a candidate mechanism for disturbed high frequency oscillations in the disorder. In vivo and in vitro electrophysiological studies using NMDA-R antagonists have revealed an increase of spontaneous power at both low (30–60 Hz) and high (60–130 Hz) gamma-band ranges as well as at ripple frequencies (130–200 Hz) (Hunt and Kasicki 2013). More recently, there is increasing evidence that TC interactions are disturbed in ScZ and could provide a core pathophysiological mechanism for cognitive deficits and certain symptoms of the disorder (Uhlhaas and Singer 2006; Parnaudeau et al. 2013).

To examine the possibility that TC networks are critically involved in the dysregulation of gamma-band oscillations following ketamine application, we investigated the impact of ketamine on resting-state activity in MEG recordings in healthy volunteers. In a single-blind crossover design, each participant ($n = 12$) received, on two different sessions, a subanesthetic dose of S-ketamine (0.006 mg/Kg) and saline injection. MEG data were analyzed at sensor and source level in the beta (13–30 Hz) and gamma (30–90 Hz) frequency ranges (Hunt and Kasicki 2013). In addition, connectivity analysis at source level was performed using TE (Vicente et al. 2011; Wibral et al. 2011, 2013).

Our data show a pronounced upregulation of gamma-band activity at both sensor and source level which occurred in subcortical and cortical areas (Figs. 4 and 5). The largest increases of gamma-band activity were observed in the right hippocampus and right/left thalami, followed by parietal, temporal, and frontal structures (Fig. 5). Decreases in beta band were localized to brain regions that were overall distinct from gamma-band generators. Maximal reductions in 13–30 Hz were localized, for example, to the cerebellum, temporal, and visual cortex.

These MEG data are consistent with previous research investigating the effects of ketamine administration in invasive electrophysiological recordings as well as with the presence of gamma-band generators in thalamo-cortical circuits. For

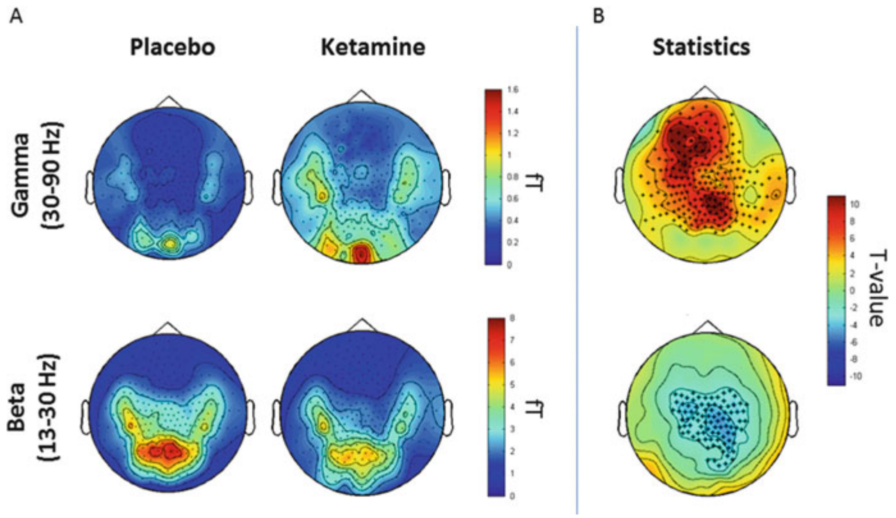

Fig. 4 Sensor-level analysis. (**a**) Topoplots representing the average power spectra (fT) of gamma (*top*) and beta (*bottom*) frequency ranges in the placebo (*left*) and ketamine (*right*) conditions. (**b**) Results of the nonparametric cluster-based statistic highlighting sensors showing a statistically significant effect for gamma (*top*) and beta (*bottom*) frequencies. *Red colors* indicate a statistically significant difference in favor of the ketamine condition, whereas *blue colors* indicate a difference in favor of the placebo condition ($* = p < 0.001$)

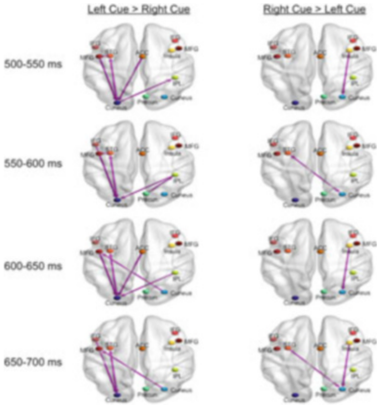

Fig. 5 Summary of significant NBTE between indicated brain regions in relevant time intervals. *Directional arrows* indicate time periods in the cue-target interval during which higher levels of information flow in the alpha band were observed for the indicated cue condition. Reprinted from Doesburg et al. (2016) with permission

example, Pinault and Deschênes (1992) showed robust 40 Hz activity of neurons in the reticular thalamic nucleus (RTN), suggesting a pacemaker function of RTN cells in the generation of 40 Hz oscillations. In addition, 30–100 Hz spontaneous activity has been recorded in other regions of the thalamus, including the ventrolateral and the intralaminar centrolateral nuclei (Timofeev and Steriade 1997). Moreover, animal models reported gamma-power increase following ketamine application in the thalamus and hippocampus: Zhang et al. (2012) reported that gamma activity increased after ketamine injection by 308 % in the hippocampus and 258 % in the thalamus.

To further examine the possibility that ketamine impacts, in particular, on TC pathways, we estimated source-level functional connectivity between regions showing spectral changes after ketamine administration with TE (Vicente et al. 2011; Wibral et al. 2011, 2013). Ketamine administration caused an increase in the average TE values (see Fig. 6a for uncorrected effects) which particularly involved connections between the thalamus and temporal and visual regions.

Our results of MEG-informed source localization, furthermore, are consistent with recent data that have highlighted the importance of thalamo-cortical interactions and hippocampal circuits in the pathophysiology of ScZ. Several resting-state fMRI studies reported increased functional connectivity between thalamus and cortical regions (Woodward et al. 2012; Monaghan and Cotman 1985; Schobel et al. 2013), albeit some report mixed findings (Schobel et al. 2013). In addition, the increase in gamma-band activity in hippocampal sources, a brain region with a large number of NMDA receptor sites (Gunduz-Bruce 2009), is consistent with the findings highlighting the possible contribution of elevated metabolism as a result of NMDA-R hypofunctioning in the early stages of ScZ (Kocsis 2012).

5 Discussion

The thalamus forms densely connected networks with many regions in the cerebral cortex (Sherman and Guillery 2001). Thus, MEG-based source reconstruction of TC interactions may provide important insights into the role of the thalamus in cognition. Furthermore, if MEG proves to be capable of monitoring thalamic activity, it may have important clinical implications, as TC dysfunctions have been centrally involved in the pathophysiology of several severe psychiatric disorders, such as schizophrenia (O’Donnell and Grace 1998; Pinault 2011).

The current data highlight the possibility to reconstruct TC interactions with MEG during resting state. While previous empirical and modelling data have suggested the possibility that MEG might be sensitive towards thalamic sources (Ribary et al. 1991; Tesche 1996; Attal and Schwartz 2013; Attal et al. 2007), the studies conducted by our group provide additional support towards this hypothesis through demonstrating that the amplitude of alpha- and gamma-band oscillations in thalamic regions can be measured with MEG. In addition, our data demonstrate that directed interactions in TC circuits can be reconstructed using novel measures of information transfer such as TE (Vicente et al. 2011; Wibral et al. 2013). Accordingly, these results provide important evidence on the contribution of TC interactions in the organization of oscillatory networks which has important implication for the understanding of large-scale networks during normal and abnormal brain functioning.

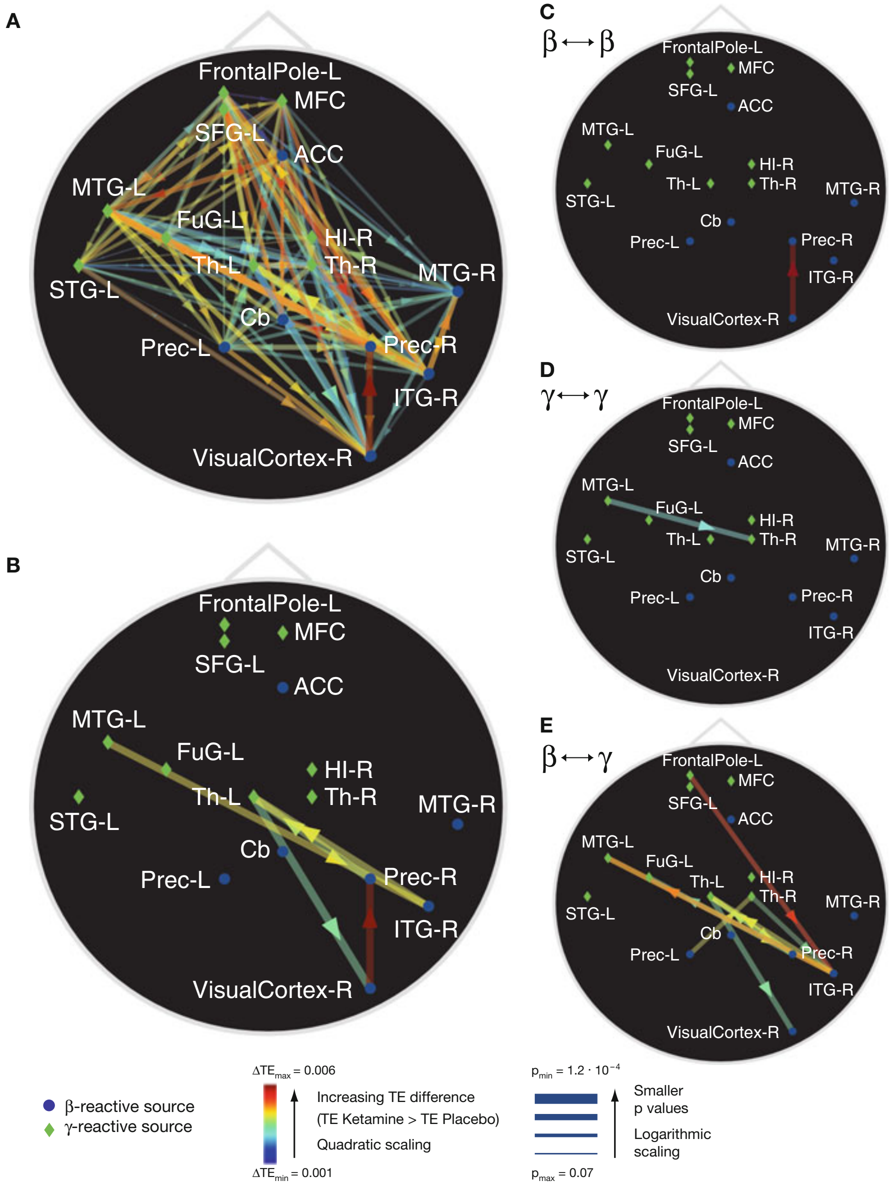

Fig. 6 Transfer entropy (TE) analysis. TE differences between ketamine and placebo conditions. *Green diamonds* indicate MEG sources reactive to ketamine in the gamma band; *blue circles* indicate sources reactive in the beta band (see Fig. 3). *Arrow colors* indicate strength of the difference. (**a**) Uncorrected differences in TE. (**b**) Statistically significant differences (Bonferroni corrected: $p < 2.08 \times 10–4$ the TE differences at a significance threshold of $p < 0.0005$ uncorrected), for the transfer entropy between (**c**) sources reactive in the beta frequency band, (**d**) in the gamma frequency band, and (**e**) between beta and gamma sources. Legend: *FrontalPole-L*, left frontal pole; *MFC*, medial frontal cortex; *SFG-L*, left superior frontal gyrus; *ACC*, anterior cingulate cortex; *MTG-L*, left middle temporal gyrus; *FuG-L,* left fusiform gyrus; *Th-L*, left thalamus; *Cb*, cerebellum; *Prec-L*, left precuneus; *HI-R*, right hippocampus; *Th-R*, right thalamus;

5.1 What Are the Requirements to Detect Such Interactions?

To discard spurious effects due to spatial leakage and volume conduction, which are often encountered in MEG measurements (Nolte et al. 2004), it is important to assess the validity of source-reconstructed TC interactions. A first step in establishing the face validity of reconstructed TC interactions is to specifically test for the existence of information transfer going from the thalamus to cortical sources. One way to achieve this is by estimating the amount of information communicated from the thalamus to a cortical source by using information theoretical measures such as Granger causality or TE. In the case that TC interactions are biased by spatial leakage from nearby cortical sources, then this should be revealed by the absence of a directed influence from thalamus to cortex. On the other hand, a directed influence from thalamus to cortex can be seen as a strong case against source leakage, thereby supporting that the measured effects reflect genuine information transfer from thalamus to cortex.

Secondly, in order to assess the physiological validity of source reconstructed TC interactions, the measured TC conduction latencies should be compared with previously reported delays measured by electrophysiological studies. Thirdly, to cross-validate functional connectivity measures between thalamic and cortical sources, a reversed seed-region analysis can be performed to further rule out the possibility of volume conduction or spatial leakage [for more details, see Roux et al. (2013)]. Finally, the accuracy of spatial filters can be assessed by quantifying the pair wise correlation between spatial filters at thalamic source coordinates and spatial filters at other locations in source space, thereby providing a map of spatial leakage around thalamic source locations.

5.2 Are Thalamic Sources Detectable in Task-Related MEG Recordings?

One issue that remains to be addressed is the question whether TC interactions can also be examined with MEG during task-related activity. The study by Attal et al. (2007) indicates that a large number of trials (400–3500) may be required to detect thalamic sources in stimulus-evoked activity, whereas thalamic generators of oscillatory activity at alpha frequencies during resting-state recording can already be identified from only 30 s of eyes closed resting-state activity. Accordingly, the sensitivity of MEG towards thalamic sources may significantly deteriorate during recordings of task-related activity. This difference could result from the shorter time windows used in cognitive experiments, which typically range between 1 and

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Fig. 6 (continued) MTG-R, right medial temporal gyrus; *Prec-R*, right precuneus; *ITG-R*, right inferior temporal gyrus; *VisualCortex-R,* right visual cortex

3 s. Indeed, the length of the recorded signals that are used for the computation of the sensor covariance matrix will determine the accuracy of the forward solution, as previously reported by Brookes and colleagues (Brookes et al. 2008). Thus, the length of the time windows used in cognitive experiments may be a critical factor influencing the detection of thalamic sources in MEG recordings. Another possibility that could influence the detection of thalamic signals in task-related activity is the fact that cortical sources will produce signals that have a greater signal-to-noise ratio (SNR) than during resting state, thereby possibly decreasing the detectability of thalamic generators in MEG signals per se (Attal and Schwartz 2013; Attal et al. 2007).

From a methodological perspective, one possible way of increasing the sensitivity of source reconstruction techniques for TC interactions in task-related activity could be to combine measures of functional connectivity and information flow in TC circuits. This approach could have the advantage of increasing the detectability of thalamic sources as compared to approaches which rely on measures of relative signal strength, which could be biased by relative differences in SNR between cortical and thalamic generators (Attal and Schwartz 2013; Attal et al. 2007). Furthermore, most actual source reconstruction techniques rely on anatomical models which do not take into account structural differences in the cytoarchitecture of subcortical regions. However, recent simulation studies demonstrate that the sensitivity of MEG for deep brain activity can be substantially improved by using anatomical priors to build realistic source models for subcortical regions (Attal and Schwartz 2013; Attal et al. 2007). Thus, future work aiming at reconstructing thalamic–cortical interactions in MEG data should apply similar techniques to improve the sensitivity of source models for thalamic sources.

5.3 Future Directions

Simultaneous MEG and intracranial LFP recordings conducted in deep brain stimulation (DBS) patients may provide an important opportunity of assessing functional interactions in TC circuits. One possible approach could be to stimulate subcortical areas such as the subthalamic nucleus (STN), a frequent target of DBS electrodes in Parkinson's disease patients (Urrestarazu et al. 2009; Toledo et al. 2014). The effect of this stimulation should generate a detectable MEG signal in the STN, given that the biophysical requirements for a measurable field are met (Ahlfors et al. 2010a, b). One could then use adapted MEG beamforming techniques designed to suppress artifacts generated by the implanted electrodes (Litvak et al. 2010) to assess how well source activity in the STN can be reconstructed from MEG recordings.

A more challenging approach could involve optogenetic techniques in nonhuman primates (Diester et al. 2011) to activate specific thalamic nuclei while recording simultaneous MEG activity. Previous work suggests that MEG source reconstruction for cortical sources can be carried out in nonhuman primates using beamformer techniques (Zumer et al. 2010; Zhu et al. 2009). If optogenetic activation of thalamic nuclei proves to be successful in nonhuman primates, then this approach could provide a promising avenue to study the contribution of specific thalamic nuclei to MEG signals during resting state and cognitive processing.

6 Summary

The thalamus has long been involved in the modulation of neuronal activity during primary perceptual processes (Sherman and Guillery 2006; Jones 2001). However, emerging evidence suggests that in addition to its function as a relay in the afferent pathway, the thalamus may also play a crucial role in the regulation of neuronal activity during higher level cognition (Saalmann and Kastner 2009, 2011; Saalmann 2014). In addition, dysfunctional thalamic interactions have been centrally involved in psychiatric disorders such as schizophrenia (O'Donnell and Grace 1998; Pinault 2011). So far, however, thalamic electrophysiology can only be investigated on the basis of intracranial recording techniques which offer only a limited number of recording sites. MEG in turn provides the possibility to reconstruct whole-brain networks and could thus provide important insights into corticothalamic and thalamo-cortical interactions at a much larger scale. We have outlined the existing evidence supporting that MEG may be suitable as a technique to reconstruct TC interactions. Specifically, we suggest that using advanced source reconstruction techniques together with information theoretical measures, it is possible to measure information transfer between the thalamus and the cortex during resting-state recordings. The spatial resolution with which MEG can detect thalamic interactions and monitor specific thalamic nuclei, however, remains an open question that needs to be addressed by future studies.

References

Ahlfors SP et al (2010a) Sensitivity of MEG and EEG to source orientation. Brain Topogr 23:227–232

Ahlfors SP et al (2010b) Cancellation of EEG and MEG signals generated by extended and distributed sources. Hum Brain Mapp 31:140–149

Attal Y, Schwartz D (2013) Assessment of subcortical source localization using deep brain activity imaging model with minimum norm operators: a MEG study. PLoS One 8, e59856

Attal Y et al (2007) Modeling and detecting deep brain activity with MEG & EEG. Conf Proc IEEE Eng Med Biol Soc 2007:4937–4940

Bastos AM et al (2014) Simultaneous recordings from the primary visual cortex and lateral geniculate nucleus reveal rhythmic interactions and a cortical source for γ-band oscillations. J Neurosci 34:7639–7644

Brookes MJ et al (2008) Optimising experimental design for MEG beamformer imaging. Neuroimage 39:1788–1802

Buzsáki G, Wang X-J (2012) Mechanisms of gamma oscillations. Annu Rev Neurosci 35:203–225

Castelo-Branco M et al (1998) Synchronization of visual responses between the cortex, lateral geniculate nucleus, and retina in the anesthetized cat. J Neurosci 18:6395–6410

Chorlian DB et al (2006) Amplitude modulation of gamma band oscillations at alpha frequency produced by photic driving. Int J Psychophysiol 61:262–278

Cohen MX et al (2009) Good vibrations: cross-frequency coupling in the human nucleus accumbens during reward processing. J Cogn Neurosci 21:875–889

Crick F (1984) Function of the thalamic reticular complex: the searchlight hypothesis. Proc Natl Acad Sci USA 81:4586–4590

de Curtis M et al (1989) Excitatory amino acids mediate responses elicited in vitro by stimulation of cortical afferents to reticularis thalami neurons of the rat. Neuroscience 33:275–283

Deschênes M, Hu B (1990) Membrane resistance increase induced in thalamic neurons by stimulation of brainstem cholinergic afferents. Brain Res 513:339–342

Diester I et al (2011) An optogenetic toolbox designed for primates. Nat Neurosci 14:387–397

Doesburg S et al (2016) Top-down alpha oscillatory network interactions during visuospatial attention orienting. Neuroimage 132:512–519

Dugué L et al (2011) The phase of ongoing oscillations mediates the causal relation between brain excitation and visual perception. J Neurosci 31:11889–11893

Dumas T et al (2013) MEG evidence for dynamic amygdala modulations by gaze and facial emotions. PLoS One 8, e74145

Foster BL, Parvizi J (2012) Resting oscillations and cross-frequency coupling in the human posteromedial cortex. Neuroimage 60:384–391

Fries P (2005) A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. Trends Cogn Sci 9:474–480

Fries P (2009) Neuronal gamma-band synchronization as a fundamental process in cortical computation. Annu Rev Neurosci 32:209–224

Ghose GM, Freeman RD (1992) Oscillatory discharge in the visual system: does it have a functional role? J Neurophysiol 68:1558–1574

Golshani P, Jones EG (1999) Synchronized paroxysmal activity in the developing thalamocortical network mediated by corticothalamic projections and "silent" synapses. J Neurosci 19:2865–2875

Golshani P et al (1998) Progression of change in NMDA, non-NMDA, and metabotropic glutamate receptor function at the developing corticothalamic synapse. J Neurophysiol 80:143–154

Gross J et al (2001) Dynamic imaging of coherent sources: studying neural interactions in the human brain. Proc Natl Acad Sci USA 98:694–699

Guillery RW, Sherman SM (2011) Branched thalamic afferents: what are the messages that they relay to the cortex? Brain Res Rev 66:205–219

Gunduz-Bruce H (2009) The acute effects of NMDA antagonism: from the rodent to the human brain. Brain Res Rev 60:279–286

Haegens S et al (2011) α-Oscillations in the monkey sensorimotor network influence discrimination performance by rhythmical inhibition of neuronal spiking. Proc Natl Acad Sci USA 108:19377–19382

Hu B et al (1989) The cellular mechanism of thalamic ponto-geniculo-occipital waves. Neuroscience 31:25–35

Hung Y et al (2010) Unattended emotional faces elicit early lateralized amygdala-frontal and fusiform activations. Neuroimage 50:727–733

Hunt MJ, Kasicki S (2013) A systematic review of the effects of NMDA receptor antagonists on oscillatory activity recorded in vivo. J Psychopharmacol (Oxf Engl) 27:972–986

Jacobsen RB et al (2001) GABA(B) and NMDA receptors contribute to spindle-like oscillations in rat thalamus in vitro. J Neurophysiol 86:1365–1375

Jensen O, Mazaheri A (2010) Shaping functional architecture by oscillatory alpha activity: gating by inhibition. Front Hum Neurosci 4:186

Jensen O et al (2014) Temporal coding organized by coupled alpha and gamma oscillations prioritize visual processing. Trends Neurosci 37:357–369

Jones EG (2001) The thalamic matrix and thalamocortical synchrony. Trends Neurosci 24:595–601

Kao CQ, Coulter DA (1997) Physiology and pharmacology of corticothalamic stimulation-evoked responses in rat somatosensory thalamic neurons in vitro. J Neurophysiol 77:2661–2676

Kirov G et al (2012) De novo CNV analysis implicates specific abnormalities of postsynaptic signalling complexes in the pathogenesis of schizophrenia. Mol Psychiatry 17:142–153

Klimesch W et al (2007) EEG alpha oscillations: the inhibition–timing hypothesis. Brain Res Rev 53:63–88

Kocsis B (2012) Differential role of NR2A and NR2B subunits in N-methyl-D-aspartate receptor antagonist-induced aberrant cortical gamma oscillations. Biol Psychiatry 71:987–995

Litvak V et al (2010) Optimized beamforming for simultaneous MEG and intracranial local field potential recordings in deep brain stimulation patients. Neuroimage 50:1578–1588

Lopes da Silva FH et al (1980) Relative contributions of intracortical and thalamo-cortical processes in the generation of alpha rhythms, revealed by partial coherence analysis. Electroencephalogr Clin Neurophysiol 50:449–456

Lorincz ML et al (2009) Temporal framing of thalamic relay-mode firing by phasic inhibition during the alpha rhythm. Neuron 63:683–696

Manning JR et al (2009) Broadband shifts in local field potential power spectra are correlated with single-neuron spiking in humans. J Neurosci 29:13613–13620

Miller KJ (2010) Broadband spectral change: evidence for a macroscale correlate of population firing rate? J Neurosci 30:6477–6479

Miller KJ et al (2010) Dynamic modulation of local population activity by rhythm phase in human occipital cortex during a visual search task. Front Hum Neurosci 4:197

Moghaddam B, Javitt D (2012) From revolution to evolution: the glutamate hypothesis of schizophrenia and its implication for treatment. Neuropsychopharmacology 37:4–15

Monaghan DT, Cotman CW (1985) Distribution of N-methyl-D-aspartate-sensitive L-[3H]glutamate-binding sites in rat brain. J Neurosci 5:2909–2919

Neuenschwander S et al (2002) Feed-forward synchronization: propagation of temporal patterns along the retinothalamocortical pathway. Philos Trans R Soc Lond B Biol Sci 357:1869–1876

Nolte G et al (2004) Localizing brain interactions from rhythmic EEG/MEG data. Conf Proc IEEE Eng Med Biol Soc 2:998–1001

O'Donnell P, Grace AA (1998) Dysfunctions in multiple interrelated systems as the neurobiological bases of schizophrenic symptom clusters. Schizophr Bull 24:267–283

Osipova D et al (2008) Gamma power is phase-locked to posterior alpha activity. PLoS One 3, e3990

Parkkonen L et al (2009) Sources of auditory brainstem responses revisited: contribution by magnetoencephalography. Hum Brain Mapp 30:1772–1782

Parnaudeau S et al (2013) Inhibition of mediodorsal thalamus disrupts thalamofrontal connectivity and cognition. Neuron 77:1151–1162

Pinault D (2011) Dysfunctional thalamus-related networks in schizophrenia. Schizophr Bull 37:238–243

Pinault D, Deschênes M (1992) Control of 40-Hz firing of reticular thalamic cells by neurotransmitters. Neuroscience 51:259–268

Rasch MJ et al (2008) Inferring spike trains from local field potentials. J Neurophysiol 99:1461–1476

Ribary U et al (1991) Magnetic field tomography of coherent thalamocortical 40-Hz oscillations in humans. Proc Natl Acad Sci USA 88:11037–11041

Roux F et al (2013) The phase of thalamic alpha activity modulates cortical gamma-band activity: evidence from resting-state MEG recordings. J Neurosci 33:17827–17835

Saalmann YB (2014) Intralaminar and medial thalamic influence on cortical synchrony, information transmission and cognition. Front Syst Neurosci 8:83

Saalmann YB, Kastner S (2009) Gain control in the visual thalamus during perception and cognition. Curr Opin Neurobiol 19:408–414

Saalmann YB, Kastner S (2011) Cognitive and perceptual functions of the visual thalamus. Neuron 71:209–223

Saalmann YB et al (2012) The pulvinar regulates information transmission between cortical areas based on attention demands. Science 337:753–756

Scharfman HE et al (1990) N-methyl-D-aspartate receptors contribute to excitatory postsynaptic potentials of cat lateral geniculate neurons recorded in thalamic slices. Proc Natl Acad Sci USA 87:4548–4552

Scheeringa R et al (2011) Modulation of visually evoked cortical FMRI responses by phase of ongoing occipital alpha oscillations. J Neurosci 31:3813–3820

Schmid MC et al (2012) Thalamic coordination of cortical communication. Neuron 75:551–552

Schobel SA et al (2013) Imaging patients with psychosis and a mouse model establishes a spreading pattern of hippocampal dysfunction and implicates glutamate as a driver. Neuron 78:81–93

Schoffelen J-M, Gross J (2009) Source connectivity analysis with MEG and EEG. Hum Brain Mapp 30:1857–1865

Sekihara K et al (2001) Reconstructing spatio-temporal activities of neural sources using an MEG vector beamformer technique. IEEE Trans Biomed Eng 48:760–771

Sherman SM (2007) The thalamus is more than just a relay. Curr Opin Neurobiol 17:417–422

Sherman SM (2012) Thalamocortical interactions. Curr Opin Neurobiol 22:575–579

Sherman SM, Guillery RW (2001) Exploring the thalamus. Academic, New York

Sherman SM, Guillery RW (2006) Exploring the thalamus and its role in cortical function. MIT, Cambridge, MA

Sherman SM, Guillery RW (2011) Distinct functions for direct and transthalamic corticocortical connections. J Neurophysiol 106:1068–1077

Sherman SM, Koch C (1986) The control of retinogeniculate transmission in the mammalian lateral geniculate nucleus. Exp Brain Res 63:1–20

Singer W (1994) Neurobiology. A new job for the thalamus. Nature 369:444–445

Spaak E et al (2012) Layer-specific entrainment of gamma-band neural activity by the alpha rhythm in monkey visual cortex. Curr Biol 22:2313–2318

Staudigl T, Hanslmayr S (2013) Theta oscillations at encoding mediate the context-dependent nature of human episodic memory. Curr Biol 23:1101–1106

Tesche CD (1996) Non-invasive imaging of neuronal population dynamics in human thalamus. Brain Res 729:253–258

Timofeev I, Steriade M (1997) Fast (mainly 30–100 Hz) oscillations in the cat cerebellothalamic pathway and their synchronization with cortical potentials. J Physiol 504(Pt 1):153–168

Toledo JB et al (2014) High beta activity in the subthalamic nucleus and freezing of gait in Parkinson's disease. Neurobiol Dis 64:60–65

Turner JP, Salt TE (1998) Characterization of sensory and corticothalamic excitatory inputs to rat thalamocortical neurones in vitro. J Physiol 510(Pt 3):829–843

Uhlhaas PJ, Singer W (2006) Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. Neuron 52:155–168

Urrestarazu E et al (2009) Beta activity in the subthalamic nucleus during sleep in patients with Parkinson's disease. Mov Disord 24:254–260

Van Veen BD et al (1997) Localization of brain electrical activity via linearly constrained minimum variance spatial filtering. IEEE Trans Biomed Eng 44:867–880

Varela FJ et al (1981) Perceptual framing and cortical alpha rhythm. Neuropsychologia 19:675–686

Vicente R et al (2011) Transfer entropy—a model-free measure of effective connectivity for the neurosciences. J Comput Neurosci 30:45–67

Vijayan S, Kopell NJ (2012) Thalamic model of awake alpha oscillations and implications for stimulus processing. Proc Natl Acad Sci USA 109:18553–18558

von Krosigk M et al (1993) Cellular mechanisms of a synchronized oscillation in the thalamus. Science 261:361–364

Voytek B et al (2010) Shifts in gamma phase-amplitude coupling frequency from theta to alpha over posterior cortex during visual tasks. Front Hum Neurosci 4:191

Whittingstall K, Logothetis NK (2009) Frequency-band coupling in surface EEG reflects spiking activity in monkey visual cortex. Neuron 64:281–289

Wibral M et al (2011) Transfer entropy in magnetoencephalographic data: quantifying information flow in cortical and cerebellar networks. Prog Biophys Mol Biol 105:80–97

Wibral M et al (2013) Measuring information-transfer delays. PLoS One 8, e55809. doi:10.1371/journal.pone.0055809

Woodward ND et al (2012) Thalamocortical dysconnectivity in schizophrenia. Am J Psychiatry 169:1092–1099

Wróbel A et al (2007) Two streams of attention-dependent beta activity in the striate recipient zone of cat's lateral posterior-pulvinar complex. J Neurosci 27:2230–2240

Yanagisawa T et al (2012) Regulation of motor representation by phase-amplitude coupling in the sensorimotor cortex. J Neurosci 32:15467–15475

Yelnik J et al (1984) A Golgi analysis of the primate globus pallidus. II. Quantitative morphology and spatial orientation of dendritic arborizations. J Comp Neurol 227:200–213

Zhang Y et al (2012) NMDAR antagonist action in thalamus imposes δ oscillations on the hippocampus. J Neurophysiol 107:3181–3189

Zhu Z et al (2009) The relationship between magnetic and electrophysiological responses to complex tactile stimuli. BMC Neurosci 10:4

Zumer JM et al (2010) MEG in the macaque monkey and human: distinguishing cortical fields in space and time. Brain Res 1345:110–124

Neurocognitive Decoding of Aesthetic Appreciation

Juan García-Prieto, Ernesto Pereda, and Fernando Maestú

1 Evolution of Aesthetics

Historically, art and beauty have been the subjects of impassioned discussions, with two big questions dominating the scene. Firstly, whether beauty is a concept actually belonging to this world—often in terms of theological versus nontheological beauty—and its consequences on the relationship between form and content and the search for universal patterns of beauty; secondly, the comprehension of the fundamental purpose of art.

1.1 Before 1900

It is hard to find a prominent figure in the history of philosophy who has not been him- or herself concerned with the notion of beauty and aesthetic pleasure, which

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S. Palva (ed.), *Multimodal Oscillation-based Connectivity Theory*,
DOI 10.1007/978-3-319-32265-0_6

underlines the importance for us, as human beings, of beauty. Yet, the foundation of aesthetic inquiry as a formal scholarly discipline is relatively recent, when the philosopher Baumgarten (1714–1762) introduced the modern use of the term in 1739 (Vessel et al. 2012). However, they were Fechner (1801–1887) and Wundt (1832–1920), two of the precursors of experimental psychology, who carried out the initial experimental research of aesthetic experience, developing an incipient methodological setup for an empirical approach to aesthetics.

Since then, a growing body of behavioral studies appears to focus mainly on artistic visual stimulus while elaborating knowledge on the visual properties of motivators of aesthetics. But, still the concepts debated by early psychologists—such as manners or style—stand distant from today's modern concepts of cognitive psychology or neuroscience. Authors usually leaned towards the idea that aesthetic evaluations rely on universal principles while emphasizing the importance of understanding aesthetic responses as strongly subjective.

1.2 1900–1990

During this period, some preliminary experimental works appeared at the intersection of philosophy and empirical sciences of perception and studied within the fledgling experiential science of psychology. After an initial exploration of a possible test for aesthetic judgment of pictures performed in 1918 (Cattell et al. 1918), works populate the literature and research began to be more liberated from academic constraints, a continuous stream of empirical behavioral studies on aesthetic judgment surged (Peters 1942), especially since the 1950s. Simultaneously, the rapid development of numerous artistic styles, sometimes organized into movements with interesting dynamics (Carbon 2012), produced increased conceptual complexity in the examples of art while coercing neuroaesthetic to stretch its models in order to include them. One of the most intriguing of such movements is the Dadaism—the anti-art or the artworld to be art—where everyday objects often become difficult to recognize as artworks. In this sense, modern art becomes a subject of scientific interest, as it involves a different need for interpretation of aesthetics than previous art by integrating the artwork's abstract interpretation much influenced by the expertise level of the perceiver.

Although already experimental, the field lacked a unified theoretical framework until the 1970s, when D. Berlyne (1920–1975) introduced a psychobiological viewpoint of aesthetics (Leder and Nadal 2014). Since then, the accumulation of experimental evidence and the growth of technical and methodological sophistication during 1980s and 1990s increased the rigor and versatility of the experimental designs.

As commented, most examples concentrated on visual features such as symmetry in artworks (Attneave and Arnoult 1956), complexity, intensity, brightness, saturation, and size (Berlyne 1970) or even ambiguity (Boselie and Leeuwenberg 1985), color (Zeki 1980), and color harmony (Granger 1955). Other works measured how arousal levels and affective state of the participants can play a role in aesthetic experience (Berlyne 1972) (Cupchik 1995), how the emotional state of participants affect aesthetic ratings (Konečni and Sargent-Pollock 1977), or studied the influence of the context around an artistic object (Frijda 1989).

Behavioral differences were observed between experts in art and students, demonstrating how technical training can affect art valuation and perception (Eysenck 1972; Gordon 1923; Lund and Anastasi 1928). An extent that was proven later behaviorally (Chokron and De Agostini 2000; Hekkert and Van Wieringen 1996; Nodine et al. 1993) and in terms of modern neuroscience regarding painting (Cupchik et al. 2009; Pihko et al. 2011) and music (Bhattacharya and Petsche 2005).

Despite all this effort, studies produced rather unsatisfactory results in terms of allowing the outline of a general framework. As commented, a high diversity of valuation of art between individuals has been reported time and again, clearly suggesting that art training considerably affects aesthetic perception and thereby a major role of individual differences in aesthetic theories (Peters 1942). Even after one of the first psychological models for aesthetic experience was proposed (Parsons 1987), only vague predictions could be assessed. Aesthetic judgments are not only subjective but also highly susceptible to cultural norms, education, and exposure. A point that has very recently been behaviorally verified in twins (Germine et al. 2015).

1.3 1990 to Today

Numerous neurobiological lines of investigation started much earlier than 1990, even as early as 1900, with pioneer works by J. M. Flourense (1794–1867), S. Ramon y Cajal (1852–1934), S. Henschen (1847–1930), or K. Lashley (1890–1958) (Gross 1999), which led to the basis for our understanding of the neurobiological basis for human behavior. Yet, it was only recently, with the advent of advances in neuroimaging such as functional magnetic resonance imaging (fMRI) technique and the improvement of electrophysiological methods—such as electroencephalography (EEG) or magnetoencephalography (MEG) among many others—that a clear progress in the field has been reached. Concerning experimental aesthetics, the application of these new techniques and fundamental approaches blossomed into the new field of *neuroaesthetics*, a term usually attributed to S. Zeki (1998).

A considerable number of conceptual models of neuroaesthetics have been proposed throughout the literature. Furthermore, each model is usually not incompatible with the rest—although with fundamental differences between their interpretations—and not many hypotheses can be easily tested to falsify each model. Generally speaking, the different models explain how aesthetic experiences arise from the interaction among sensorimotor, emotion-valuation, and meaning-knowledge neural systems (Chatterjee and Vartanian 2014), one main influence of these models being that they helped to normalize a sometimes variable set of keywords. An integrative perspective of the knowledge attained through these models can be found in Nadal et al. (2008). Henceforth, we briefly describe the most important ones.

1.3.1 Zeki's Model

In this model (Zeki 1998), the brain's and art's function are in fact the same: to build up true knowledge about the world around us through asynchronous and parallel processes, while discarding specific nonessential information and searching for consistencies. The model explains how artists—whether consciously or unconsciously—use these properties to achieve their goal of triggering specific aesthetic experiences—an idea sustained by other researchers (Livingstone 2002), yet one which dodges an explicit description of how cognitive functions intervene during aesthetic experience.

1.3.2 Ramachandran and Hirstein's Model

First exposed in Ramachandran et al. (1998) and later explained in Ramachandran and Hirstein (1999), this model is more elaborated than Zelki's, including more neurophysiological support as well as an evolutionary and etiological approach, although its description of the processing hierarchy among cognitive and emotional functions during the aesthetic experience itself remains elusive. The model stands that aesthetic experience is due to a reinforcing mechanism triggered when a certain feature of the world around us is of *special importance*. It is a reinforcing signal that produces limbic activation and draws attention to that feature's processing, thereby facilitating the processing while producing pleasurable reward associated with feature binding.

1.3.3 Chatterjee's Model

Adapted from the cognitive neuroscience of visual perception, this model (Chatterjee 2004) is based on two basic assumptions: the nervous system processes information both hierarchically and in parallel, while accounting for multiple components, so that aesthetic experience is derived from responses to such different components. The model delves into the contrast between visual objects that might give pleasure by appealing to basic drives such as the desire for food or sex and aesthetic stimuli that evoke a *disinterested* interest, one which the observer experiences preference and liking, yet without explicit functional apprehensions.

1.3.4 Leder's Model

This model (Leder et al. 2004; Leder and Nadal 2014) is the first to integrate the previous ones within superior cognitive hierarchies, constituting a comprehensive psychological model for aesthetic experience. It was committed to the double proposition that aesthetic experience is the result of multiple perceptual cognitive and affective processes and that the panoply of possible aesthetic experiences owes to the virtually unbounded number of ways in which the components interact and to variations in the relevance of their role in each particular experience (Leder and Nadal 2014).

Following the model, information processing is divided into five self-rewarding and overlapping stages, involving perception, implicit classification, explicit classification, cognitive mastering, and evaluation, all influenced by emotive processing. Therefore, an aesthetic experience is a cognitive process accompanied by continuously upgrading affective states, resulting in an aesthetic emotion. The influence of affective state is of maximal importance, parallel, and distributed over all previous stages, bearing a strong intrinsic motivational potential. Interestingly, Leder's model differentiates between aesthetic emotion and aesthetic judgments as independent *outputs* of the aesthetic experience.

1.4 The Role of Brain Connectivity in the Study of Aesthetic Perception

As it has been the norm throughout the history of aesthetics, the field recruits concepts from other more fundamental developments. That of human brain networks is a good example, where the methodological developments for characterizing brain connectivity (Sporns 2014), despite not being directly related with neuroaesthetics, fit particularly well within previous neuroaesthetic theoretical frameworks. Hence, the number of studies focusing on underlining the interactions between different brain areas is continuously growing in the literature, although in general terms, connectivity studies within neuroaesthetics are still not very common.

The possibility of networks being involved in the aesthetic experience was already suggested in the early 1990s (Lang et al. 1993), although the idea was not seriously considered until much later (Cela-Conde et al. 2004; Jacobsen et al. 2005; Jacobsen 2006). Indeed, Ramachandran and Hirstein's, Leder's, and Jacobsen's models—though most clearly the former—underline the importance of attentional and emotional reinforcement of neural processing of the stimulus during aesthetic experience. We will first review the main brain areas activated during the different stages of aesthetic perception and will proceed to analyze the main brain connectivity networks involving many of these areas, which has been already found to be associated with the aesthetic experience.

2 Neural Activations During Aesthetic Experience

During the last decade, several studies—mainly focused on visual stimuli processing—described a landscape of different brain regions involved in the aesthetic experience. Guided by the conceptual models described above, we can distinguish four main circuits: sensory regions, attentional and evaluative networks, memory involvement, and rewarding networks involving cortical and subcortical regions (and sometimes motor cortices). A recent work has already reviewed many of these results (Nadal 2013).

2.1 *Sensory Regions*

Regarding low- and mid-level hierarchical processing, statistically significant activations have been consistently reported across the literature. Therefore, it is thought that this processing stage is profoundly influenced by aesthetic quality, and probably this influence materializes itself through top-down attentional reinforcement of these early processing stages, although this extent remains to be proved (Cupchik et al. 2009). Visual processing of stimuli, conceived as a multistage integration of visual consciousness, is based on the evidence that the visual brain consists of several parallel multistage processing systems, each specialized in a given attribute such as color or motion (Cela-Conde et al. 2004).

Occipital cortex activity and fusiform gyri (FFG) correlate with aesthetic ratings (Calvo-Merino et al. 2010; Vartanian and Goel 2004) (Cupchik et al. 2009; Kirk et al. 2009a; Lacey et al. 2011) (Höfel and Jacobsen 2007). Bilateral angular gyrus (AG) activity also has demonstrated to register greater activation during beautiful stimuli processing (Cela-Conde et al. 2009) probably as support for enhancement of spatial processing strategies while viewing images by each subject, such as forms and color (Bartels and Zeki 2000) or symmetry and complexity (Jacobsen et al. 2005). Similarly, it has also been reported increased auditory cortex activity during aesthetic judgment of music (Koelsch et al. 2006).

Hierarchically, higher association areas are also related to aesthetic processing. Knowledge and experience facilitate the processing of visual stimuli (Solso 2001); however, results are not simple to interpret, as some areas show decreased activity as the expertise level increases (Aviv 2014; Solso 2001, 2011). To facilitate additional analysis of certain features of the perceived stimulus, several processing cortices can probably signal limbic centers, which subsequently reinforce this further processing. Although the separation of such processes and their related cortices among rewarding and attentional evaluative is adventurous, this is usually the case in neuroaesthetic literature. To complicate things further, motor cortex activation during aesthetic experience has been also reported (Calvo-Merino et al. 2008; Calvo-Merino et al. 2010; Ishizu and Zeki 2013; Kawabata and Zeki

2004; Lacey et al. 2011), particularly in medial premotor supplementary areas such as the medial superior frontal gyrus and possibly due to processing of potential actions delaying response time.

2.2 *Attentional and Evaluative Networks and Memory*

While executive top-down modulatory processes take place and the aesthetic decision is being made, aesthetic experience triggers networks of cortical regions related to evaluative judgment based on internally and externally generated information, the allocation of resources, and the retrieval of information to contextualize the stimuli (Nadal 2013). However, a straightforward model that integrates all this evidence is still missing.

The dorsolateral prefrontal cortex (DLPC)—specifically the left one—is a brain region that participates as a center of perception–action interface in multiple brain functions, which presents increased activation during aesthetic experience (Cela-Conde et al. 2004; Cupchik et al. 2009; Vartanian and Goel 2004; Zeki and Marini 1998). Yet, the eventual implication of prefrontal cortex in aesthetic perception deserves a more detailed study (Cela-Conde et al. 2004), as anatomical evidence shows that there is no single area to which all of the specialized visual areas connect, which would enable to act as an integrator capable of binding signals coming from all of the different visual sources (Zeki and Bartels 1999).

Apparently, when the decision takes place with increased contextual information—and generated externally—the DLPC shows activity, which in addition to the fact that typically more information leads to more aesthetic experience, makes it reasonable to associate these cortices to the inherent aesthetic judgment taking place (Nadal 2013).

The medial prefrontal cortex (Blood et al. 1999; Cela-Conde et al. 2004; Cinzia and Vittorio 2009; Ishizu and Zeki 2011; Jacobsen 2006; Kawabata and Zeki 2004; Kirk et al. 2009b; Lacey et al. 2011; Salimpoor et al. 2011; Vartanian and Goel 2004; Vessel et al. 2012), left temporal pole (LTP) (Jacobsen and Höfel 2003; Jacobsen 2006), the precuneus (PCUN) (Vartanian and Goel 2004), hippocampus (HC), and the left parahippocampal cortex (PHC) (Vessel et al. 2012) show increased activity in association with top-down modulation of attention, memory recruitment, and self-referential evaluative judgments based on internally generated information (Cela-Conde et al. 2011). Ventrolateral prefrontal cortex (VPC) activity is associated with superior attentional loads (Jacobsen 2006; Kirk et al. 2009a) and probably mediated by the thalamus, which has also been reported to interact in the process (Vessel et al. 2012). Posterior cingulate cortex and PCUN activity are associated with semantic memory and familiarity (Jacobsen 2006; Kirk et al. 2009a, 2009b).

2.3 Rewarding Circuit

The rewarding circuit is usually considered to be formed by the ventral striatum (VS), the nucleus accumbens (NAcc) extending into the olfactory tubercle, substantia nigra, ventromedial putamen, and caudate nucleus and interconnected with prefrontal cortex such as the MPC and the orbitofrontal cortex (OFC), the insula, the anterior cingular cortex (ACC), amygdala (Am), and dopaminergic midbrain nuclei (Mbn). In neuroaesthetic literature, it is considered that a key function of this circuit is the reinforcement of particular goal-related outcomes under conditions of uncertainty, where the dopamine pathway is a central component. This way, the central question regarding the rewarding dimension of aesthetic experience is to shed light on the difference between "liking" and "wanting" processes—see (Berridge et al. 2009; Berridge and Robinson 2003) for details.

Findings on aesthetic reward suggest the existence of a mechanism between desired and achieved reward that maps onto dorsal and VS, respectively (Kirk et al. 2009a; Vessel et al. 2012). Indeed, it is well known that the VS is engaged both in coding the reward probability and magnitude; however, ventral STR activation shows involvement with no explicit gain/loss consequences to viewing art or nonart images (Lacey et al. 2011), which complicates the model. A suggested hypothesis is that STR may integrate perceptual, evaluative, and reward components of aesthetic response for the purpose of aesthetic judgment (Vessel et al. 2012).

Salimpoor et al. (2011) have reported increased NAcc and caudate nucleus activity, a direct evidence that the intense pleasure experienced when listening to music is associated with dopamine activity in the mesolimbic reward system, including both dorsal and ventral striatum. It is, nonetheless, hard to imagine the likelihood of a satisfactory quantitative assessment of aesthetic judgment as a sole function of reward, for instance, verifying the relationship between executive rewarding and expectancy. In fact, some authors hypothesize that aesthetic judgment may not be mediated by reward systems at all (Aharon et al. 2001), as they find dissociation between beauty and quantified measures of reward valuation, particularly for beautiful male faces—considering all heterosexual male subjects. A negative deflection in the NAcc is reported when viewing rewarding faces (beautiful female versus average female) and relative negative deflection for nonrewarding faces (beautiful male vs average male), distinguishing then "aesthetic" beauty and "desirable" beauty and probably approaching an understanding of the "sublime" (Armstrong and Detweiler-Bedell 2008).

Similarly, the involvement of amygdalar activity has been hesitantly reported positively in some studies (Aharon et al. 2001; Di Dio et al. 2007; Elliott 2003; Kawabata and Zeki 2004; Kirk et al. 2009b; Lacey et al. 2011; Nadal et al. 2008) and negatively in others (Kawabata and Zeki 2004; Kirk et al. 2009a; Lacey et al. 2011; Vartanian and Goel 2004), which underlines the difficulties of studying this fundamental aspect of aesthetic experience, especially when related to emotional processing, such as the Am contribution to the detection and attribution of salience (Liberzon et al. 2003).

Regarding other areas, the one most profusely mentioned in neuroaesthetic studies is the OFC, a region known to be involved in representing stimulus-reward value (Aharon et al. 2001; Ishizu and Zeki 2013; Ishizu and Zeki 2011; Kawabata and Zeki 2004; Kirk et al. 2009a, b; Lacey et al. 2011; O'Doherty et al. 2003; Tsukiura and Cabeza 2011; Vessel et al. 2012), along with the ventromedial prefrontal cortex (Kawabata and Zeki 2004; Kirk et al. 2009a, b), the ACC (Brown et al. 2004; Cupchik et al. 2009; Petersson et al. 1999; Vartanian and Goel 2004), the insula (Vartanian and Goel 2004), the right caudate nucleus (Vartanian and Goel 2004), and the hypothalamus (Lacey et al. 2011). It is, therefore, reasonable to expect that part of the neural response to art should reflect the rewarding aspects of this experience by activating the reward circuit (Lacey et al. 2011).

A subject of major discussion (Ishizu and Zeki 2013) is whether aesthetic judgments engage areas over and above those that are also engaged in other judgments such as the medial OFC and lateral OFC, although probably separate subdivisions within the medial OFC may be active when judgments are made and beauty is experienced. The medial OFC is heavily connected with the lateral OFC, and the role of each subdivision is not clear. Almost all the studies of aesthetic experience tend to underline the medial OFC as an area of major importance, while the lateral OFC is related to the evaluation of punishers or related to overriding previously rewarded stimuli.

2.4 Temporal Dynamics of Aesthetic Perception

Typically, a two-phase dynamic has been described as the most probable structure occurring during an aesthetic appreciation task. It consists of an initial brief and autonomous—implicit—processing phase of 300–400 ms after stimuli onset, where the beholder captures low- and mid-level of processing features of the perceived object. Subsequently, followed by a high-level associated processing stage, where, most probably, the response decision takes place. This second stage, beginning close to 600 ms after stimulus presentation, involves a deeper aesthetic evaluation related to right hemisphere activity (Jacobsen 2002). However, the actual time ranges might vary due to stimulus-dependent latencies associated with different modalities. For instance, processing of style starts later and develops more slowly than the processing of content (50 ms vs 10 ms) (Augustin et al. 2011).

A rather elusive question is whether each process could be decomposed to identify the contributions of the different hierarchies of processing, all modulated by previous knowledge and top-down attentional processes and conditioned by emotional cadence. So much so, considering the evidence, that some properties of aesthetic objects can be attained in a fraction of a second (Leder and Nadal 2014), with exposures as short as 50 ms (Locher and Nagy 1996).

From a neurobiological perspective, the dynamics of dopamine release may contribute to reward processing over time, as it has been found that hemodynamic activity in regions showing dopamine release is not constant through the episode, but is restricted to moments during peak experience, and specifically in the NAcc and right caudate (RC) (Salimpoor et al. 2011).

3 Aesthetic Brain Networks

Aesthetic experience allows the beholder "to perceive–feel–sense" an artwork, which in turn implies the activation of sensorimotor, emotional, and cognitive mechanisms (Cinzia and Vittorio 2009). As we have already seen, the experience of art is complex and entails multiple cognitive levels, involving a network of multiple brain cortical and subcortical regions. From this point of view, it is reasonable to study aesthetic experience within the framework of functional brain networks. This relatively new field of systems neurosciences is based on a broader, older scientific discipline termed as complex network science. Understood as the study of interactions between complex systems, it provides, with the help of tools borrowed from graph theory, a solid framework for the study of the interaction between specialized brain's subsystems, their hierarchy, and their *emerging properties*.

The dynamics of neurophysiologic systems and the temporal and spatial variability of neural signals generated by the cortex make the analysis of brain activity a challenge that is similar to other complex systems (Bucolo et al. 2008). This way, this approach is not just a theoretical outset of different cognitive functions being conceived as a whole, but rather an actual attempt to measure their relationship.

3.1 Measuring Brain Networks

Functional connectivity (Friston 1994) is understood as the existence of statistical interdependence between neuroimaging data stemming from different brain areas. It has proven to be a very useful concept to underline interactions between brain regions and provides a perspective of brain function complementary to that of the (in)activation of individual areas (Bassett and Bullmore 2009; Sporns 2013; van den Heuvel and Sporns 2013). In simpler terms, brain connectivity can be understood as a measure of information sharing between functional systems in the brain. This way, FC aims to underline information flow between two cortical/subcortical brain regions unveiling brain networks involved in the process. Once such networks are highlighted, graph theory metrics characterize different properties of the network, like clustering coefficient, characteristic path length, efficiency, and small-worldness (Rubinov and Sporns 2010).

3.2 Functional Connectivity During Aesthetic Experience

A model of aesthetic processing relies on the interaction between the anterior insula and the OFC—though in no way restricted to aesthetic processing—which may be related to the assignment of valence to objects (Brown et al. 2011). This model is further supported by other structural connectivity-based evidences, which relate specifically to the possible mechanisms by which OFC might engage during the task (Cohen et al. 2008).

Another well-established hypothesis is that synchronization of neural oscillations across brain areas is important for flexibly linking different task-relevant neuronal populations (Fries 2005; Varela et al. 2001). Recently, using mutual information as a measure of association, Lin et al. (2013) studied the effect of artistic training in the features of resting-state functional brain networks. This study demonstrated that artistic training does not alter the general efficiency of the brain networks in terms of short- and long-range connectedness and communication efficiency, with no significant differences in modularity, which agrees with previous results considering controversial inquiries such as the contribution of the mirror neural system to aesthetic experience (Casati and Pignocchi 2007). However, when studying the actual modules, differences in their structure were indeed visible, mainly in the cerebellum—bilaterally—among other areas. This art-specific organization in the cerebellum may be determined by control circuitry for complex voluntary movements associated with each task. This result matches other evidences related to the formation of task-relevant networks during learning when studied through beta and gamma oscillations (Hipp et al. 2012).

Lacey et al. (2011) used Granger causality applied to fMRI and found that the VS—bilaterally—selectively engages during aesthetic contemplation of art images. Yet, the VS is driven by visual cortex but not by regions that were correlated with aesthetic preference.

Informative as these studies may be, the dynamic nature of the aesthetic appreciation task described above cannot be tackled with the slow fMRI signal. Instead, MEG data have recently been used for this purpose by means of phase synchronization FC methods (Cela-Conde et al. 2013). Despite the difficulties inherent to study fast dynamics during a cognitive task (Roland et al. 2014), a distinctive functional brain network in the beta frequency band could be identified in each of two temporal windows used, associated with different processes with fronto-medial cortex, PCUN, and the posterior cingulate cortex, among other regions, playing a significant role. Consistently with the two-phase model described in Sect. 2.4, a fast aesthetic appreciative perception is first formed within the 250- to 750-ms time window—after the stimulus onset—activating an *initial aesthetic network,* which is engaged during both beautiful and non-beautiful stimuli. And then, a *delayed aesthetic network* is later highlighted during a 1000- to 1500 ms time window, more engaged during beautiful stimuli, which involves mainly the left frontal and parieto-occipital regions.

Interestingly, the OFC—mainly the left one—along with the anterior medial prefrontal cortex (MPFC) and the superior frontal gyrus has shown a deep involvement in aversive processing, which could account for these underlined links (Nitschke et al. 2006) and a step-like response (Aharon et al. 2001; Cupchik et al. 2009), while probably supporting the analysis of emotional responses and personal relevance of a perceived object.

3.3 Reinforcing Processing

The straightforward interpretation of the previous results within the different neuroaesthetic frameworks is the highlighting of the reinforcing effect of attention modulating hubs and rewarding processes in the frontal lobe. As frontal areas involved in high integrative functions support the combination of information, working memory, direction, and maintenance of attention, it is possible that aesthetic stimuli are endowed with more attention.

This explanation has been theorized as a possible cause for findings regarding attentional networks (Lengger et al. 2007). Indeed, during normal brain functioning, isolating a single feature of a perceived object, allocating attention, and fully devoting resources for processing such feature will probably be facilitated if such feature is *pleasing*. Such is the actual substrate of Ramachandran and Hirstein's model (Ramachandran and Hirstein 1999). Being all properties of the brain geared towards discovering interesting object-like entities in the world around us. Of particular interest are the ACC and the left parietal cortex, whose connectivity was enhanced during the contrast of beautiful vs neutral stimuli (Kawabata and Zeki 2004) [see also (Cela-Conde et al. 2013)].

Regarding visual stimuli, Vessel et al. (2012) reported a step-like response for the most moving images of the protocol, frontal regions, and subcortically in the SN, thalamus, and hippocampus. Likewise, the experience of pleasure while listening to music is associated with dopamine release in striatal reward systems (Salimpoor et al. 2011), interestingly in the right caudate and the right NAcc.

3.4 Networks for Aesthetic and Perceptual Judgment

While studies of aesthetic preference are reasonably consistent in their findings, they may also reveal processes that are not unique to aesthetic preference. Indeed, aesthetic preference is personal. Thus, it is necessary to question each subject for his/her individual thought on each stimulus, which unfortunately engages other processes related to judgment that, while being part of the aesthetic judgment process, are probably not unique to it. For instance, Jacobsen et al. (2005) found that networks related to judgment of beauty partially overlap those underlying evaluative judgments on social and moral cues. Some studies have tried to isolate responses attributable to the status of an image as art by focusing on finding neural responses to art images in contrast to nonart images (Lacey et al. 2011) and, therefore, verifying if visual art is intrinsically rewarding and thus elicits activity in the reward centers of the brain, such as the VS. This approach can be considered as orthogonal to prior ones exploring the neural correlates of aesthetic preference. Other studies have deliberately avoided using art images and, yet, have found implication of the VS (Kirk et al. 2009a). The recursive activation of VS might suggest the involvement of dopaminergic mechanisms (Salimpoor et al. 2011).

Yet, it might also be that these two qualitatively different kinds of judgment are not completely independent, so that to uncover each process separately, the differences regarding each stimulus must be as subtle as possible. A recent study tried to distinguish between the neural networks engaged in aesthetic judgments about paintings from those concerning their brightness (Ishizu and Zeki 2013). These authors described two overlapping networks: one involved in perceptual and aesthetic judgment formed by the insula, the DLPC, and the intraparietal sulcus and a second one, involved only in aesthetic judgments, consisting of the medial and lateral OFC. The study also segregates two different motor pathways: one involved in both types of judgments and formed by the premotor cortex and supplementary motor areas and a second system formed by the basal ganglia and the cerebellum. As for these results, the question is whether the previously reported fronto-parietal connectivity considered as part of the aesthetic experience is part of the necessary judgement task that takes place during the aesthetic experiment.

3.5 The Default Mode Network Hypothesis

The default mode network (DMN) is one among several resting-state networks (RSNs) that include the medial prefrontal cortex, the posterior cingulate cortex, the temporo-parietal junction, lateral temporal cortex, superior frontal gyrus, and the hippocampus. The activation/deactivation of the DMN is a matter of much interest (Greicius et al. 2003). Typically, its coherent activity is reduced when subjects engage in externally oriented tasks and the beholder performs central-executive related activities (Sridharan 2008), whereas it is activated in the absence of directed tasks (resting state) suggesting that the DMN is a network of brain areas associated with inward contemplation and self-assessment and is probably a prior for task-driven patterns of activity (Raichle and Jarrett 2009).

RSN can be studied both with fMRI and with EEG/MEG, among other methods, as several techniques allow to recover the network dynamics (Betti et al. 2013; Brookes et al. 2011a, b; Liu et al. 2010; Pasquale et al. 2010). This way, it has become apparent by means of different techniques that networks of brain regions maintain, even at rest or in the absence of any stimulus, neural activity with a high degree of temporal correlation (Betti et al. 2013; Biswal et al. 1995; Deco and Corbetta 2011).

A bold model presented in Vessel et al. (2012) and later elaborated in Vessel et al. (2013) suggests that certain artworks may be so well-matched to an individual's unique makeup that they obtain access to the neural substrates concerned with the self and facilitate a sense of being "moved." The DMN activity may hint this *self-relevance* in a physiological sense. Indeed, the anterior MPFC, an area belonging to the DMN, has previously been associated with self-referential mentation. Vessel's model is supported by empirical evidence that those artworks, regarded as the best in terms of aesthetic quality, show a fundamentally different pattern of neurophysiological activation. This aesthetic experience of objects rated as top quality is not only revealed by the amount of activation but also by the level of engagement of additional networks, of which the anterior MPFC, the left PCUN, and the hippocampus are key nodes. In other words, highly rated images led to greater correlations than baseline, whereas low-rated images led to decreased activity with regard to resting baseline. Thus, the anterior MPFC may function as a gateway into the DMN, signaling personal relevance and allowing a better integration of external sensations related to an art object and internal evaluative and emotional states.

It is possible to find reinforcing reports on the validity of the DMN hypothesis in relation to aesthetics, and the fact that RSN closely resembles that of functional systems identified during task performance is not unique to this field (Kelly et al. 2012). When actively looking for the time-course dynamics of aesthetic experience, similarities with the DMN have been reported to occur only during a late time window of 1 s after the stimulus onset Cela-Conde et al. 2013). Besides, a multimodal study using both MEG and fMRI (Lin et al. 2013), when focusing on non-DMN resting-state networks, found robust decrease in network strength in alpha and beta bands' activity, while other task-dependent networks, such as the occipital visual network, are engaged during the execution. However, hierarchical modular network organization can be effectively sculpted through long-term interaction with artworks (Lin et al. 2013), which can be interpreted as the learning-related brain neuroplasticity mechanism by which expertise influences aesthetic responses.

4 Conclusions

We have seen that despite the difficulties inherent to the study of neuroaesthetics due to the subjective nature of the aesthetic judgement, a series of recent works have already ventured to analyze it from the point of view of FC and functional brain networks. Although fMRI has been the technique mostly used in these works, there have been some MEG and multimodal studies, which have already shed some light into both the oscillatory nature of FC and its dynamics in aesthetic perception. In particular, they have shown the existence of two phases in the aesthetic judgement and the predominant role of alpha and beta bands on this complex cognitive process. Thus, brand new as it is, we believe that these results clearly suggest that the paradigm of FC can be successfully applied to uncover the neural mechanisms associated to aesthetic perception; yet, further studies are necessary to elucidate whether it will be able to provide insight into which of the current models is closest to the actual set of processes that takes place in our brain when perceiving a stimulus and judging it aesthetically.

Bibliography

Aharon I, Etcoff N, Ariely D, Chabris CF, O'Connor E, Breiter HC (2001) Beautiful faces have variable reward value: fMRI and behavioral evidence. Neuron 32(3):537–551. doi:10.1016/S0896-6273(01)00491-3

Armstrong T, Detweiler-Bedell B (2008) Beauty as an emotion: the exhilarating prospect of mastering a challenging world. Rev Gen Psychol 12(4):305–329. doi:10.1037/a0012558

Attneave F, Arnoult MD (1956) The quantitative study of shape and pattern perception. Psychol Bull 53(6):452–471. doi:10.1037/h0044049

Augustin MD, Defranceschi B, Fuchs HK, Carbon C-CC, Hutzler F, Dorothee AM et al (2011) The neural time course of art perception: an ERP study on the processing of style versus content in art. Neuropsychologia 49(7):2071–2081. doi:10.1016/j.neuropsychologia.2011.03.038

Aviv V (2014) What does the brain tell us about abstract art? Front Hum Neurosci 8:85. doi:10.3389/fnhum.2014.00085

Bartels A, Zeki S (2000) The architecture of the colour centre in the human visual brain: new results and a review. Eur J Neurosci 12(1):172–193. doi:10.1046/j.1460-9568.2000.00905.x

Bassett DS, Bullmore ET (2009) Human brain networks in health and disease. Curr Opin Neurol 22(4):1015–1026. doi:10.1016/j.tics.2011.03.006.Understanding

Berlyne DE (1970) Novelty, complexity, and hedonic value. Percept Psychophys 8:279–286. doi:10.3758/BF03212593

Berlyne DE (1972) Ends and means of experimental aesthetics. Can J Psychol/Revue Canadienne de Psychologie 26(4):303–325. doi:10.1037/h0082439

Berridge KC, Robinson TE (2003) Parsing reward. Trends Neurosci 26(9):507–513. doi:10.1016/S0166-2236(03)00233-9

Berridge KC, Robinson TE, Aldridge JW (2009) Dissecting components of reward: "liking", "wanting", and learning. Curr Opin Pharmacol 9(1):65–73. doi:10.1016/j.coph.2008.12.014

Betti V, DellaPenna S, de Pasquale F, Mantini D, Marzetti L, Romani G, Corbetta M (2013) Natural scenes viewing alters the dynamics of functional connectivity in the human brain. Neuron 79(4):782–797. doi:10.1016/j.neuron.2013.06.022

Bhattacharya J, Petsche H (2005) Phase synchrony analysis of EEG during music perception reveals changes in functional connectivity due to musical expertise. Signal Process 85:2161–2177. doi:10.1016/j.sigpro.2005.07.007

Biswal B, Yetkin FZ, Haughton VM, Hyde JS (1995) Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Reson Med 34(4):537–541. doi:10.1002/mrm.1910340409

Blood AJ, Zatorre RJ, Bermudez P, Evans AC (1999) Emotional responses to pleasant and unpleasant music correlate with activity in paralimbic brain regions. Nat Neurosci 2 (4):382–387. doi:10.1038/7299

Boselie F, Leeuwenberg E (1985) Birkhoff revisited: beauty as a function of effect and means. Am J Psychol 98(1):1–39. doi:10.2307/1422765

Brookes MJ, Hale JR, Zumer JM, Stevenson CM, Francis ST, Barnes GR et al (2011a) Measuring functional connectivity using MEG: methodology and comparison with fcMRI. Neuroimage 56(3):1082–1104. doi:10.1016/j.neuroimage.2011.02.054

Brookes MJ, Woolrich M, Luckhoo H, Price D, Hale JR, Stephenson MC et al (2011b) Investigating the electrophysiological basis of resting state networks using magnetoencephalography. Proc Natl Acad Sci USA 108(40):16783–16788. doi:10.1073/pnas.1112685108

Brown S, Martinez MJ, Parsons LM (2004) Passive music listening spontaneously engages limbic and paralimbic systems. Neuroreport 15(13):2033–2037. doi:10.1097/00001756-200409150-00008

Brown S, Gao X, Tisdelle L, Eickhoff SB, Liotti M (2011) Naturalizing aesthetics: brain areas for aesthetic appraisal across sensory modalities. Neuroimage 58(1):250–258. doi:10.1016/j.neuroimage.2011.06.012

Bucolo M, Grazia FD, Frasca M, Sapuppo F, Shannahoff-Khalsa D (2008) From synchronization to network theory: a strategy for MEG data analysis. In: 2008 Mediterranean conference on control and automation—conference proceedings, MED'08, pp 854–859. doi:10.1109/MED.2008.4602069

Calvo-Merino B, Jola C, Glaser DEE, Haggard P (2008) Towards a sensorimotor aesthetics of performing art. Conscious Cogn 17(3):911–922. doi:10.1016/j.concog.2007.11.003

Calvo-Merino B, Urgesi C, Orgs G, Aglioti SM, Haggard P (2010) Extrastriate body area underlies aesthetic evaluation of body stimuli. Exp Brain Res 204:447–456. doi:10.1007/s00221-010-2283-6

Carbon C-CC (2012) Dynamics of aesthetic appreciation. In: Human vision and electronic imaging XVII, 8291, 82911A–82911A–6. doi:10.1117/12.916468

Casati R, Pignocchi A (2007) Mirror and canonical neurons are not constitutive of aesthetic response. Trends Cogn Sci 11(10):410. doi:10.1016/j.tics.2007.07.007

Cattell J, Glascock J, Washburn MF (1918) Experiments on a possible test of aesthetic judgment of pictures. Am J Psychol 29(3):333. doi:10.2307/1414125

Cela-Conde CJ, Marty G, Maestu F, Ortiz T, Munar E, Fernández A et al (2004) Activation of the prefrontal cortex in the human visual aesthetic perception. Proc Natl Acad Sci USA 101(16):6321–6325. doi:10.1073/pnas.0401427101

Cela-Conde CJ, Ayala FJ, Munar E, Maestú F, Nadal M, Capó M a et al (2009) Sex-related similarities and differences in the neural correlates of beauty. Proc Natl Acad Sci USA 106(10):3847–3852. doi:10.1073/pnas.0900304106

Cela-Conde CJ, Agnati L, Huston JP, Mora F, Nadal M (2011) The neural foundations of aesthetic appreciation. Prog Neurobiol 94(1):39–48. doi:10.1016/j.pneurobio.2011.03.003

Cela-Conde CJ, García-Prieto J, Ramasco JJ, Mirasso CR, Bajo R, Munar E et al (2013) Dynamics of brain networks in the aesthetic appreciation. Proc Natl Acad Sci USA 110(Supplement_2):10454–10461. doi:10.1073/pnas.1302855110

Chatterjee A (2004) Prospects for a cognitive neuroscience of visual aesthetics. Bull Psychol Arts 4:55–60. doi:10.1017/S0140525X00040607

Chatterjee A (2011) Neuroaesthetics: a coming of age story. J Cogn Neurosci 23(1):53–62. doi:10.1162/jocn.2010.21457

Chatterjee A, Vartanian O (2014) Neuroaesthetics. Trends Cogn Sci 18(7):370–375. doi:10.1016/j.tics.2014.03.003

Chokron S, De Agostini M (2000) Reading habits influence aesthetic preference. Cogn Brain Res 10(1–2):45–49. doi:10.1016/S0926-6410(00)00021-5

Cinzia DD, Vittorio G (2009) Neuroaesthetics: a review. Curr Opin Neurobiol 19(6):682–687. doi:10.1016/j.conb.2009.09.001

Cohen MX, Elger CE, Weber B (2008) Amygdala tractography predicts functional connectivity and learning during feedback-guided decision-making. Neuroimage 39(3):1396–1407. doi:10.1016/j.neuroimage.2007.10.004

Cohen MX, Axmacher N, Lenartz D, Elger CE, Sturm V, Schlaepfer TE (2009) Good vibrations: cross-frequency coupling in the human nucleus accumbens during reward processing. J Cogn Neurosci 21(5):875–889. doi:10.1162/jocn.2009.21062

Cupchik GC (1995) The legacy of Daniel E. Berlyne. Empir Stud Arts. doi:10.2190/FLM8-6NQ7-N5WM-WLLT

Cupchik GC, Vartanian O, Crawley A, Mikulis DJ (2009) Viewing artworks: contributions of cognitive control and perceptual facilitation to aesthetic experience. Brain Cogn 70(1):84–91. doi:10.1016/j.bandc.2009.01.003

Deco G, Corbetta M (2011) The dynamical balance of the brain at rest. Neuroscientist 17 (1):107–123. doi:10.1177/1073858409354384

Di Dio C, Macaluso E, Rizzolatti G (2007) The golden beauty: brain response to classical and renaissance sculptures. PLoS One 2(11), e1201. doi:10.1371/journal.pone.0001201

Dutton D (2009) The art instinct: beauty, pleasure, & human evolution. Oxford University Press. Retrieved from https://books.google.com/books?hl=en&lr=&id=jqb6WrXS68kC&pgis=1

Elliott R (2003) Executive functions and their disorders. Br Med Bull 65:49–59. doi:10.1093/bmb/ldg65.049

Eysenck HJ (1972) Personal preferences, aesthetic sensitivity and personality in trained and untrained subjects. J Pers 40(4):544–557. doi:10.1111/1467-6494.ep8970054

Fries P (2005) A mechanism for cognitive dynamics: neuronal communication through neuronal coherence. Trends Cogn Sci 9(10):474–480. doi:10.1016/j.tics.2005.08.011

Frijda NH (1989) Aesthetic emotions and reality. Am Psychol. doi:10.1037/0003-066X.44.12.1546

Friston KJ (1994) Functional and effective connectivity in neuroimaging: a synthesis. Hum Brain Mapp 2(1–2):56–78. doi:10.1002/hbm.460020107

Germine L, Russell R, Bronstad PM, Blokland GAM, Smoller JW, Kwok H et al (2015) Individual aesthetic preferences for faces are shaped mostly by environments, not genes. Curr Biol 25 (20):2684–2689. doi:10.1016/j.cub.2015.08.048

Gordon K (1923) A study of esthetic judgments. J Exp Psychol 6(1):36–43. doi:10.1037/h0071285

Granger GW (1955) Aesthetic measure applied to color harmony: an experimental test. J Gen Psychol 52(2):205–212. doi:10.1080/00221309.1955.9920239

Greicius MD, Krasnow B, Reiss AL, Menon V (2003) Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc Natl Acad Sci USA 100(1):253–258. doi:10.1073/pnas.0135058100

Gross CG (1999) Brain, vision, memory: tales in the history of neuroscience. MIT Press. Retrieved from https://books.google.com/books?hl=en&lr=&id=rHvbFhA76AkC&pgis=1

Hekkert P, Van Wieringen PCW (1996) Beauty in the eye of expert and nonexpert beholders: a study in the appraisal of art. Am J Psychol 109(3):389. doi:10.2307/1423013

Hipp JF, Hawellek DJ, Corbetta M, Siegel M, Engel AK (2012) Large-scale cortical correlation structure of spontaneous oscillatory activity. Nat Neurosci 15(6):884–890. doi:10.1038/nn.3101

Höfel L, Jacobsen T (2007) Electrophysiological indices of processing aesthetics: spontaneous or intentional processes? Int J Psychophysiol 65(1):20–31. doi:10.1016/j.ijpsycho.2007.02.007

Ione A (2003) Examining Semir Zeki's "Neural Concept Formation and Art: Dante, Michelangelo, Wagner". J Conscious Stud 10(2):58–66

Ishizu T, Zeki S (2011) Toward a brain-based theory of beauty. PLoS One 6(7), e21852. doi:10.1371/journal.pone.0021852

Ishizu T, Zeki S (2013) The brain's specialized systems for aesthetic and perceptual judgment. Eur J Neurosci 37(9):1413–1420. doi:10.1111/ejn.12135

Jacobsen T (2002) Aesthetic judgments of novel graphic patterns: analyses of individual judgments. Percept Mot Skills 95(7):755. doi:10.2466/PMS.95.7.755-766

Jacobsen T (2006) Bridging the arts and sciences: a framework for the psychology of aesthetics. Leonardo 39(2):155–162. doi:10.1162/leon.2006.39.2.155

Jacobsen T, Höfel L (2003) Descriptive and evaluative judgment processes: behavioral and electrophysiological indices of processing symmetry and aesthetics. Cogn Affect Behav Neurosci 3(4):289–299. doi:10.3758/CABN.3.4.289

Jacobsen T, Schubotz RI, Höfel L, Cramon DYV (2005) Brain correlates of aesthetic judgment of beauty. Neuroimage 29(1):276–285. doi:10.1016/j.neuroimage.2005.07.010

Kawabata H, Zeki S (2004) Neural correlates of beauty. J Neurophysiol 91(4):1699–1705. doi:10.1152/jn.00696.2003

Kelly C, Biswal BB, Craddock RC, Castellanos FX, Milham MP (2012) Characterizing variation in the functional connectome: promise and pitfalls. Trends Cogn Sci 16(3):181–188. doi:10.1016/j.tics.2012.02.001

Kirk U, Skov M, Christensen MS, Nygaard N (2009a) Brain correlates of aesthetic expertise: a parametric fMRI study. Brain Cogn 69(2):306–315. doi:10.1016/j.bandc.2008.08.004

Kirk U, Skov M, Hulme O, Christensen MS, Zeki S (2009b) Modulation of aesthetic value by semantic context: an fMRI study. Neuroimage 44(3):1125–1132. doi:10.1016/j.neuroimage.2008.10.009

Koelsch S, Fritz T, v. Cramon DY, Müller K, Friederici AD (2006) Investigating emotion with music: an fMRI study. Hum Brain Mapp 27(3):239–250. doi:10.1002/hbm.20180

Konečni VJ, Sargent-Pollock D (1977) Arousal, positive and negative affect, and preference for Renaissance and 20th-century paintings. Motiv Emot 1(1):75–93. doi:10.1007/BF00997582

Lacey S, Hagtvedt H, Patrick VM, Anderson A, Stilla R, Deshpande G et al (2011) Art for reward's sake: visual art recruits the ventral striatum. Neuroimage 55(1):420–433. doi:10.1016/j.neuroimage.2010.11.027

Lang PJ, Greenwald MK, Bradley MM, Hamm AO (1993) Looking at pictures: affective, facial, visceral, and behavioral reactions. Psychophysiology 30(3):261–273. doi:10.1111/j.1469-8986.1993.tb03352.x

Leder H, Nadal M (2014) Ten years of a model of aesthetic appreciation and aesthetic judgments: the aesthetic episode—developments and challenges in empirical aesthetics. Br J Psychol (London, England: 1953) 105(4):443–464. doi:10.1111/bjop.12084

Leder H, Belke B, Oeberst A, Augustin D (2004) A model of aesthetic appreciation and aesthetic judgments. Br J Psychol (London, England: 1953) 95(Pt 4):489–508. doi:10.1348/0007126042369811

Lengger PG, Fischmeister FPS, Leder H, Bauer H (2007) Functional neuroanatomy of the perception of modern art: a DC–EEG study on the influence of stylistic information on aesthetic experience. Brain Res 1158(1):93–102. doi:10.1016/j.brainres.2007.05.001

Liberzon I, Phan KL, Decker LR, Taylor SF (2003) Extended amygdala and emotional salience: a PET activation study of positive and negative affect. Neuropsychopharmacology 28(4):726–733. doi:10.1038/sj.npp.1300113

Lin C-S, Liu Y, Huang W-Y, Lu C-F, Teng S, Ju T-C et al (2013) Sculpting the intrinsic modular organization of spontaneous brain activity by art. PLoS One 8(6), e66761. doi:10.1371/journal.pone.0066761

Liu Y (2003) Engineering aesthetics and aesthetic ergonomics: theoretical foundations and a dual-process research methodology. Ergonomics 46(13–14):1273–1292. doi:10.1080/00140130310001610829

Liu Z, Fukunaga M, de Zwart JA, Duyn JH (2010) Large-scale spontaneous fluctuations and correlations in brain electrical activity observed with magnetoencephalography. Neuroimage 51(1):102–111. doi:10.1016/j.neuroimage.2010.01.092

Livingstone M (2002) Vision and art: the biology of seeing. Abrams, New York, Retrieved from http://www.amazon.com/Vision-Art-The-Biology-Seeing/dp/0810995549

Locher P, Nagy Y (1996) Vision spontaneously establishes the percept of pictorial balance. Empir Stud Arts. doi:10.2190/X8U3-CTQ6-A7J1-8JQ8

Lund FH, Anastasi A (1928) An interpretation of aesthetic experience. Am J Psychol 40(3):434. doi:10.2307/1414460

Nadal M (2013) The experience of art. Insights from neuroimaging. Prog Brain Res 204:135–158. doi:10.1016/B978-0-444-63287-6.00007-5

Nadal M, Munar E, Capo MA, Rossello J, Cela-Conde CJ (2008) Towards a framework for the study of the neural correlates of aesthetic preference. Spat Vis 21(3–5):379. doi:10.1163/156856808784532653

Nitschke JB, Sarinopoulos I, MacKiewicz KL, Schaefer HS, Davidson RJ (2006) Functional neuroanatomy of aversion and its anticipation. Neuroimage 29(1):106–116. doi:10.1016/j.neuroimage.2005.06.068

Nodine C, Locher P, Krupinski E (1993) The role of formal art training on perception and aesthetic judgment of art compositions. Leonardo 26(3):219–227. doi:10.2307/1575815

O'Doherty J, Winston J, Critchley H, Perrett D, Burt DM, Dolan RJ et al (2003) Beauty in a smile: the role of medial orbitofrontal cortex in facial attractiveness. Neuropsychologia 41 (2):147–155. doi:10.1016/S0028-3932(02)00145-8

Parsons MJ (1987) How we understand art: a cognitive developmental account of aesthetic experience. Cambridge University Press, New York, NY, Retrieved from http://psycnet.apa.org/psycinfo/1987-98081-000

Pasquale FD, Della S, Snyder AZ, Lewis C, Mantini D, de Pasquale F et al (2010) Temporal dynamics of spontaneous MEG activity in brain networks. Proc Natl Acad Sci USA 107 (13):6040–6045. doi:10.1073/pnas.0913863107

Peters HN (1942) The experimental study of aesthetic judgments. Psychol Bull 39(5):273–305. doi:10.1037/h0057008

Petersson KM, Nichols TE, Poline JB, Holmes AP (1999) Statistical limitations in functional neuroimaging. I. Non-inferential methods and statistical models. Philos Trans R Soc London Ser B Biol Sci 354(1387):1239–1260. doi:10.1098/rstb.1999.0477

Pihko E, Virtanen A, Saarinen V-M, Pannasch S, Hirvenkari L, Tossavainen T et al (2011) Experiencing art: the influence of expertise and painting abstraction level. Front Hum Neurosci 5:94. doi:10.3389/fnhum.2011.00094

Raichle ME, Jarrett C (2009) The restless brain. Psychologist 22(10):836–839. doi:10.1089/brain.2011.0019

Ramachandran VS, Hirstein W (1999) The science of art. J Conscious Stud 6(6–7):15–35

Ramachandran VS, Blakeslee S, Sacks OW (1998) Phantoms in the brain: probing the mysteries of the human mind. William Morrow, New York

Roland PE, Hilgetag CC, Deco G (2014) Cortico-cortical communication dynamics. Front Syst Neurosci 8(May):19. doi:10.3389/fnsys.2014.00019

Rolls ET (2013) A biased activation theory of the cognitive and attentional modulation of emotion. Front Hum Neurosci 7:74. doi:10.3389/fnhum.2013.00074

Rubinov M, Sporns O (2010) Complex network measures of brain connectivity: uses and interpretations. Neuroimage 52(3):1059–1069. doi:10.1016/j.neuroimage.2009.10.003

Salimpoor VN, Benovoy M, Larcher K, Dagher A, Zatorre RJ (2011) Anatomically distinct dopamine release during anticipation and experience of peak emotion to music. Nat Neurosci 14(2):257–262. doi:10.1038/nn.2726

Santayana G (1896) The sense of beauty: being the outline of aesthetic theory. Indipublish.com, Boston, MA, Retrieved from http://www.amazon.com/The-Sense-Beauty-Outline-Aesthetic/dp/0486202380

Singer, W. (2010). Temporal coherence: a versatile code for the definition of relations. In The senses: a comprehensive reference, vol 2, pp 1–9. doi:10.1016/B978-012370880-9.00287-5

Solso RL (2001) Brain activities in a skilled versus a novice artist: an fMRI study. Leonardo 34 (1):31–34. doi:10.1162/002409401300052479

Solso RL (2011) The cognitive neuroscience of art a preliminary FMRI observation. J Conscious Stud 8:75–85, Retrieved from http://www.ingentaconnect.com/content/imp/jcs/2000/00000007/F0020008/1043

Sporns O (2013) Making sense of brain network data. Nat Methods 10(6):491–493. doi:10.1038/nmeth.2485

Sporns O (2014) Contributions and challenges for network models in cognitive neuroscience. Nat Neurosci 17(5):652–660. doi:10.1038/nn.3690

Sridharan D, Levitin DJ, Menon V (2008) A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. Proc Natl Acad Sci 105 (34):12569–12574. doi:10.1073/pnas.0800005105

Stein JL, Wiedholz LM, Bassett DS, Weinberger DR, Zink CF, Mattay VS, Meyer-Lindenberg A (2007) A validated network of effective amygdala connectivity. Neuroimage 36(3):736–745. doi:10.1016/j.neuroimage.2007.03.022

Tsukiura T, Cabeza R (2011) Remembering beauty: roles of orbitofrontal and hippocampal regions in successful memory encoding of attractive faces. Neuroimage 54(1):653–660. doi:10.1016/j.neuroimage.2010.07.046

van den Heuvel MP, Sporns O (2013) Network hubs in the human brain. Trends Cogn Sci 17 (12):683–696. doi:10.1016/j.tics.2013.09.012

Varela F, Lachaux JP, Rodriguez E, Martinerie J (2001) The brainweb: phase synchronization and large-scale integration. Nat Rev Neurosci 2(4):229–239. doi:10.1038/35067550

Vartanian O, Goel V (2004) Neuroanatomical correlates of aesthetic preference for paintings. Neuroreport 15(5):893–897. doi:10.1097/00001756-200404090-00032

Vessel EA, Starr GG, Rubin N (2012) The brain on art: intense aesthetic experience activates the default mode network. Front Hum Neurosci 6:66. doi:10.3389/fnhum.2012.00066

Vessel E a, Starr GG, Rubin N (2013) Art reaches within: aesthetic experience, the self and the default mode network. Front Neurosci 7:258. doi:10.3389/fnins.2013.00258

Zeki S (1980) The representation of colours in the cerebral cortex. Nature 284(5755):412–418. doi:10.1038/284412a0

Zeki S (1998) Art and the brain. Daedalus Proc Am Acad Arts Sci 127(2):71–102. doi:10.2307/20027491

Zeki S, Bartels A (1999) Toward a theory of visual consciousness. Conscious Cogn 8(2):225–259. doi:10.1006/ccog.1999.0390

Zeki S, Marini L (1998) Three cortical stages of colour processing in the human brain. Brain 121 (9):1669–1685. doi:10.1093/brain/121.9.1669

Development of Human Neurophysiological Activity and Network Dynamics

Vasily A. Vakorin and Sam M. Doesburg

1 Neural Oscillations, Synchronization, and Cognitive Development

Neurophysiological oscillations reflect fluctuations in the excitability of populations of neurons and are expressed at a variety of timescales. Such rhythms are understood to reflect temporal windows for integration and to play a critical role in cortical information processing and computation, supporting cognition, perception, and motor control (Ward 2003). The coordination of rhythms across brain areas has been purported to deflect functional interactions among brain areas and to provide a mechanism for dynamic communication patterns in the central nervous system (Fries 2015). In this view, the synchronization of neural oscillations across brain areas allows action potentials to arrive at peak windows of excitability, thereby increasing their impact.

Complex cognitive acts require the coordinated activity of many groups of neurons which are often distributed in the brain. Moreover, the same group of neurons may play different functional roles at different times, which is largely defined by other neurons which are coactive and interacting at any given time (McIntosh 2000). Neural oscillations and their synchronization provide a spatial and temporal architecture for the selection and integration of relevant neuronal elements into a task-dependent large-scale functional ensemble supporting cognitive, perceptual, and/or motor control process required at any given moment (Varela et al. 2001). Theoretically, neural oscillations and synchronization provide a mechanism for network integration and dynamics supporting the diverse repertoire of human cognition and behavior. The emergence of these neurophysiological

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S. Palva (ed.), *Multimodal Oscillation-based Connectivity Theory*,
DOI 10.1007/978-3-319-32265-0_7

processes plays a critical role in neurocognitive development. This chapter reviews the research on the development of brain oscillations, their synchronization among brain areas, and their relation to aspects of human neurophysiological activity such as complexity and metastability. From such a perspective, the maturation of local brain oscillations, reflected in spectral power, provides fluctuations in excitation/inhibition which provide temporal windows for integration within and among brain areas. Accordingly, examination of the maturation of neurophysiological networks should rightly begin with an understanding of the developmental trajectory of spectral power.

2 Spectral Power and Development

Local spontaneous neurophysiological oscillations are reflected in the spectral power of electroencephalographic (EEG) and magnetoencephalographic (MEG) recordings. A number of studies have characterized human brain development by tracking the changes in EEG and MEG spectral power, which reflects the average amplitude of the brain signals at specific frequencies. Two main effects have been identified. First, studies have observed the redistribution of frequencies around the alpha band toward higher frequencies. Second, the report included both increases and decreases in the signal power at lower and higher frequencies, respectively, defined with respect to the alpha band. Specifically, Stroganova et al. (1999) explored the properties of the 5–10 Hz occipital EEG rhythm in infants. They found that it expressed the classical properties of alpha rhythm, a spectral peak at approximately 10 Hz in the adult EEG, with the group mean of alpha peak frequency increasing approximately from 6 Hz at 8 months to 7 Hz at 11 months of age. Similar results were obtained by Marshall et al. (2002) who studied infants and children up to 51 months of age.

A maturational shift of the alpha peak toward higher frequencies can also be observed in adolescence. To determine developmental changes of quantitative EEG development, Martinović et al. (1998) investigated the EEG power spectra in healthy twins (with approximately equal number of girls and boys) ranging in age from 7 to 15 years. The authors reported a progressive increase of higher alpha power inversely related to lower alpha and theta power. In addition, the mean frequency of activity increased with age, with females showing a significantly higher mean frequency of higher alpha power. In a longitudinal study, Cragg et al. (2011) explored the development of the EEG power spectra covering 10–13 years of age. A small but significant increase in peak alpha frequency was detected with age. Interestingly, males demonstrated higher alpha power than females, but the method was not sensitive enough to detect possible gender differences in peak frequency. The view that such maturational shifts in peak alpha frequency correspond to development of brain function relevant for cognitive abilities is supported by observations that peak alpha oscillatory frequency is “slowed” in school-age children born very preterm and that slower peak frequency was correlated with lower visual–perceptual abilities in this group (Doesburg et al. 2011, 2013).

Another important observation regarding the maturation of neurophysiological activity was made by Marshall et al. (2002), who studied infants and children and described the general developmental decrease in EEG signal power at lower frequencies (<6 Hz) and a increase at higher frequencies (>6 Hz). This trend continues into adolescence. A number of studies have replicated the findings of decreases at lower, and increases at higher, frequencies with age. In the longitudinal study by Cragg et al. (2011), it was shown that delta and theta frequencies power decreased as a function of age and higher alpha and beta frequencies increased. Similar results have been reported by Gasser et al. (1988) and McIntosh et al. (2008) based on evoked EEG activity. Gómez et al. (2013) also reported an increase in power at gamma frequencies of resting-state MEG recordings. Importantly, maturation of such power spectra has been linked to development of abilities such as language with such associations being observed as early as infancy (Benasich et al. 2008; Gou et al. 2011).

3 The Development of Spontaneous Neurophysiological Network Connectivity

The development of local oscillatory activity is relevant for spontaneous expressions in the periodic excitability of neuronal groups and is accordingly relevant for the maturation of neurophysiological interactions among brain areas. Specifically, alignment of oscillatory phase between neural populations can promote communication by allowing bursts of action potentials to be exchanged during the depolarized phase of fluctuations in the receiving neuron's membrane potentials (Fries 2015). A recent study of developmental changes of such resting phase synchrony in a large group of children 5–7 years of age with scalp EEG revealed a shift toward decreased synchronization in all analyzed frequency ranges with coincident with increasing tendency toward "small-world" network topologies (Boersma et al. 2011). Subsequent study using the "minimum spanning tree" technique indicated increasing the regularity of brain networks with age and suggested that girls may be ahead of boys in the restructuring of neurophysiological networks (Boersma et al. 2013). Analysis of developmental changes in resting phase locking among scalp EEG electrodes in infants and children between 1 and 66 months revealed increasing synchrony in the theta and alpha bands, together with decreasing connectivity in the higher beta and lower gamma bands (Vakorin et al. 2011a). Analysis of resting MEG amplitude correlations among regions comprising fMRI-defined resting-state networks indicates increasing connectivity with age, particularly in the beta and alpha bands, across childhood, adolescence, and early adulthood (Schäfer et al. 2014). No differences between maturational changes were observed between intra-network and inter-network connections. This stands in contrast to fMRI studies that indicate that development involves a shift from a local to a distributed pattern of connectivity (Fair et al. 2009), characterized by a strengthening of within-network connections and a weakening of connectivity between regions involved in different resting-state networks (Dosenbach et al. 2010).

4 Task-Dependent Network Synchronization, Cognition, and Development

Considerable evidence indicates that modulation of local neural oscillations, as well as interregional oscillatory synchronization, supports transient network connectivity supporting a plethora of cognitive, perceptual, and motor processes (Ward 2003). From this point of view, maturation of neurophysiological oscillations contributes critical to the development of functional cortical networks (Uhlhaas et al. 2010). Such phenomena are expressed at multiple scales (Varela et al. 2001), and large-scale network dynamics are most effectively noninvasively measured using MEG as it is a direct measure of neural activity with an unparalleled combination of spatial and temporal resolution (Palva and Palva 2012). The functional roles of synchronization in different frequency ranges remain a subject of ongoing research. It has been proposed that oscillations at different frequencies correspond to different scales of integration (von Stein and Sarnthein 2000) or to feed-forward and feed-back interactions (Donner and Siegel 2011). This view is complicated by observations that synchronous oscillations may play different roles at different cortical scales. For example, alpha oscillations are thought to reflect inhibition locally but may mediate integration in large-scale brain networks (Palva and Palva 2007). Oscillations in specific frequency ranges have also been associated with specific brain systems and cognitive processes. For example, alpha rhythms are prominent in visual cortex and are associated with visual attention and working memory and can also be strongly modulated by opening and closing the eyes. Further complicating the interpretation of oscillatory network coherence, it is becoming clear that interregional cross-frequency phase synchronization (Palva et al. 2005), amplitude correlations (Engel et al. 2013), and phase-amplitude coupling (Canolty and Knight 2010) play a role in cognitive processing. Though the precise mechanics of how neurophysiological network interactions support cognition remains incompletely understood, it is clear that processes that require the coordinated participation of numerous brain regions are associated with increased interregional oscillatory coherence.

The recruitment of neurophysiological synchronization among brain regions changes with development. Using a well-characterized response of synchronization among brain areas during perceptual integration, Uhlhaas et al. (2009) demonstrated a complex maturational course for perception-dependent network synchronization which involved multiple frequency ranges and suggested late restructuring of integrative network responses in adolescence. Expressive language processing has also been associated with increasing MEG network synchronization with age, particularly in the theta band, and this increased recruitment of task-dependent synchronization associated with the development of language abilities (Doesburg et al. 2010). Reduced network task-dependent network synchronization is also associated with selective developmental difficulties in school-age children born very preterm suggesting that the maturation of task-dependent neurophysiological network integration is pertinent for both typical and atypical cognitive developments (Doesburg et al. 2011).

5 Neurophysiological Signal Complexity and Development

Signal complexity relates to the information content or unpredictability of a signal and potentially also provides information regarding interactions among brain rhythms at different frequencies (Vakorin and McIntosh 2012). Moreover, signal complexity has been linked with the connectivity of a brain region in a neurophysiological network (Mišić et al. 2011, Vakorin et al. 2011b). In general, signal complexity is notoriously difficult to define. In practice, the definition of complexity is essentially reduced to an interpretation of a specific measure used to estimate the signal complexity. One popular type of measure is based on nonlinear dynamics. In this case, one assumes that time series is viewed as a realization of a nonlinear dynamic system, which is, in general, multidimensional and is potentially interacting with other systems. Under this assumption, signal complexity can be understood as a global property of a dynamic system underlying the observed time series. Examples of such approach can include information-theoretic estimates of complexity, such as all kind of entropy measures, or chaos-based estimates of complexity.

The modeling of dynamical systems is based on the concept of a phase space, which is defined as a set of all possible states of a dynamic system. Each state of a dynamic system can be characterized by a unique point in the phase space. In a nonlinear analysis of EEG or MEG, mathematical descriptions of dynamical models are unknown. Thus, the state space has to be reconstructed. One typical approach is based on the procedure called time delay embedding, wherein an observed EEG or MEG time series is converted to a sequence of vectors in a multidimensional space. In doing so, the ultimate goal is not to reconstruct an orbit in the phase space that is closest to the true one, but rather to estimate the macro-characteristics of a dynamic such as complexity. Takens' embedding theorem provides the conditions under which this can be done (Takens 1981).

One popular measure to estimate complexity of a nonlinear dynamical system is sample entropy (Richman and Randall Moorman 2000). Sample entropy is a refined version of approximate entropy (Pincus 1991), which was proposed to quantify the Kolmogorov entropy from short and noisy time series. In turn, the Kolmogorov entropy is a measure of the mean rate of information generated by a dynamical system (Kolmogorov 1959; Sinai 1959). It measures the unpredictability of the system. In particular, it represents the uncertainty that remains in the next state under the condition that the complete history of all the previous states of the dynamical system is known. Sample entropy and approximate entropy are examples of the information-theoretic approach to estimate signal complexity.

Among chaos-based measures of complexity, Lyapunov's components and correlation dimension have been used in EEG analysis. The largest Laypunov exponent of a dynamical system reflects the rate at which two nearby trajectories of the system separate over time, thus indicating the system unpredictability. Correlation dimension is a measure for the dimensionality of the space occupied by the points in the phase space and, thus, can provide insights into the variability of the dynamic repertoire of neural activity.

Several studies have demonstrated developmental changes in the complexity of neurophysiological signals which can be observed quite early in life. Meyer-Lindenberg (1996) estimated the Laypunov exponent and correlation dimension to analyze the marked changes in resting-state EEG of healthy infants and children (from newborns to 14 years old) during normal development. The study provided the evidence for the presence of nonlinear dynamics, even in newborns. Also, brain development was characterized by increases in correlation dimension. Janjarasjitt et al. (2008) explored the relations between the correlation dimension of sleep EEG and neurodevelopment for premature and full-term neonates up to 43 weeks of postmenstrual age (PMA). The EEG signals were low-passed filtered with a cut-off frequency of 29 Hz. First, the authors found that EEG complexity increased with age. Second, the brain dynamics of neonates born prematurely was found to be less complex than that of full-term neonates even at the same PMA. Similar results were previously found by Scher et al. (2005) and Pereda et al. (2006) who studied the topography of neonatal EEG as a function of PMA and sleep stage. Specifically, the same trends were reported for age-related increases in dimensional complexity during active and quite sleep. Also, dimensional complexity was higher in the state of active sleep than during quite sleep in central and temporal channels.

The results obtained in neonates using the dimensional complexity have been complimented by the results based on sample entropy. For example, Zhang et al. (2009) explored the changes in sample entropy of EEG recorded from newborns with PMA ranging from 25 to 60 weeks. Importantly, they studied not only the age-related changes in mean values but also age-related changes in the variability (interquartile range) of sample entropy. They reported higher sample entropy values (higher information content) during active sleep than during quite sleep, similar to studies based on dimensional complexity. At the same time, sample entropy was first increasing, but after approximately 42 weeks this trend was stopped in quite sleep, and even was reversed in active sleep as newborns were reaching term age. In addition, a district increase in the variability of sample entropy was reported from 25 to 50 weeks of PMA, followed by maintenance of lower fluctuations in sample entropy.

One disadvantage of the above-mentioned studies is that the signal complexity was estimated using the broadband signals, and thus it lacks temporal specificity, as it is not clear which frequency bands contribute the most to the reported effects.

However, signal complexity can be estimated at different scales. Zhang (1991) introduced a complexity measure based on entropy (or more specifically, Shannon entropy or, as it is defined in the information theory, an expected amount of information contained in a message) of various scales. Essentially, coarse-grained signals were generated through down-sampling the original time series by averaging adjacent data points within nonoverlapping windows of varying lengths. Such approach is in essence equivalent to applying the low-pass filter with a lower and lower cut-off frequency. Then, entropy is calculated for each of the coarse-grained signals. Costa et al. (2002) proposed to unify sample entropy with an idea of coarse-grained time series. This approach is known as multi-scale entropy (MSE).

McIntosh et al. (2008) applied MSE to characterize the relationships between the brain development and variability of EEG signals in children (6–16 years) and young adults (20–33 years). EEG was recorded from the typically developing participants performing a rapid face recognition task, when a novel or familiar face was present, and the participants responded by pressing one of two buttons depending on whether or not they recognized the face. Changes in EEG were characterized in terms of complexity estimated as MSE, and the pre- and post-dimensionality of trial-to-trial variability, defined as the number of principal components that capture 90 % of the variance across trials. A robust gradual increase both in MSE and principal component analyses was observed across age groups. The maturation-related increase in sample entropy was widely distributed across almost all the electrodes at all scales. Given similar age-related changes in SampEn across the scales, a cumulative index of maturational changes in the complexity of EEG signals was computed as the area under the MSE curve. McIntosh et al. (2008) found that signal complexity negatively correlated with response times and positively with accuracy. In other words, higher complexity (information content) was associated with more stable and accurate behavior. Atypical task modulation of source-resolved neuromagnetic MSE measures has also been reported in adolescents with autism, suggesting that altered development of neurophysiological complexity may be linked to developmental difficulties in pediatric populations (Mišić et al. 2015).

Changes in EEG signal complexity were obtained during early development. Specifically, Lippé et al. (2009) studied typically developing infants and children from 1 to 60 months of age, as well as young adults between 20 and 30 years old. The visual- and auditory-evoked potentials were measured in response to a black and white checkerboard presented binocularly and broadband noise presented binaurally in a soundproof room. Typically, in such studies, morphological differences in the waveforms of the event-related responses prevent direct comparison of the developmental trajectories between the visual and auditory systems. Complexity measures, however, do not depend on these specific features and, thus, provide tools to directly compare the different sensory systems. For both conditions, age-related differences were found significant and robustly expressed across all the studied scales. Meanwhile, differences in signal complexity between the visual and auditory systems were significant only for children, but not for adults, with values of signal complexity for the responses to visual stimuli.

Thus, complexity can be a very sensitive measure to characterize the brain signals, adding richer interpretations to data, which may also reflect the presence of nonlinear effects. Caution should be exercised, however, when interpreting the results based on statistics that presumably can capture nonlinear dynamics. Complexity measures can represent not only the information generated by deterministic nonlinear systems as models for neural dynamics but also the variability related to the instrumental or physiological noise described as stochastic processes. It is worth noting here that some stochastic processes such as filtered noise can mimic low-dimensional deterministic nonlinear dynamics (Rapp et al. 1993).

One of the confounding factors for interpreting differences in complexity between groups or conditions is spectral power. A number of studies have reported correlations between spectral power and complexity measures. For example, sample entropy computed on the original time series was found to be negatively correlated with the power at the lowest frequencies (delta band) and positively correlated with the power at the highest frequencies explored (beta band) in a study comparing middle-aged and elderly female adults during different stages of sleep (Bruce et al. 2009). A better predictor of sample entropy was the power ratio of the higher frequencies (alpha and beta) over lowest frequencies (delta and theta). As discussed in Kaffashi et al. (2008), linear properties of a signal may significantly contribute to sample entropy computed at the original, not coarse-grained, signals.

A number of studies on development and aging reported similar observations. As previously discussed, McIntosh et al. (2008) showed that brain maturation was characterized by increases and decreases in spectral power at higher ($<$15 Hz) and lower ($<$10 Hz) frequencies, respectively, and simultaneously age-related increases in complexity. In particular, increasing the magnitude of the Fourier coefficients of EEG in adults at low frequencies led to the MSE curves that were close to those in children. Similar results were found by Lippé et al. (2009), wherein age-related changes in sample entropy were accompanied by both increases and decreases in power at higher ($>$7 Hz) and lower ($<$5 Hz) frequencies, respectively. Several studies on the neuropathology of aging reported analogous correlations between sample entropy and power (Park et al. 2007; Mizuno et al. 2010).

A question remaining from such studies is whether differences in complexity measures between groups or conditions can be reduced to or fully explained by corresponding differences in spectral power. Vakorin and McIntosh (2012) tested normalized age-related changes in sample entropy in a longitudinal study on brain development in adolescence. The authors explored how differences in multi-scale entropy computed on the original EEG and on surrogated data, which were normalized to the MSE computed for the surrogate signals, evolve from 10 to 13 years of age. Artificial or surrogate signals were constructed through a procedure, wherein spectral and cross-spectral power remains unchanged, but interactions between frequencies, if any, are destroyed. Specifically, surrogate signals were generated by applying Fourier transform, randomizing the phase of Fourier coefficients, and then applying the inverse Fourier transform. Two effects were reported. First, there were significant differences between the MSE curves computed from the original and surrogate data, the differences increasing toward the coarse scales.

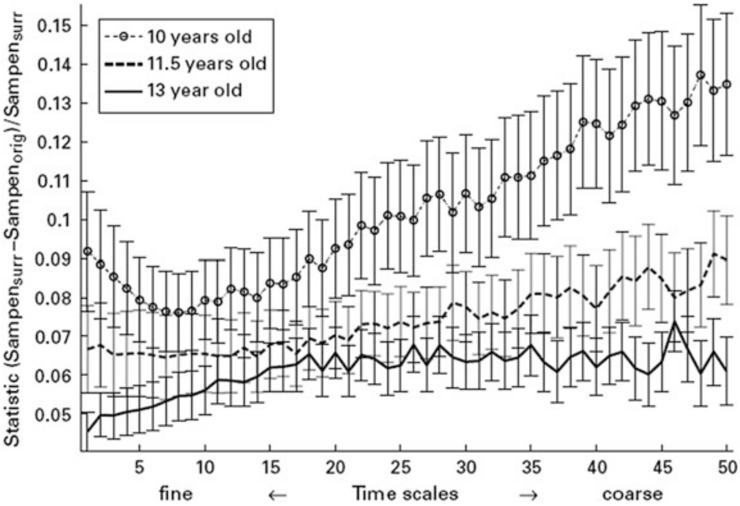

Fig. 1 Age-related changes in sample entropy, normalized with respect to sample entropy computed from surrogate data (original signals with destroyed interactions between frequencies)

Expectedly, the sample entropy was higher for the surrogate data than for the original signals, as with phase randomization the signals become more unpredicted. Second, the relative differences in the MSE curves between the original and surrogate data decreased with age (Fig. 1). One possible interpretation is that both linear (individual frequencies) and nonlinear (interactions between frequencies) components contribute to overall complexity; however, linear components by themselves become more complex in brain development.

Finally, it is noteworthy that signal complexity is highly reflective of functional connectivity. For example, in a study of adolescents, Mišić et al. (2015) explored correlations between the complexity of individual EEG channels (MSE) and the structure of a functional network defined by the same channels. Signal complexity was estimated as MSE. Network structure was characterized by node strength, that is, overall connectivity for a given node (channel) averaged across all its connections, and regional efficiency estimated as minimum path length between the channels. The authors found positive correlations between signal complexity and these two properties of the EEG network. In other words, the more connectivity a node of functional network has, the higher the complexity of this node. These results would indicate that the complexity of regional neural dynamics represents not only local information but also reflects the properties of the entire functional network.

Conceptually, similar results were found in a study by Vakorin et al. (2011b) who considered a network of neuromagnetic sources activated in reaction to a face recognition task. Specifically, the amount of information transferred from one source to another was correlated with the difference in complexity between the dynamics of these two sources. This asymmetry in information transfer was scale dependent. It is interesting to note that in a simulated network, at the scales of characteristic frequencies of coupled oscillatory systems, the directionality of coupling defined the directionality of net information transfer between the systems. In other words, propagation of information in a network can be described as accumulation of complexity of the brain signals.

Finally, Vakorin et al. (2011a) proposed a method for decomposing the total complexity of regional neural activity into information processed locally and information shared with other regions (functional connectivity), which was also used for studying healthy brain aging (McIntosh et al. 2013). They applied this approach to characterize age-related changes in infants and children between 1 and 66 months. This was an attempt to distinguish two key mechanisms, which may contribute to increasing complexity of the brain signals. Specifically, both a larger repertoire of the physiological states of individual regions that become more specialized and increased integration between distributed neuronal populations can lead to increased signal complexity. The authors showed that the integration mechanism is a main factor contributing the increased complexity during brain development.

6 Development of Metastability in Human Neurophysiological Activity

The concept of complexity is close to that of metastability. These two frameworks are complimentary, as they both are thought to reflect the dynamic repertoire of neural ensembles. In general, metastability is the principle describing the ability of a neural system to deviate from equilibrium and to stay in another state for an extended period of time. In the resting state, patterns of short oscillatory sequences can be mixed with periods of what seems to be stochastic activity. The oscillatory sequences are thought to be a result of the interaction and integration of local circuits exhibiting tendencies to function autonomously. From a computational perspective, the metastability of the EEG or MEG signals can be described by exploring nonstationarity phenomena.

There was a long tradition of defining EEG microstates as transient quasi-stable patterns based on the analysis of the spatial configuration scalp electric fields (Lehmann 1971). A state would be defined by the topography maps showing the distribution of signals at a given moment of time. Koenig et al. (2002) applied this approach for analysis of EEG microstates in a resting state obtained from several databases of subjects between the age of 6 and 80 years. The authors identified and quantified 4 brain microstates (the number was specified a priori) as subsecond time epochs with stable field topography. It was found that the mean microstate duration decreased with brain development. In other words, EEG signals became more nonstationary with age. It should be noted that the above-mentioned analysis is essentially based on the concept of stationarity as it is used in the theory of stochastic processes. There are two definitions of a stationary process: in a strict and weak sense. In analysis of finite time series, a weaker form of stationarity is routinely used. A weak stationary process is characterized by constant mean and variance, with autocorrelation function depending only on a time lag. A signal with constant spectral power is an example of stationarity in a weak sense.

Another approach to look into nonstationarity can be based on nonlinear dynamics. Similar to what we discussed on complexity, a key assumption in nonlinear analysis of EEG or MEG is that there exists a deterministic dynamic system which underlies the observed brain signals. From a theoretical point of view, single oscillators were considered reasonable candidates to model the activity of neural ensembles (Haken 2013), which can be coupled together with long-range connections forming a large-scale network. In particular, realistic fluctuations of the resting-state network dynamics were modeled using coupled nonlinear systems with time delays in coupling (Ghosh et al. 2008; Deco et al. 2009).

A number of studies on nonlinear properties of brain signals coined a term of dynamical nonstationarity (Dikanev et al. 2005), which, in contrast to stochastic nonstationarity, implies the existence of a nonlinear system associated with an observed signal. Mathematical models to describe multi-stability can be constructed focusing on either complexity of model themselves or complexity of parameters of the models. The first approach is based on choosing a priori a nonlinear system, which is relatively complex and is able to express nonstationary chaotic behavior for a given set of parameter values. For example, using chaos theory, Freyer et al. (2011) modeled bi-stability of the alpha rhythms, which was manifested as switching between high- and low-amplitude oscillations, as arising from a bifurcation wherein a dynamical system loses stability. The bursts of two types of activity thus corresponded to two noise-induced attractors or sets of states in the phase space, toward which a system tends to evolve from a wide variety of starting points. The second approach is based on an idea that although the nonlinear system underlying the observed neural activity, in general, remains unknown, it can be approximated with a set of basis functions. Furthermore, parameters of a model can be estimated by fitting a combination of relatively simple functions to different segments of brain signals. Within such approach, dynamical nonstationarity can be understood as external or internal events that are causing abrupt changes or drifts in the parameters of the model.

A number of studies have been proposed to explore nonstationarity by breaking relatively long time series into small, possibly overlapping, presumably stationary segments, with subsequent classification of these segments into the classes of similar dynamics (Manuca and Savit 1996; Schreiber and Schmitz 1997). Such approach has been used to characterize EEG in healthy and clinical populations such as in epilepsy (Dikanev et al. 2005), Alzheimer's disease (Latchoumane et al. 2008), or during different sleep changes (Kohlmorgen et al. 2000). Vakorin et al. (2013) used a similar approach to describe age-related changes in eyes closed and open resting-state EEG recorded from adolescents between 10 and 13 years of age. In contrast to Koenig et al. (2002), wherein the number of map classes was fixed a priori, Vakorin et al. (2013) estimated both the number of microstates and their mean durations. It should be noted that, in general, these two measures are not necessarily correlated. For example, if we assume that the number of microstates is constant, higher segment alteration leads to a smaller mean duration (segment length), that is, to higher nonstationarity (Fig. 2a). At the same time, the number of microstates can be increased

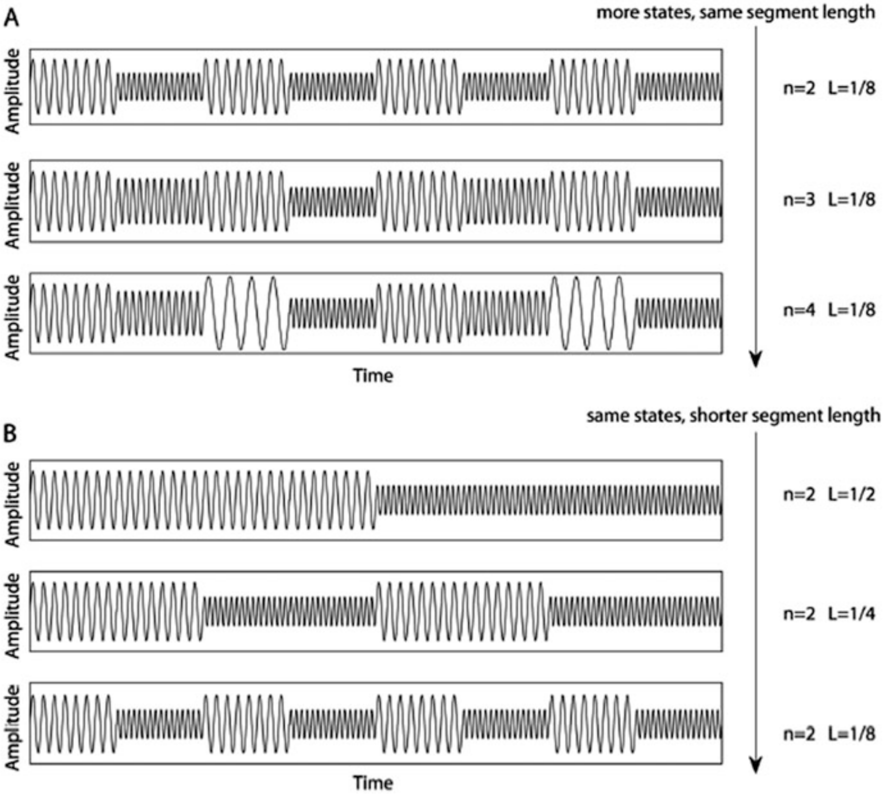

Fig. 2 Schematic illustration of two mechanisms showing how nonstationary effects can become stronger: (**a**) by increasing the number of microstates and (**b**) by shortening the duration of the microstates

without modifying their durations, as illustrated in Fig. 2b. It was found that nonstationarity becomes stronger with age during early adolescence. More specifically, the mean duration of stationary states increased with age and correlated with spectral power at lower frequencies. These effects were widely distributed across almost all the electrodes (Fig. 3a). At the same time, the number of states increased with age as well and correlated with spectral power at the alpha frequency band. These effects were localized to the parieto-occipital channels (Fig. 3b).

Neural oscillations are relevant for information processing and provide temporal windows for coherent interactions among brain areas to dynamically coordinate information flow supporting cognition, perception, and behavior. This capacity for neurophysiological activity and communication to dynamically explore its repertoire is reflected in the metastability and complexity of EEG and MEG. In sum, development is accompanied by coordinated shifts in spectral power, network synchrony, complexity, and metastability of neurophysiological activity. This, in turn, reflects the maturation of the set of apparatus necessary to support function,

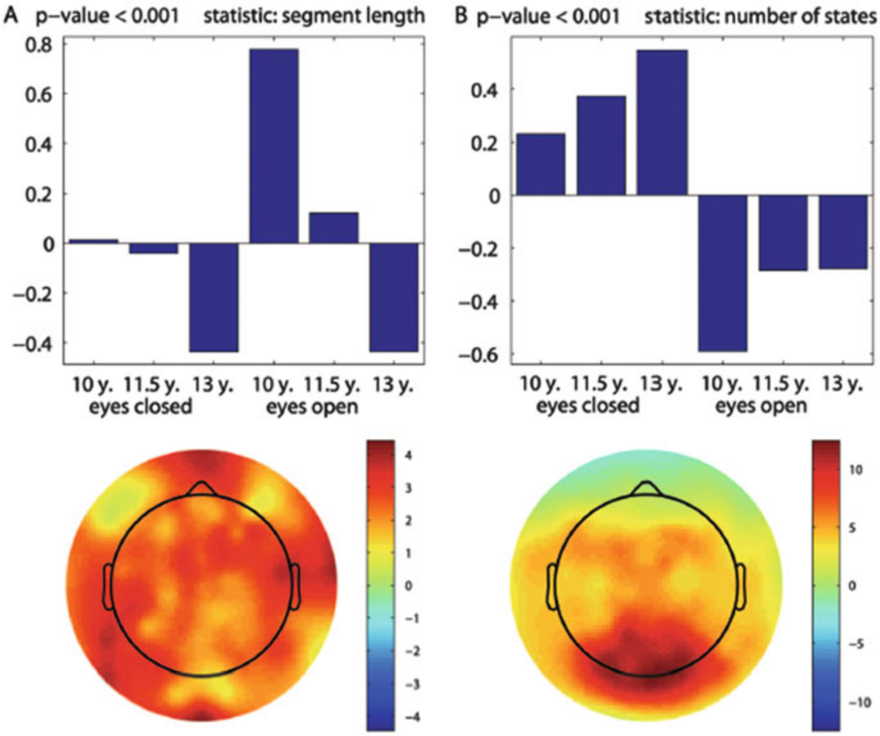

Fig. 3 Two mechanisms underlying the age-related changes in nonstationarity of resting-state EEG from adolescents between 10 and 13 years of age: (**a**) mean duration of the microstates is decreasing with age and (**b**) number of microstates is increasing with age. The *upper panels* show data-driven contrasts between the age groups, which can be interpreted as age-related trends in the measures of nonstationarity. The *lower panels* (topographic maps) show how the contrasts are expressed across the channels

and conversely, disruption of the normal maturation of such mechanism often heralds dysfunction in development.

References

Benasich AA, Gou Z, Choudhury N, Harris KD (2008) Early cognitive and language skills are linked to resting frontal gamma power across the first 3 years. Behav Brain Res 195 (2):215–222

Boersma M, Smit DJ, de Bie H, Van Baal GC, Boomsma DI, de Geus EJ, Delemarre-van de Waal HA, Stam CJ (2011) Network analysis of resting state EEG in the developing young brain: structure comes with maturation. Hum Brain Mapp 32(3):413–425

Boersma M, Smit DJ, Boomsma DI, Geus EJ, Delemarre-van de Waal HA, Stam C (2013) Growing trees in child brains: graph theoretical analysis of EEG derived minimum spanning tree in 5 and 7 year old children reflects brain maturation. Brain Connect 3:50–60

Bruce EN, Bruce MC, Vennelaganti S (2009) Sample entropy tracks changes in EEG power spectrum with sleep state and aging. J Clin Neurophysiol 26(4):257

Canolty RT, Knight RT (2010) The functional role of cross-frequency coupling. Trends Cogn Sci 14(11):506–515

Costa M, Goldberger AL, Peng CK (2002) Multiscale entropy analysis of complex physiologic time series. Phys Rev Lett 89(6):068102

Cragg L, Kovacevic N, McIntosh AR, Poulsen C, Martinu K, Leonard G, Paus T (2011) Maturation of EEG power spectra in early adolescence: a longitudinal study. Dev Sci 14(5):935–943

Deco G, Jirsa V, McIntosh AR, Sporns O, Kötter R (2009) Key role of coupling, delay, and noise in resting brain fluctuations. Proc Natl Acad Sci 106(25):10302–10307

Dikanev T, Smirnov D, Wennberg R, Velazquez JP, Bezruchko B (2005) EEG nonstationarity during intracranially recorded seizures: statistical and dynamical analysis. Clin Neurophysiol 116(8):1796–1807

Doesburg SM, Ribary U, Herdman AT, Moiseev A, Cheung T, Miller SP, Poskitt KJ, Weinberg H, Whitfield MF, Synnes A, Grunau RE (2010) Magnetoencephalography reveals slowing of resting peak oscillatory frequency in children born very preterm. Pediatr Res 70(2):171–175

Doesburg SM, Ribary U, Herdman AT, Miller SP, Poskitt KJ, Moiseev A, Whitfield MF, Synnes A, Grunau RE (2011) Altered long-range alpha-band synchronization during visual short-term memory retention in children born very preterm. Neuroimage 54(3):2330–2339

Doesburg SM, Moiseev A, Herdman AT, Ribary U, Grunau RE (2013) Region-specific slowing of alpha oscillations is associated with visual-perceptual abilities in children born very preterm. Front Hum Neurosci 7:791

Donner TH, Siegel M (2011) A framework for local cortical oscillation patterns. Trends Cogn Sci 15(5):191–199

Dosenbach NU, Nardos B, Cohen AL, Fair DA, Power JD, Church JA, Nelson SM, Wig GS, Vogel AC, Lessov-Schlaggar CN, Barnes KA, Dubis JW, Feczko E, Coalson RS, Pruett JR Jr, Barch DM, Petersen SE, Schlaggar BL (2010) Prediction of individual brain maturity using fMRI. Science 329(5997):1358–1361

Engel AK, Gerloff C, Hilgetag CC, Nolte G (2013) Intrinsic coupling modes: multiscale interactions in ongoing brain activity. Neuron 80(4):867–886

Fair DA, Cohen AL, Power JD, Dosenbach NU, Church JA, Miezin FM, Schlaggar BL, Petersen SE (2009) Functional brain networks develop from a "local to distributed" organization. PLoS Comput Biol 5(5), e1000381

Freyer F, Roberts JA, Becker R, Robinson PA, Ritter P, Breakspear M (2011) Biophysical mechanisms of multistability in resting-state cortical rhythms. J Neurosci 31(17):6353–6361

Fries P (2015) Rhythms for cognition: communication through coherence. Neuron 88(1):220–235

Gasser T, Verleger R, Bächer P, Sroka L (1988) Development of the EEG of school-age children and adolescents. I. Analysis of band power. Electroencephalogr Clin Neurophysiol 69 (2):91–99

Ghosh A, Rho Y, McIntosh AR, Kötter R, Jirsa VK (2008) Cortical network dynamics with time delays reveals functional connectivity in the resting brain. Cogn Neurodyn 2(2):115–120

Gómez C, Pérez-Macías JM, Poza J, Fernández A, Hornero R (2013) Spectral changes in spontaneous MEG activity across the lifespan. J Neural Eng 10(6):066006

Gou Z, Choudhury N, Benasich AA (2011) Resting frontal gamma power at 16, 24 and 36 months predicts individual differences in language and cognition at 4 and 5 years. Behav Brain Res 220 (2):263–270

Haken H (2013) Principles of brain functioning: a synergetic approach to brain activity, behavior and cognition, vol 67. Springer, Berlin

Janjarasjitt S, Scher MS, Loparo KA (2008) Nonlinear dynamical analysis of the neonatal EEG time series: the relationship between neurodevelopment and complexity. Clin Neurophysiol 119(4):822–836

Kaffashi F, Foglyano R, Wilson CG, Loparo KA (2008) The effect of time delay on Approximate & Sample Entropy calculations. Physica D Nonlinear Phenom 237(23):3069–3074

Koenig T, Prichep L, Lehmann D, Sosa PV, Braeker E, Kleinlogel H et al (2002) Millisecond by millisecond, year by year: normative EEG microstates and developmental stages. Neuroimage 16(1):41–48

Kohlmorgen J, Müller KR, Rittweger J, Pawelzik K (2000) Identification of nonstationary dynamics in physiological recordings. Biol Cybern 83(1):73–84

Kolmogorov AN (1959) Entropy per unit time as a metric invariant of automorphism. Doklady Russ Acad Sci 124:754–755

Latchoumane CFV, Ifeachor E, Hudson N, Wimalaratna S, Jeong J (2008) Dynamical nonstationarity analysis of resting EEGs in Alzheimer's disease. In: Neural information processing. Springer, Berlin, pp 921–929

Lehmann D (1971) Multichannel topography of human alpha EEG fields. Electroencephalogr Clin Neurophysiol 31(5):439–449

Lippé S, Kovacevic N, McIntosh AR (2009) Differential maturation of brain signal complexity in the human auditory and visual system. Front Hum Neurosci 3:48

Manuca R, Savit R (1996) Stationarity and nonstationarity in time series analysis. Physica D Nonlinear Phenom 99(2):134–161

Marshall PJ, Bar-Haim Y, Fox NA (2002) Development of the EEG from 5 months to 4 years of age. Clin Neurophysiol 113(8):1199–1208

Martinović Z, Jovanović V, Ristanović D (1998) EEG power spectra of normal preadolescent twins. Gender differences of quantitative EEG maturation. Clin Neurophysiol 28(3):231–248

McIntosh AR (2000) Towards a network theory of cognition. Neural Netw 13(8–9):861–870

McIntosh AR, Kovacevic N, Itier RJ (2008) Increased brain signal variability accompanies lower behavioral variability in development. PLoS Comput Biol 4(7):e1000106

McIntosh AR, Vakorin V, Kovacevic N, Wang H, Diaconescu A, Protzner AB (2013) Spatiotemporal dependency of age-related changes in brain signal variability. Cereb Cortex 24(7):1806–1817

Meyer-Lindenberg A (1996) The evolution of complexity in human brain development: an EEG study. Electroencephalogr Clin Neurophysiol 99(5):405–411

Mišić B, Vakorin VA, Paus T, McIntosh AR (2011) Functional embedding predicts the variability of neural activity. Front Syst Neurosci 5:90

Mišić B, Doesburg SM, Fatima Z, Vidal J, Vakorin VA, Taylor MJ, McIntosh AR (2015) Coordinated information generation and mental flexibility: large-scale network disruption in children with autism. Cereb Cortex 25(9):2815–2827

Mizuno T, Takahashi T, Cho RY, Kikuchi M, Murata T, Takahashi K, Wada Y (2010) Assessment of EEG dynamical complexity in Alzheimer's disease using multiscale entropy. Clin Neurophysiol 121(9):1438–1446

Palva S, Palva JM (2007) New vistas for alpha-frequency band oscillations. Trends Neurosci 30 (4):150–158

Palva S, Palva JM (2012) Discovering oscillatory interaction networks with M/EEG: challenges and breakthroughs. Trends Cogn Sci 16(4):219–230

Palva JM, Palva S, Kaila K (2005) Phase synchrony among neuronal oscillations in the human cortex. J Neurosci 25(15):3962–3972

Park JH, Kim S, Kim CH, Cichocki A, Kim K (2007) Multiscale entropy analysis of EEG from patients under different pathological conditions. Fractals 15(04):399–404

Pereda E, de La Cruz DM, Manas S, Garrido JM, López S, González JJ (2006) Topography of EEG complexity in human neonates: effect of the postmenstrual age and the sleep state. Neurosci Lett 394(2):152–157

Pincus SM (1991) Approximate entropy as a measure of system complexity. Proc Natl Acad Sci 88 (6):2297–2301

Rapp PE, Albano AM, Schmah TI, Farwell LA (1993) Filtered noise can mimic low-dimensional chaotic attractors. Phys Rev E 47(4):2289

Richman JS, Moorman JR (2000) Physiological time-series analysis using approximate entropy and sample entropy. Am J Phys Heart Circ Phys 278(6):H2039–H2049

Schäfer CB, Morgan BR, Ye AX, Taylor MJ, Doesburg SM (2014) Oscillations, networks, and their development: MEG connectivity changes with age. Hum Brain Mapp 35(10):5249–5261

Scher MS, Waisanen H, Loparo K, Johnson MW (2005) Prediction of neonatal state and maturational change using dimensional analysis. J Clin Neurophysiol 22(3):159–165

Schreiber T, Schmitz A (1997) Classification of time series data with nonlinear similarity measures. Phys Rev Lett 79(8):1475

Sinai YG (1959) On the notion of entropy of a dynamical system. Doklady Russ Acad Sci 124:768–771

Stroganova TA, Orekhova EV, Posikera IN (1999) EEG alpha rhythm in infants. Clin Neurophysiol 110(6):997–1012

Takens F (1981) Detecting strange attractors in turbulence. Springer, Berlin

Uhlhaas PJ, Roux F, Singer W, Haenschel C, Sireteanu R, Rodriguez E (2009) The development of neural synchrony reflects late maturation and restructuring of functional networks in humans. Proc Natl Acad Sci USA 106(24):9866–9871

Uhlhaas PJ, Roux F, Rodriguez E, Rotarska-Jagiela A, Singer W (2010) Neural synchrony and the development of cortical networks. Trends Cogn Sci 14(2):72–80

Vakorin VA, McIntosh AR (2012) Mapping the multi-scale information content of complex brain signals. In: Principles of brain dynamics: global state interactions, pp 183–208

Vakorin VA, Lippé S, McIntosh AR (2011a) Variability of brain signals processed locally transforms into higher connectivity with brain development. J Neurosci 31(17):6405–6413

Vakorin VA, Mišić B, Krakovska O, McIntosh AR (2011b) Empirical and theoretical aspects of generation and transfer of information in a neuromagnetic source network. Front Syst Neurosci 5:96

Vakorin VA, McIntosh AR, Mišić B, Krakovska O, Poulsen C, Martinu K, Paus T (2013) Exploring age-related changes in dynamical non-stationarity in electroencephalographic signals during early adolescence. PLoS One 8(3), e57217

Varela F, Lachaux JP, Rodriguez E, Martinerie J (2001) The brainweb: phase synchronization and large-scale integration. Nat Rev Neurosci 2(4):229–239

von Stein A, Sarnthein J (2000) Different frequencies for different scales of cortical integration: from local gamma to long range alpha/theta synchronization. Int J Psychophysiol 38 (3):301–313

Ward LM (2003) Synchronous neural oscillations and cognitive processes. Trends Cogn Sci 7 (12):553–559

Zhang D, Ding H, Liu Y, Zhou C, Ding H, Ye D (2009) Neurodevelopment in newborns: a sample entropy analysis of electroencephalogram. Physiol Meas 30(5):491

Zhang YC (1991) Complexity and 1/f noise. A phase space approach. J Phys I 1(7):971–977

The Role of Functional Networks in Neuropsychiatric Disorders

Leonides Canuet, Yasunori Aoki, Ryouhei Ishii, and Fernando Maestú

1 Introduction

The impact of neurological and psychiatric diseases on the functional organization of the brain has been a topic of growing interest in the last decade. Looking for new explanations and better understanding of neuropsychiatric diseases such as epilepsy, Alzheimer's Disease (AD), or schizophrenia, different research groups have started to apply the network theory to these disorders.

The study of neurological diseases has suffered the consequences of a long-lasting discussion about the functional and structural organization of the brain. Two main theories have been considered: segregation and integration. The first approach claims that brain regions are functionally segregated supporting specific functions. Initially, the idea was proposed by Joseph Gall in the nineteenth century in the theory called phrenology. The influential work of Paul Broca and Karl Wernicke on the study of productive or receptive aphasia provided additional support for the notion of functional specialization in the human brain. The use of electrocortical stimulation later on, producing transient motor or language impairments, constituted a further evidence of the predictions of the segregation model. Because segregation predicts a certain grade

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S. Palva (ed.), *Multimodal Oscillation-based Connectivity Theory*,
DOI 10.1007/978-3-319-32265-0_8

of collaboration between functionally separated brain regions to efficiently process external stimuli, the integration model remained in the background.

Norman Geschwind was one of the first to indicate that some of the neurological diseases could be considered as disconnection syndromes (Geschwind 1965). In fact, he literally said "disconnection of cortical regions can be achieved by lesions involving either white matter connections or by damage to association areas which constitute obligatory way stations between the primary sensory, motor, and limbic regions of the brain in primates" (page 290). What he called at that time "obligatory way stations" is what we are probably calling nowadays structural hubs. A hub can be defined as a brain region with high density of structural or functional connections which may serve as a facilitator for interregional communication in the brain. A lesion in a brain region considered a hub may cause the loss of a particular brain function supported by a particular brain network in which that hub plays a crucial role for an efficient communication. Therefore, these two apparently contradictory theories are probably being reconciliated nowadays by highlighting the importance of certain brain regions in the functional organization of the brain. Cognitive abilities can be represented in particular brain networks, and a lesion of a hub could devastate a particular cognitive function (see Crossley et al. 2014). That may be why during more than 100 years, hub lesions have been misinterpreted as a demonstration of brain functional segregation.

AD may represent a perfect example of how these two theories lead to a completely different perspective. The segregation theory predicts that the atrophy of particular brain regions, such as the medial temporal lobe, is responsible for the cognitive symptoms of the disease. However, the functional integration approach or what is called the "network theory" predicts that AD is a disconnection syndrome, and the progressive loss of connections between brain regions is responsible for the main cognitive symptoms seen in this disease. These two perspectives lead to two completely different views of the disease which influence on the development of intervention approaches. We will come back later to these ideas in AD.

The integration model, related to the network theory, is based on the idea that the brain is a complex system of interacting units, composed of a series of functional and structural connections organized under a particular architecture. The assessment of functional connections is based on the statistical dependency between time series or the evaluation of the information directionality (effective connectivity). This approach far from just constituting a nice theoretical hypothesis is changing the way we understand neurological and psychiatric diseases. Unanswered questions such as how local lesions (e.g., tumors), focal epilepsy, or local strokes can affect the organization of the whole functional network or how some diseases are using networks to spread their histopathological abnormalities (Nath et al. 2012) have attracted much attention and will help develop this new brain network perspective.

This chapter focuses on two main neurological disorders: Alzheimer's Disease and epilepsy and on three psychiatric disorders: schizophrenia, autism, and major depressive disorder. The main purpose is to provide the readers with recent evidence of how this new network approach can shed some light to the pathophysiological mechanisms underlying neuropsychiatric disorders.

2 Functional Networks in the Alzheimer's Disease Continuum

The network theory is changing the way we understand AD. From the idea of the disease starting in local regions of the brain (such as medial temporal lobe) to considering that the disease affects and develops through brain circuits. Based on this assumption, the cause of cognitive symptoms, including progressive episodic memory loss, could be due to the progressive loss of connections between brain regions. Therefore, AD can be viewed as a disconnection syndrome (Morrison et al. 1986; Delbeuck et al. 2003). The phosphorylation of the Tau protein, the accumulation of the amyloid protein, or the progressive loss of dendritic spines and neurons affect brain structural connectivity affecting the functional organization (Pineda-Pardo et al. 2014a; Garcés et al. 2014). In addition, the network theory is helping in the understanding of how the pathology spreads across the brain. It seems that amyloid neuropathology spreads by neuronal to neuronal connections using well-established neuronal circuits (Nath et al. 2012). Furthermore, amyloid protein tends to accumulate through the nodes of the default mode network (DMN; Myers et al. 2014), a network mainly active at resting state (see Fig. 1). Thus, it seems that the study of the network organization has important consequences not just to understand the development of cognitive symptoms but also to unravel how the disease spreads through the brain.

A seminal MEG study showing connectivity impairment between brain regions was published by Berendse et al. (2000). They noted lower inter- and intrahemispheric coherence in all frequency bands in AD patients compared to controls. Similarly, Stam et al. (2002) showed lower synchronization values in AD patients in the upper alpha band, the upper beta band, and the gamma band, which tend to be located over the left frontotemporal/parietal long distance intrahemispheric interactions in the alpha 1 and beta band (Stam et al. 2006). In a subsequent study, Stam et al. (2009) applied the graph theory approach to MEG data in AD patients. AD patients showed a decrease in the clustering coefficient and path length in the lower alpha band, indicating a loss of the small world architecture, which represents the most efficient functional organization. They also developed a computational model where they demonstrate that by attacking targeted links, the functional network become disrupted. Following this vein, De Haan et al. (2012a) assessed the role of functional subnetworks (modules) in AD patients. The overall modular strength and the number of modules changed significantly in Alzheimer patients. The parietal cortex showed the strongest intramodular losses. However, intermodular connectivity losses were strongly related to cognitive impairment. Then, network connectivity, synchronizability, and node centrality were assessed (De Haan et al. 2012b). A global loss of network connectivity and disrupted synchronizability was found along with centrality disruption of hubs at parietal and temporal regions. All these series of studies led this group to develop a computational model (De Haan et al. 2012c) based on the notion that increased brain activity in certain cortical hubs induces hub vulnerability. An interesting insight from this study was to coin the term "activity dependent degeneration" (ADD). This term is referring to the fact that by lowering synaptic strength of excitatory neurons they were

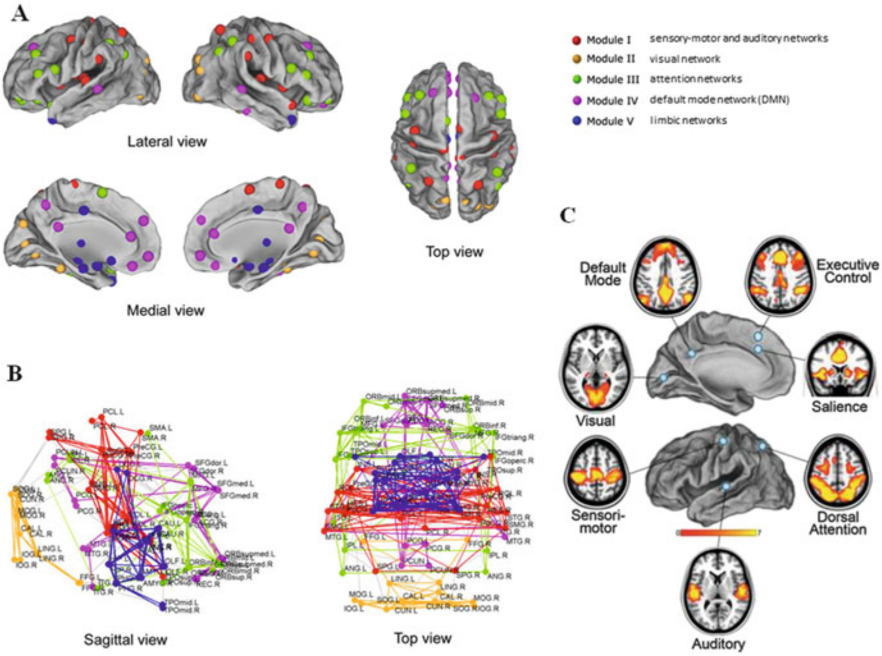


Fig. 1 Representation of resting-state networks. (**a**) Cortical nodes of functional resting-state networks. (**b**) Anatomical representation of modular architecture of the human brain functional network (He et al. 2009). (**c**) Major brain networks analyzed with fMRI (Raichle 2011)

able to reproduce the majority of the previous findings in the literature of MEG-AD, such as oscillatory slowing, loss of spectral power and long-range synchronization, hub vulnerability, and disrupted functional network topology.

One way to demonstrate that functional connectivity is a kind of reflection of the cognitive symptoms of the disease (i.e., lower functional connectivity is associated with memory loss) is to experimentally induce amnesia to healthy elderly subjects and test the effects on the functional architecture of the brain. To answer this question, Osipova et al. (2003) recorded MEG activity before and after the injection of scopolamine, an anticholinergic agent, in healthy elders. Scopolamine administration resulted in a desynchronization of the alpha band (8–13 Hz) in the posterior regions. In addition, interhemispheric and left intrahemispheric coherence was significantly decreased in the theta band (4–8 Hz). In a subsequent analysis of these data done in the source space, Bajo et al. (2015) showed decreased functional connectivity between several brain areas in the scopolamine condition compared to placebo in most frequency bands analyzed. In particular, it was found a reduced connectivity in the alpha band between the left superior frontal and left angular cortex, the left superior temporal pole and the right precentral cortex, and between the right angular and the left lingual cortex. In the beta band, it was found a significantly reduced connectivity, specifically between the left medial superior frontal and the left superior parietal cortex, the left precuneus and the right lingual cortex, and between the left superior parietal and right fusiform cortex. Finally, in the gamma band, there was significantly reduced connectivity between the right middle frontal cortex and the left rolandic operculum and between the right middle orbitofrontal cortex and the right precuneus. It was also found that gamma-band connectivity of the left inferior frontal operculum with the right lingual and left paracentral lobule was reduced. However, in the delta band, scopolamine condition showed increased connectivity between the left parahippocampal and the right inferior occipital cortex. The functional connectivity in this frequency band is normally enhanced in the injured brain, reflecting cognitive impairment (Castellanos et al. 2010). As for the network architecture indices, clustering (local connectivity) showed a significant reduction in the alpha band, while shortest path length (long distance connections) significantly increased also in alpha band both after scopolamine administration. This profile could mirror a random configuration. All these neurophysiological signs were associated with transient amnesia in healthy elderly subjects, eliciting similar cognitive and functional connectivity profiles as those observed in AD patients.

The comparison between different dementia conditions is crucial to better understand the sensitivity and specificity of these findings. Franciotti et al. (2006) showed that coherence in the alpha band was disrupted in AD and Lewy Body Dementia patients, which mainly involved long connections. This paper remains as one of the few studies comparing biomagnetic activity in different types of dementia syndromes.

As indicated above, AD is a continuum formed by different stages, from preclinical stages to very early clinical stages. Patients with mild cognitive impairment (MCI) convert to dementia with a rate of about 15 % per year. Those with amnestic MCI, with memory impairment as the main cognitive symptom, tend to develop specifically AD. In this population, Bajo et al. (2010) assessed the integrity of functional networks during performance of a memory task. These patients showed an increase in synchronization over the prefrontal and central regions in several frequency bands. This increased synchronization pattern achieved 82 % correct classification of the MCI patients in the beta band. An important question was whether this increased synchronization represents compensatory activity or not. To try to answer this question Buldú et al. (2011) evaluated the functional architecture of those networks with increased synchronizability by using a graph theory approach. MCI subjects showed a reduction of the clustering values along with an increase in the outreach parameter. All these reveals a tendency toward a random structure with a high energy cost and increased link strength, which is not an ideal architecture for information processing, and it suggests an early network disruption in the continuum of AD.

Healthy elders with subjective memory complaints (SMC) or any other cognitive complaints constitute a group of subjects with an increased risk for the development of dementia (Jessen et al. 2014). They perform neuropsychological tests within the normal range. Thus, there is no objective sign for considering them as having a medical condition. If neuropsychological tests are not sensitive enough to evaluate clinical impairment, it might be possible to assess disruptions at the neurophysiological level. In an attempt to answer this question, Bajo et al. (2012a; see also Maestú et al. 2011) assessed functional network organization in SMC subjects and healthy elders without SMC. Subjects with SMC exhibited weaker synchronization in the alpha 2, beta 1, and beta 2 frequency bands in frontal regions, indicating an early connectivity disruption not detected by neuropsychological tests. This likely reflects a preclinical deflection of the strength of the brain function connectivity.

An important clinical issue is whether these functional connectivity profiles can predict subsequent stages in the AD continuum. This idea was evaluated by Bajo et al. (2012b). By analyzing data recorded during a memory task they reported increased synchronization values in the alpha 1 and 2 frequency bands over the posterior parieto-occipital regions and in prefrontal regions in MCI patients who subsequently convert to AD, in comparison to non-converters. In a subsequent study, López et al. (2014) assessed whether these profiles can be reproduced during a resting-state condition. MCI converters showed increased connectivity between the anterior cingulate cortex and the posterior brain regions. These two studies indicate that the higher the synchronization, the higher the likelihood for developing dementia. Thus, these MEG profiles may serve as a potential biomarker for the prediction of the development of dementia.

In order to evaluate all these findings from a multilevel approach, functional connectivity findings were combined with genetic profiles, white matter disruption, and the accumulation of amyloid and phospho-tau (p-Tau) proteins in the cerebrospinal fluid (CSF). Cuesta et al. (2015) study indicated that being carrier of the APOE-ε4 modifies the functional network organization. Controls carrying the APOE-ε4 allele showed increased synchronization compared with healthy elderly noncarriers, although these results did not achieve statistically significant values. However, patients with MCI carrying the APOE-ε4 allele showed lower synchronization values than any of the healthy control groups (carriers or noncarriers) and MCI noncarriers. This lower synchronization affects mainly connections between prefrontal regions and parietal regions. Thus, it seems that MCI carriers are closer to show a typical AD profile in comparison to the other groups. This hypersynchronization profile was as well found in an international multicenter blind-study (Maestú et al. 2015).

The evaluation of how white matter integrity affects the organization of the functional network was assessed by combining information from diffusion tensor imaging and MEG. Pineda-Pardo et al. (2014a) showed the dependency of the Fractional Anisotropy (FA; a measure of white matter integrity) with the random normalized graph metrics in MCI patients. These comparison revealed a higher clustering coefficient loss, in delta, theta, and alpha frequency bands, as a function of the lower white matter integrity over different regions such as the cingulum of the medial temporal lobe, inferior longitudinal fasciculus, anterior thalamic radiation, forceps minor, and the inferior fronto-occipital fasciculus. This means that the lower the white matter integrity in these regions, the lower the clustering values in the whole functional network. This may indicate that the random structure found by Buldú et al. (2011) could be due to the loss of white matter integrity in certain white matter regions. The assessment of specific brain networks such as the DMN

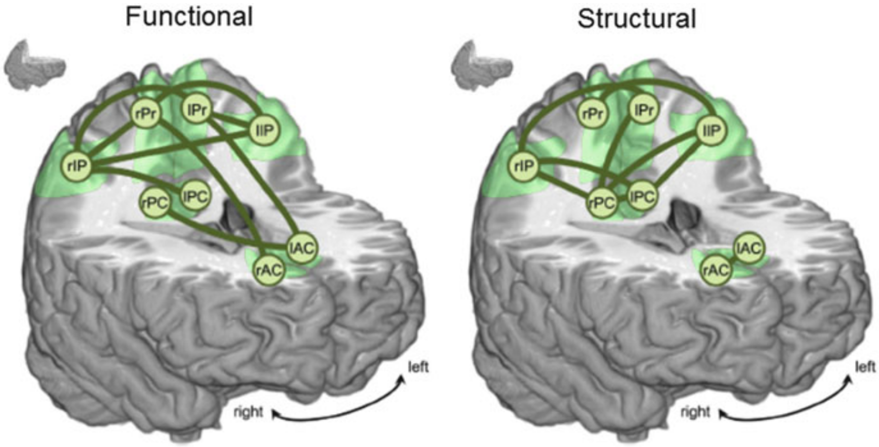


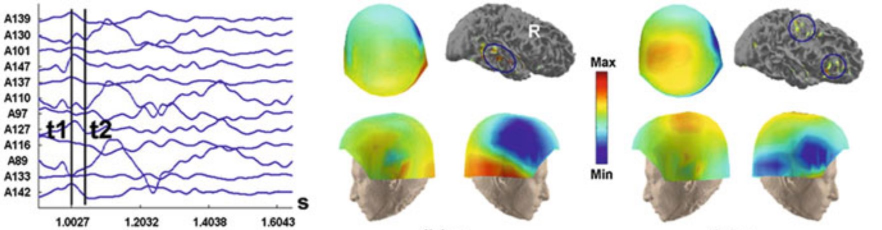
Fig. 2 Functional and anatomical connectivity of nodes within the default mode network that are disrupted in patients with MCI compared to controls (Garcés et al. 2014)

revealed interesting results. Garcés et al. (2014) showed a reduced structural connectivity between the nodes of the default mode network in MCI patients along with a reduced functional connectivity in the same anteroposterior regions (Fig. 2). This can be an indication of how functional brain properties can be influenced by the structural connectivity. To further explore this hypothesis, Pineda-Pardo et al. (2014b) showed how functional connections in MCI patients can be predicted by the structural connectivity matrix. All these combinations of the structural and functional networks were done with resting-state MEG data, thus if functional networks during task mirrored the disruptions found in the structural connections is a question which remain unresolved.

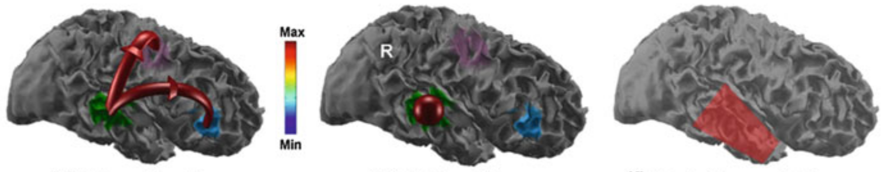
A relevant issue was to test whether MEG functional connectivity at resting depends on the values of amyloid protein and tau protein at the CSF. Given that amyloid tends to accumulate in the brain with disease progression, its values in the CSF are lower than in healthy subjects. The opposite is true for the total tau and phosphorylated tau (p-tau) derived from axonal filaments. High values of the tau protein at the CSF are associated with neuronal loss and, therefore, are considered as a neuronal injury biomarker. Canuet et al. (2015) evaluated how anatomo-functional networks were modulated by CSF concentration of p-tau and amyloid proteins in MCI patients. Patients with abnormal CSF p-tau and Aβ42 levels exhibited both reduced and increased functional connectivity affecting limbic structures such as the anterior/posterior cingulate cortex, orbitofrontal cortex, and medial temporal areas in different frequency bands. A reduction in posterior cingulate functional connectivity mediated by p-tau was associated with impaired axonal integrity of the hippocampal cingulum. It was found that several connectivity abnormalities were predicted by CSF biomarkers and cognitive scores. These preliminary results indicate that CSF markers of amyloid deposition and neuronal injury in early AD are associated with a dual pattern of cortical network disruption, affecting key regions of the default mode network and the temporal cortex.

3 Functional Networks in Epilepsy

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition. An epileptic seizure, the defining element of the disorder, is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain (Fisher et al. 2005). Based on the increased interneuronal synchrony in epileptic seizures, it can be assumed that connectivity is at the center of the problem of epilepsy (Lemieux et al. 2011). In support to this view, abnormal functional connectivity within brain networks has been found in association with transient epileptic discharges (Constable et al. 2013). In addition, increasing evidence indicates that epilepsy is due to a dysfunction within an epileptic network rather than due to pathological activity of single cortical sources (Fig. 3). Epileptic networks underlying focal epilepsies and specific epileptic syndromes may be of great importance both for localizing the seizure onset or the epileptogenic zone and for predicting postsurgical cognitive impairment (Pittau and Vulliemoz 2015). Furthermore, functional connectivity may help understand clinically relevant issues in epilepsy such as ictal activity spreading, variations in seizure semiology, and the persistence of seizures after surgical resection (Lemieux et al. 2011).



(a) Interictal spike (b) t1 (c) t2



(d) Information flow (e) Total outflow (f) Clinically resected zone

Fig. 3 Source connectivity analysis of magnetoencephalographic interictal spikes in temporal lobe epilepsy. Epileptiform activity propagates from the right temporal lobe to ipsilateral anterior and posterior frontal regions. The identified primary source overlapped with the clinically resected zone. *R*, right view and *t*, time points around the peak of an interictal spike (Dai et al. 2012)

3.1 Functional Connectivity in the Clinical Diagnosis of Epilepsy

Functional connectivity has been proposed to play a role in the diagnosis of epilepsy in clinical practice, at least in some cases. It is well established that the diagnosis of epilepsy is based on clinical criteria (ILAE—English International League Against Epilepsy). The identification of ictal or interictal epileptiform discharges using EEG, video-EEG, or MEG aids in the diagnosis of epilepsy and additionally allows for a correct classification of the seizure type (focal vs. generalized) and the epileptic syndrome. However, the first EEG recording is not sensitive enough, allowing for a detection of epileptiform activity in about 30–50 % of the patients (Douw et al. 2010). Moreover, up to 18 % of patients do not show EEG epileptiform activity in repeated recordings and up to 0.5 % of the general population may have EEG spikes without clinical significance. It is, therefore, necessary to use other analysis tools that do not depend exclusively on epileptic discharges to support the diagnosis or to predict the development of epilepsy after a first seizure. Preliminary studies have shown that in patients who do not show interictal epileptiform discharges on their first EEG recording, a pronounced increase in theta-band connectivity may be used as predictor of a diagnosis of epilepsy combined with seizure semiology. A precise localization of the epileptogenic focus in patients with neocortical epilepsy who underwent surgery has been possible using connectivity analysis of resting-state MEG data irrespective of the presence or absence of epileptic spikes (Krishnan et al. 2015). Furthermore, functional connectivity networks have successfully been used to discriminate children with epilepsy from controls blindly to clinical data, with an accuracy of 88.8 %, a sensitivity of 81.8 %, and 100 % specificity (Sargolzaei et al. 2015). Although more research is needed, it is promising that brain connectivity analysis can provide valuable information for an early diagnosis of epilepsy or for identification of the epileptogenic zone in patients without epileptiform discharges or without structural lesions.

3.2 Generalized Epilepsies

Network disruption in generalized epilepsy has mainly been investigated in the most common types of idiopathic or genetic epileptic syndromes, in particular in childhood absence epilepsy (CAE) and juvenile mioclonic epilepsy (JME). Results of recent functional connectivity studies, however, provide compelling evidence that the concept of "generalized epilepsy" may be outdate. Even in cases of CAE, JME, and idiopathic epilepsy with generalized tonic–clonic seizures there is evidence that the seizures may start in a defined brain area and spread rapidly to connected brain areas, recruiting specific neuronal networks into typical oscillatory behavior. For instance, the distribution of 3-Hz generalized spike-wave discharges in patients with CAE involved the prefrontal–insular–thalamic network. In patients with myoclonic components, the dominant networks appear to be frontal (motor)–insular–thalamic (Stefan and Lopes da Silva 2013). Patients with CAE also exhibit an altered integration among three resting-state networks: dorsal attention (DAN), salience (SN), and DMN networks (Fig. 1). This functional connectivity abnormality is thought to represent a pathological mechanism associated with the accumulative influence of epileptic activity. Based on the role of these networks in the intrinsic organization of the brain, as well as in behavior and cognition, this functional network disintegration may contribute to behavioral abnormalities that are seen in some patients, including executive and attentional deficits (Li et al. 2015). Other idiopathic generalized epilepsies, in particular that characterized by generalized tonic–clonic seizures have been associated with a disrupted brain network organization derived from abnormal functional interactions among resting-state networks, including the DMN, attentional network (ATN), and frontoparietal central executive network (CEN) (Fig. 1). This is thought to contribute to the mild behavioral and attentional deficits seen in some patients with these generalized epilepsies (Wei et al. 2015).

In patients with JME, interictal, and preictal disruption of network dynamics in different frequency bands have been found using EEG. Compared to controls, these patients were mainly characterized by an interictal increase in slow-frequency (i.e., delta, theta, alpha 1) functional connectivity, with a concomitant decrease in alpha 2 and beta bands affecting cortical areas involved in sensorimotor integration. A further increase in delta connectivity between frontal nodes occurred during the preictal state (Clemens et al. 2013). These results suggest a frontal epileptic network in JME, which is consistent with the presence of dominant spike-wave discharges in frontal areas, frontal lobe dysfunction, and abnormal thalamo-frontal functional connectivity in patients with this epileptic syndrome (O'Muircheartaigh et al. 2012). Niso et al.'s (2015) MEG study using graph analysis found that brain networks of patients with JME are characterized by lower eccentricity for higher frequency bands (i.e., beta and gamma), with no clear topography compared with healthy subjects. Based on the idea that JME might actually represents a fast spreading frontal epilepsy, these authors also performed graph analysis in patients with focal frontal epilepsy, reporting that JME and frontal epilepsy have different network dynamics and organization. These data support the notion of a network disruption underlying clinical manifestations in JME, and that functional connectivity and graph theoretical analysis are valuable for understanding pathophysiological mechanisms in generalized and focal epilepsies.

In symptomatic forms of generalized epilepsy like the West syndrome, oscillation-based functional connectivity appears to play a role in the development of clinical manifestations. Compared to age-matched healthy controls, children with infantile spasms and hypsarrhythmia have a marked increase in long-distance connectivity, as measured with coherence in delta, theta, alpha, and beta frequency bands during sleep. This occurred in association with a decrease in theta and beta connectivity in the frontal region at short interelectrode distances. Children with persistent abnormalities in coherence were those with continued seizures and severe developmental delay. This likely indicates a lack of functional differentiation in wide cortical regions in patients with West syndrome having a better local integration of frontal regions (Burroughs et al. 2014).

3.3 Focal Epilepsies

As mentioned above, a potential clinical application of functional connectivity in epilepsy lies in a precise localization of the epileptogenic zone in patients with focal and drug-resistant epilepsy. This step is essential for planning epilepsy surgery, which is often the only therapeutic option to reduce or eliminate seizures in these patients. To date, high-frequency oscillations in intracranial recordings, in particular the so-called fast ripples (250–500 Hz), are considered to be markers for the epileptogenic zone. This is why the removal of the cortex generating these oscillations which occur in association with epileptic discharges or preceding seizures is generally linked to a good surgical outcome (Lemieux et al. 2011). However, recent evidence suggests that functional connectivity results may be associated with epileptogenicity as well. Imaginary coherence of MEG epileptic activity has proven to be as reliable as spike localization methods, namely, equivalent current dipoles (ECDs) and synthetic aperture magnetometry (SAM), to identify the seizure onset and epileptogenic zones. In a study performed by Wu et al. (2014), the locations of abnormal imaginary coherence, ECDs, and SAM were in agreement with intra/extraoperative EEG in 76.7 %, 56.7 %, and 66.7 % of the patients, respectively. Others have found that the application of source connectivity analysis to MEG interictal spikes using directed transfer function allows for estimation of the propagation of epileptiform activity along the interconnected neuronal networks in patients with focal epilepsy and drug-resistant epilepsy (Fig. 3). Interestingly, the results of this connectivity analysis were consistent with the location of surgically resected areas (Dai et al. 2012). These findings suggest the feasibility of using functional connectivity of MEG interictal spikes as part of the presurgical evaluation of patients with focal epilepsy refractory to medical treatment.

Focal cortical dysplasia is an intrinsically epileptogenic lesion that is commonly associated with drug-resistant epilepsy and, therefore, requires surgical resection to achieve seizure freedom. There is evidence obtained from MEG studies indicating that cortical dysplasia is linked to a pattern of increased resting-state functional connectivity in the beta and gamma frequency bands compared to controls. In addition, patients exhibit different network characteristics depending on the type of cortical dysplasia, and these abnormalities can be observed even in the absence of prominent interictal spike activity (Jeong et al. 2014). EEG studies have also reported an abnormal functional connectivity pattern, mainly in the gamma band, which allows us to identify the epileptogenic zone during the ictal event, as well as during the inter and preictal periods, even when the structural lesion is not detected by MRI scanning. These results suggest that the lesional nodes play a leading role in the generation and propagation of ictal activity by acting as hubs of the epileptic network. Furthermore, the cortical regions beyond the dysplasia involved in the ictal activity appear to act as "secondary" generators of synchronous activity (Varotto et al. 2012). Hippocampal sclerosis is another epileptogenic lesion that is associated with the most frequent type of symptomatic focal epilepsy, the mesial temporal epilepsy. MEG studies revealed that this cortical lesion induces local and remote changes in the dynamic organization of a frontotemporal network subserving working memory processing. This can explain a variety of memory disturbance and other neuropsychological deficits seen in patients with hippocampal sclerosis (Campo et al. 2013). Overall, this evidence indicates that resting-state functional connectivity may potentially be used in clinical setting to identify epileptic networks associated with cortical dysplasia or other epileptogenic lesions.

The benign epilepsy with centro-temporal spikes (BECTS) or Rolandic epilepsy is a very common form of idiopathic focal epilepsy in childhood that generally has a benign course (e.g., good response to treatment and cure in adolescence). However, despite their favorable seizure outcome, some children show attention deficits. This has led researchers to believe that beyond seizure activity other functional abnormalities may be implicated in the pathophysiology of this disorder. Functional connectivity analysis has shed light to this problem. It has been found that the global topologic organization of the functional brain network is disrupted in patients with BECTS, as manifested by a reduction in clustering coefficient and local and global efficiency, and by an increased path length. Reduced mean functional connectivity is mainly observed between the sensorimotor areas; this abnormality correlates with altered global small-world properties. In addition, these patients show reduced nodal centralities, predominantly in central regions and the superior temporal cortex and in areas related to linguistics and attention control that associate with language or behavioral disturbance (Xiao et al. 2015a). Patients with BECTS that develop attention deficit hyperactivity disorder (ADHD) show decreased functional connectivity of the DAN and ventral attention network (VAN), as well as increased connectivity of the DMN. These findings indicate that network disruption underlies language and behavioral problems in children with BECTS that presents with a less benign form of the disorder (Xiao et al. 2015b).

DMN connectivity is also altered in patients with temporal lobe epilepsy, the most common type of symptomatic focal epilepsy. Using resting-state MEG during spike-free periods and imaginary coherence, a measure of linear functional connectivity, patients with drug-resistant temporal lobe epilepsy have shown increased connectivity between the DMN and the right medial temporal cortex in the delta band. In addition, increased connectivity has been found between the DMN and the bilateral anterior cingulate cortex in the theta band (Hsiao et al. 2015). In patients with temporal lobe epilepsy and interictal psychosis, the chronic psychotic symptoms have been attributed to abnormal theta-band oscillations in the DMN and to resting-state beta-band connectivity disruption. This network abnormality affects particularly the connections of the medial temporal cortex with DMN regions or with prefrontal areas implicated in psychopathological dysfunction (Canuet et al. 2011). Taken together, the DMN connectivity abnormalities reported in these patients indicate that an intrinsic functional disintegration of the brain plays a role in the pathophysiology of temporal lobe epilepsy.

4 Functional Networks in Psychiatric Disorders

Neuroimaging studies of human brain activities have elucidated many functional networks which engage in specific motor, sensory, or cognitive functions (Fig. 1). The CEN is involved in frontal executive functions and activated during performance of a variety of cognitive tasks (Koechlin and Summerfield 2007). The DMN is composed of a set of regions that are particularly active in resting state and temporally interrupted or desynchronized during sensory, motor, or cognitive tasks. The DMN shows anti-correlation with other networks and exerts a strong influence on functions of their anti-correlated networks (Uddin et al. 2009). The SN has an important role in attributing salience to perceived stimuli and has shown a close association with auditory verbal hallucination (AVH) and delusions (Wotruba et al. 2014). These three networks (triple network model) are supposed to be essential for understanding pathogenic mechanisms of psychiatric diseases, including schizophrenia, autism spectrum disorder (ASD), and major depressive disorder (MDD) (Menon 2011; Wotruba et al. 2014).

The CEN is a frontoparietal system anchored in the dorsolateral prefrontal cortex (DLPFC) and the lateral posterior parietal cortex (PPC). This network is involved in manipulating information of working memory in goal-directed behavior (Koechlin and Summerfield 2007; Menon 2011). The DMN is anchored in the medial PFC (mPFC) and posterior cingulate cortex (PCC), with nodes in the lateral inferior parietal cortex, including the angular gyrus, and some consider the medial temporal lobe (MTL) as part of this functional network. The DMN is involved in internally focused activities such as self-referential thoughts, mind wandering, envisioning one's future, and autobiographical memory retrieval (Raichle et al. 2001). However, there is a functional specificity within the DMN (Aoki et al. 2015): mPFC is associated with self-referential processing (Kim 2012), whereas PCC, MTL, and angular gyrus are associated with autobiographical memory retrieval (Spreng et al. 2009) and episodic memory retrieval (Sestieri et al. 2011). The SN is a cingulate-frontal operculum system anchored by the anterior insula, ventrolateral PFC, and the dorsal anterior cingulate cortex (dACC) with robust connectivity with subcortical and limbic structures, including the amygdala, substantia nigra/ventral tegmental area, and thalamus (Seeley et al. 2007). This network is involved in detecting, integrating, and filtering relevant internal (interoceptive, autonomic, and emotional information) and external information (stimulus driven information) and attribution of salience to this information (Menon 2011). Causality analysis has revealed that the SN, in particular the right anterior insula, plays a crucial role in network switching, activating the CEN, and deactivating the DMN (Sridharan et al. 2008).

Neuroimaging connectivity studies have revealed that psychiatric diseases show disruption in these three networks and that this network disruption associates with symptoms of these diseases. This may explain underlying pathogenic mechanisms in schizophrenia (e.g., increased SN–DMN internetwork connectivity and its relation with positive symptom), in ASD (e.g., hypoactivation in the SN and the DMN during social processes), and in MDD (e.g., enhanced internetwork connectivity of the DMN and PFC-thalamo-limbic pathway and its relation with rumination and the length of the current depressive episode).

4.1 Schizophrenia

Schizophrenia is a chronic and severe brain disorder characterized by positive symptoms (e.g., auditory verbal hallucinations and delusions), negative symptoms (e.g., diminished emotional expression or avolition), and cognitive deficits (e.g., poor executive function). fMRI connectivity studies of resting states in patients with schizophrenia showed that configuration of functional networks is mostly preserved, but connectivity within the DMN appears to be disturbed (i.e., reduced connectivity of the hippocampus with the DMN) (Alonso-Solís et al. 2015; Rotarska-Jagiela et al. 2010). In addition, the connectivity of the hippocampus with the DMN is negatively correlated with positive symptoms (Rotarska-Jagiela et al. 2010). This finding suggesting the involvement of hippocampus in positive symptoms fits with MEG evidence that AVH in schizophrenia is initiated by a short reduction of theta-band activity in the right hippocampus, followed by a reduction of beta-band activity in left temporal language areas during the experience of AVH (van Lutterveld et al. 2012). Additionally, schizophrenia patients with AVH showed disturbed internetwork connectivity between the SN and the DMN compared to non-hallucination patients and healthy controls (Alonso-Solís et al. 2015). Moreover, subjects with ultra-high risk and high risk for psychosis showed that the typically observed antagonistic relationship of the DMN with the CEN and the SN was absent in both at-risk groups. Importantly, the internetwork connectivity of the SN with the DMN, measured by right anterior insula–PCC connectivity, was increased during disease progression and was positively correlated with positive symptom sum scores and body perception disturbances. On the other hand, in line with previous findings of internetwork connectivity of the DMN, DMN–CEN internetwork connectivity was negatively correlated with the quality of performance on a selective attention task and the performance on executive function tasks (Wotruba et al. 2014). Taking these findings into consideration, it can be speculated that functional deficits of the SN attribute excessive salience to internal information, which may lead to AVH and delusions in schizophrenia (Menon 2011; Wotruba et al. 2014). In addition to disturbance of intranetwork connectivity of the DMN and internetwork connectivity between the SN and the DMN, Sommer et al. (2012) reported a reduced connectivity of the left superior temporal gyrus (language areas) with the left hippocampus and its negative correlation with the severity of AVH. Consistent with this finding, EEG coherence analysis revealed that beta coherence of the left frontal (F7)–temporal (T5) electrode pair was less than that of the corresponding right pair (F8–T6) at the time of hospital admission for acute exacerbation of schizophrenia. After symptoms improved due to antipsychotic medication, the left frontal–temporal beta coherence increased, resulting in disappearance of the laterality. This change in beta coherence of the left frontal–temporal pair correlated negatively with the changes in the positive symptom score (Higashima et al. 2007).

EEG connectivity between cortical regions in first-episode schizophrenia has been investigated using exact low-resolution electromagnetic tomography (eLORETA) source estimation (Pascual-Marqui et al. 2011) and imaginary coherence-based multivariate interaction measure. Patients with schizophrenia displayed increased theta connectivity across midline, sensorimotor, orbitofrontal regions, and the left temporoparietal junction. High-risk individuals displayed intermediate left hemisphere theta connectivity between schizophrenia and healthy controls. The mean theta connectivity within the above network correlated negatively with the verbal memory factor score in all subjects, i.e., increased theta connectivity in left hemisphere regions reflects worse verbal memory performance (Andreou et al. 2015). This finding is in line with the hemispheric specification of cortical functions, i.e., word deficits in negative symptoms have close link with functional deficit in the left hemisphere, while face deficits in positive symptoms have close link with functional deficit in the right hemisphere (Burgess and Gruzelier 1997).

Alterations in EEG connectivity during various tasks at high frequency bands (beta and gamma) have been reported. Schizophrenia patients have a selective deficit in Gestalt perception, i.e., grouping stimulus elements into a meaningful percept. Uhlhaas et al. (2006) using phase locking value of EEG data and Gestalt perception task (Mooney face test) demonstrated reduced mean beta-band connectivity for all electrodes compared to healthy controls during Gestalt perception in upright Mooney face presentation. Mulert et al. (2011) using eLORETA lagged phase synchronization of EEG data and stimuli of 40 Hz binaural click trains investigated gamma-band connectivity of the auditory steady-state evoked potentials between the left and right auditory cortices and its association with auditory hallucination. The gamma band interhemispheric connectivity was reduced in patients compared to healthy controls for the primary auditory cortices. Furthermore, the gamma band interhemispheric connectivity of the primary auditory cortices in patients had positive correlation with AVH. Consistent with this result, the auditory fibers link the auditory cortices of both hemispheres through the corpus callosum. Also, speech stimuli entering the right auditory cortices need callosal transfer to the left auditory cortex for language comprehension. This is related to the fact that emotional prosody is processed in the right hemisphere, whereas identification of phonemes, words, and the syntactic relation between them is processed mainly in the left hemisphere (Bamiou et al. 2007). Thus, disturbed interhemispheric connectivity between the primary auditory cortices may cause miscomprehension of language, leading to AVH.

4.2 Autism Spectrum Disorder

ASD is a neurodevelopmental disorder characterized by persistent deficits in social communication and cognitive flexibility (i.e., restricted, repetitive patterns of behavior and interests). fMRI connectivity studies in young adults with ASD showed reduction of resting-state connectivity within the DMN, particularly at the mPFC (Kennedy and Courchesne 2008a, b). Consistently, fMRI studies showed that in young adults with ASD had absence of deactivation of the DMN during task performance (Stroop Task vs Rest and self-referential process vs other-referential process). Importantly, deactivation of the ventral mPFC (anterior hub of the DMN) during tasks correlated with social symptom severity, i.e., the lower the deactivation of the ventral mPFC, the worse the social behavior (Kennedy et al. 2006). Finally, recent meta-analysis of 24 neuroimaging studies in ASD examining social processes (e.g., theory of mind, face perception) revealed that the mPFC and the PCC (anterior and posterior hub of the DMN) and right anterior insula (hub of the SN) were hypoactive relative to controls (Di Martino et al. 2009).

An EEG resting-state connectivity study using synchronization likelihood of delta frequency band in young adults with ASD demonstrated decreased long-range connectivity, with the most prominent deficits being found in fronto-occipital connections and increased short-range connectivity affecting lateral–frontal connections. Both decreased long-range connections and increased short-range connections correlated with ASD symptom severity. Additionally, graph analysis demonstrated less clustering coefficient and greater characteristic path length than controls. These results indicate that ASD network topology is different from that of a small world network which has been shown to be optimal for information transfer and storage (Barttfeld et al. 2011). Taking into account these findings, it can be assumed that ASD has an atypical network with enhanced local connections lacking central nodes and hubs and a more modular structure. This network structure has strength in parallel processing of information and weakness in proper integration of information. This may explain the ASD core symptom, a lack of cognitive flexibility (Barttfeld et al. 2011). MEG resting state connectivity studies in young adults with ASD, using robust interdependence measure, mutual information, and partial directed coherence, also displayed reduced long-range connectivity in broadband frequency band. Furthermore, robust interdependence measure showed that connectivity of frontal sensors and temporal sensors with other sensors were attenuated (Tsiaras et al. 2011). It is noteworthy that Kikuchi et al. (2015) found that the reduced long-range connectivity (6 Hz coherence between the left-anterior sensor and the right-posterior sensor) was already seen in young children with ASD.

Alterations in connectivity during tasks at low frequency bands have also been reported. ASD cognitive inflexibility can be assessed with intradimensional–extradimensional shift task. Extradimensional attentional shifts demand greater cognitive flexibility to successfully perform the task than intradimensional shifts. MEG connectivity during this task in children with ASD was investigated using beamformer source estimation and phase lag index. Children with ASD showed reduced long-range theta connectivity during extradimensional set-shifting compared to controls (Doesburg et al. 2013). These findings are consistent with the supposed role of connectivity in low frequency band (delta and theta) long-distance communication among brain regions (Bhattacharya 2001). Our group investigated young adults with ASD measuring post-movement MEG beta rebound during observation and execution of hand actions. We found reduced post-movement beta rebound in mirror neuron system areas and the mPFC exclusively during the observation condition in patients relative to controls (Fig. 4). These results demonstrated a dysfunction of execution/observation matching system related to mirror neuron system, which may explain the difficulty in understanding other people's intentions or emotions in ASD (Honaga et al. 2010).

4.3 Major Depressive Disorder

MDD is a mood disorder characterized by a persistent depressed mood and markedly diminished interest or pleasure in all or most activities. fMRI connectivity studies in patients with MDD showed enhanced resting-state connectivity of the subgenual cingulate cortex and the thalamus with the DMN. Importantly, the subgenual cingulate cortex connectivity with the DMN is correlated with rumination (recurrent thinking about the self, past upsetting events, and unsolved concerns) and the length of the current depressive episode (Berman et al. 2011). The subgenual cingulate cortex and the thalamus are part of the PFC-thalamo-limbic pathway which is engaged in emotional processing (Drevets et al. 2008). Therefore, the increased connectivity between the subgenual cingulate cortex and the thalamus may reflect enhanced emotional processing in patients with MDD.

Functional connectivities between alpha band activity in the PFC and the metabolism in the thalamus before and after repetitive transcranial magnetic stimulation (rTMS) treatment were investigated using combined MEG and positron emission tomography (PET). Patients with drug treatment-resistant depression showed absence of the PFC–thalamic connectivity and its recovery after successful rTMS treatment. This result may indicate deficits of inhibitory function of the PFC to the thalamus and its recovery with symptomatic improvement in this disorder (Li et al. 2013). In addition, MEG connectivity between the amygdala, ACC, inferior frontal gyrus, and visual cortex in response to sad facial stimuli has been investigated using multiple sparse prior source estimation and Granger causality analysis. Relative to controls, MDD was characterized by an enhanced connectivity of the amygdala after exposure to sad facial stimuli in the early stage and reduced inhibitory connectivity from the inferior frontal cortex to the amygdala in the late stage (Lu et al. 2013). Taking these findings into consideration, abnormal connectivity of the amygdala and the thalamus with the DMN appears to be a key feature of MDD and may reflect the increased emotional processing seen in MDD, including rumination and brooding.

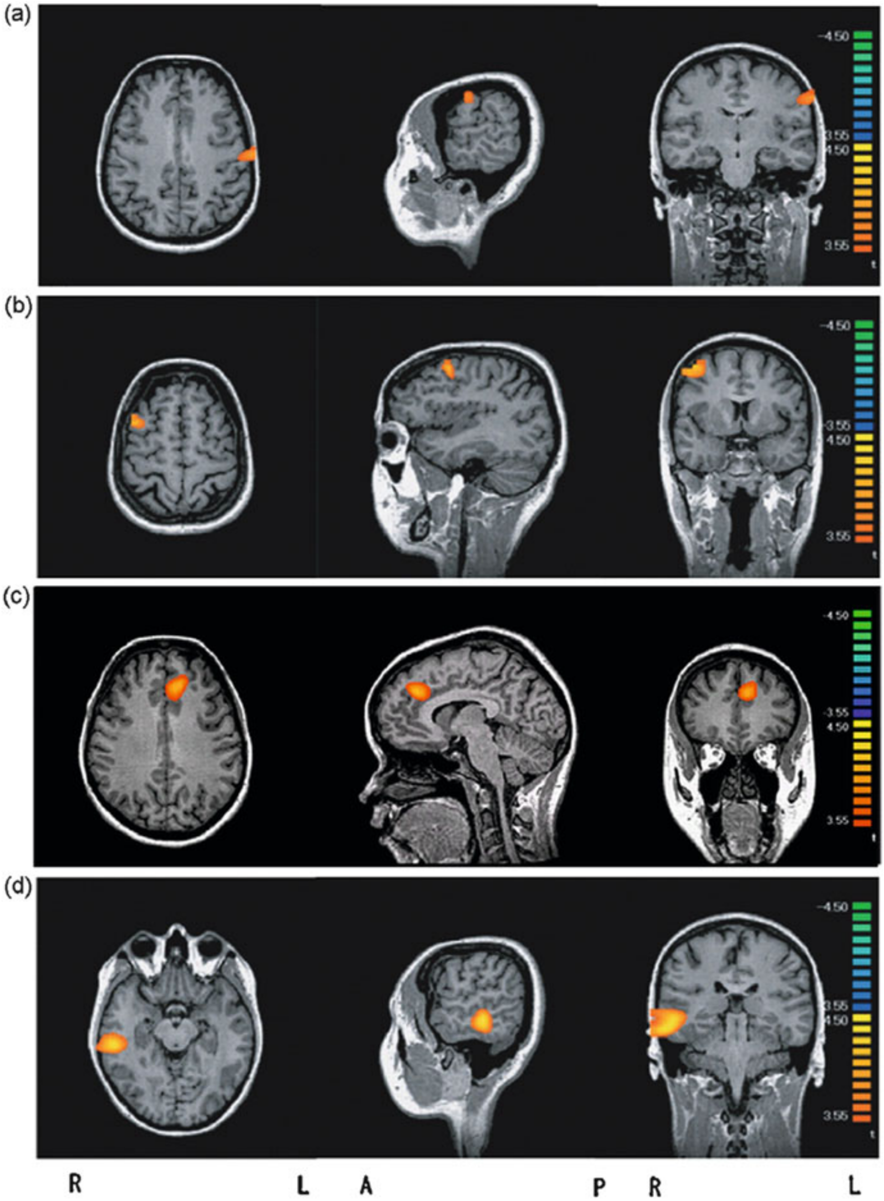


Fig. 4 Statistical maps of post-movement beta rebound during movement observation. Significant activation (increased beta rebound) can be seen in (**a**) the contralateral sensorimotor cortex, (**b**) right premotor area, (**c**) anterior cingulate cortex, and (**d**) right posterior–superior and middle temporal cortex in normal subjects relative to patients with autistic spectrum disorder (ASD). *R*, right; *L*, left; *A*, anterior; *P*, posterior (Honaga et al. 2010)

5 Summary

This chapter attempts to show the utility of a network approach for a better understanding of neurological and psychiatric disorders. In the study of the functional networks in the AD continuum, we can conclude that network analysis revealed specific profiles that could discriminate AD patients as well as MCI patients from controls. Furthermore, using this approach it is possible to predict which of the MCI patients will develop AD or not. Preclinical stages such as SMC have also been characterized by an early disruption of functional networks. In particular, the preclinical stage is characterized by an early decrease in functional connectivity between certain regions followed by an increase in intrinsic connectivity at the MCI stage. In fact, those patients that progress to dementia show the higher synchronization values. Later on, at the AD stage the network decreases its synchronization. These increased and decreased functional networks tend to show a random configuration indicating lower network efficiency in association with cognitive impairment. All these profiles can be modulated by anatomical connectivity disruption, being carrier of the APOE-ε4 as well as by the accumulation of amyloid beta and p-tau protein.

The functional network approach is also changing our view of epilepsy. Given that seizure, the defining feature of epilepsy, is related to an abnormal excessive or synchronous neuronal activity in the brain, connectivity is at the center of this disorder. Epileptic networks underlying focal epilepsies are of great value for localizing the epileptogenic zone and, therefore, are crucial for the presurgical mapping of epilepsy. This is particularly important in the case of intrinsically epileptogenic focal cortical dysplasia, where oscillation-based connectivity abnormalities in the gamma band may precisely define the epileptogenic zone, leading to good surgical outcomes. It is promising that brain connectivity analysis can also provide valuable information for an early diagnosis of epilepsy in patients without epileptiform discharges in initial interictal or ictal EEG recordings or in those without structural lesions on MRI. Of note, disruption in resting-state networks may help understand functional, behavioral, and cognitive deficits in patients with symptomatic epilepsies and in some cases of idiopathic focal/generalized epilepsy. Overall, resting-state functional connectivity is considered as an important tool for understanding functional brain organization in epilepsy. In addition, functional connectivity may potentially be used in clinical setting as part of the presurgical evaluation and for prediction of cognitive impairment.

With regard to psychiatric disorders, fMRI, EEG, and MEG connectivity analyses have elucidated disturbances of the connectivity between specific brain regions and their associations with psychiatric symptoms in schizophrenia, ASD, and MDD. These findings suggest that each psychiatric disease has specific patterns of disruption of functional networks, particularly for the CEN, the DMN, and the SN. These disease-specific disturbances of functional networks characterize the psychiatric diseases and reveal core pathogenic mechanisms. Therefore, network theory perspective may be helpful in the objective assessment of psychiatric symptoms, differential diagnosis of psychiatric diseases, and investigation of underlying pathogenic mechanisms.

Overall, in these neurological and psychiatric disorders, the study of brain functional networks is providing a new perspective for diagnosis and for achieving a better understanding of these disorders. However, whether this new approach will be useful in the clinical scenario is still a matter of debate and more clinical research is needed. Multicenter and blind studies are particularly encouraged. In addition, the high technical background needed to compute fMRI, EEG, or MEG temporal series with functional connectivity metrics is also making harder the use of this approach in a clinical environment. Friendly interfaces are still needed. However, the valuable information provided by functional connectivity and network analyses could inspire new therapeutical approaches and new views for diagnosis and prognosis. Thus, the difficulties mentioned above will probably be overcome in the near future because of the clear benefits of a network approach, particularly in neuropsychiatric disorders.

References

Alonso-Solís A, Vives-Gilabert Y, Grasa E, Portella MJ, Rabella M, Sauras RB, Roldán A, Núñez-Marín F, Gómez-Ansón B, Pérez V, Alvarez E, Corripio I (2015) Resting-state functional connectivity alterations in the default network of schizophrenia patients with persistent auditory verbal hallucinations. Schizophr Res 161(2–3):261–268

Andreou C, Leicht G, Nolte G, Polomac N, Moritz S, Karow A, Hanganu-Opatz IL, Engel AK, Mulert C (2015) Resting-state theta-band connectivity and verbal memory in schizophrenia and in the high-risk state. Schizophr Res 161(2–3):299–307

Aoki Y, Ishii R, Pascual-Marqui RD, Canuet L, Ikeda S, Hata M, Imajo K, Matsuzaki H, Musha T, Asada T, Iwase M, Takeda M (2015) Detection of EEG-resting state independent networks by eLORETA-ICA method. Front Hum Neurosci 9:31

Bajo R, Maestú F, Nevado A, Sancho M, Gutiérrez R, Campo P, Castellanos NP, Gil P, Moratti S, Pereda E, Del-Pozo F (2010) Functional connectivity in mild cognitive impairment during a memory task: implications for the disconnection hypothesis. J Alzheimers Dis 22(1):183–193

Bajo R, Castellanos NP, López ME, Ruiz JM, Montejo P, Montenegro M, Llanero M, Gil P, Yubero R, Baykova E, Paul N, Aurtenetxe S, Del Pozo F, Maestu F (2012a) Early dysfunction of functional connectivity in healthy elderly with subjective memory complaints. Age (Dordr) 34(2):497–506

Bajo R, Castellanos NP, Cuesta P, Aurtenetxe S, Garcia-Prieto J, Gil-Gregorio P, del-Pozo F, Maestu F (2012b) Differential patterns of connectivity in progressive mild cognitive impairment. Brain Connect 2(1):21–24

Bajo R, Pusil S, López ME, Canuet L, Pereda E, Osipova D, Maestú F, Pekkonen E (2015) Scopolamine effects on functional brain connectivity: a pharmacological model of Alzheimer's disease. Sci Rep 1(5):9748

Bamiou DE, Sisodiya S, Musiek FE, Luxon LM (2007) The role of the interhemispheric pathway in hearing. Brain Res Rev 56(1):170–182, Review

Barttfeld P, Wicker B, Cukier S, Navarta S, Lew S, Sigman M (2011) A big-world network in ASD: dynamical connectivity analysis reflects a deficit in long-range connections and an excess of short-range connections. Neuropsychologia 49(2):254–263

Berendse HW, Verbunt JP, Scheltens P, van Dijk BW, Jonkman EJ (2000) Magnetoencephalographic analysis of cortical activity in Alzheimer's disease: a pilot study. Clin Neurophysiol 111(4):604–612

Berman MG, Peltier S, Nee DE, Kross E, Deldin PJ, Jonides J (2011) Depression, rumination and the default network. Soc Cogn Affect Neurosci 6(5):548–555

Bhattacharya J (2001) Reduced degree of long-range phase synchrony in pathological human brain. Acta Neurobiol Exp (Wars) 61(4):309–318

Buldú JM, Bajo R, Maestú F, Castellanos N, Leyva I, Gil P, Sendiña-Nadal I, Almendral JA, Nevado A, del-Pozo F, Boccaletti S (2011) Reorganization of functional networks in mild cognitive impairment. PLoS One 6(5), e19584

Burgess AP, Gruzelier JH (1997) Localization of word and face recognition memory using topographical EEG. Psychophysiology 34(1):7–16

Burroughs SA, Morse RP, Mott SH, Holmes GL (2014) Brain connectivity in West syndrome. Seizure 23(7):576–579

Campo P, Garrido MI, Moran RJ, García-Morales I, Poch C, Toledano R, Gil-Nagel A, Dolan RJ, Friston KJ (2013) Network reconfiguration and working memory impairment in mesial temporal lobe epilepsy. Neuroimage 72:48–54

Canuet L, Ishii R, Pascual-Marqui RD, Iwase M, Kurimoto R, Aoki Y, Ikeda S, Takahashi H, Nakahachi T, Takeda M (2011) Resting-state EEG source localization and functional connectivity in schizophrenia-like psychosis of epilepsy. PLoS One 6(11), e27863

Canuet L, Pusil S, López ME, Bajo R, Pineda-Pardo J, Cuesta P, Galvez G, Gaztelu JM, Lourido D, García-Ribas G, Maestú F (2015) Network disruption and cerebrospinal fluid amyloid-beta and phospho-tau levels in mild cognitive impairment. J Neurosci 35 (28):10325–10330

Castellanos N, Paul N, Ordoñez V, Demuynck O, Bajo R, Campo P, Bilbao A, Ortiz T, Pozo F, Maestú F (2010) Reorganization of functional connectivity as a correlate of cognitive recovery in acquired brain injury. Brain 133:2365–2381

Clemens B, Puskás S, Besenyei M, Spisák T, Opposits G, Hollódy K, Fogarasi A, Fekete I, Emri M (2013) Neurophysiology of juvenile myoclonic epilepsy: EEG-based network and graph analysis of the interictal and immediate preictal states. Epilepsy Res 106(3):357–369

Constable RT, Scheinost D, Finn ES, Shen X, Hampson M, Winstanley FS, Spencer DD, Papademetris X (2013) Potential use and challenges of functional connectivity mapping in intractable epilepsy. Front Neurol 4:39

Crossley N, Mechelli A, Scott J, Carletti F, Fox P, McGuire P, Bullmore ET (2014) The hubs of the human connectome are generally implicated in the anatomy of brain disorders. Brain 1:1–14

Cuesta P, Garcés P, Castellanos NP, López ME, Aurtenetxe S, Bajo R, Pineda-Pardo JA, Bruña R, Marín AG, Delgado M, Barabash A, Ancín I, Cabranes JA, Fernandez A, Del Pozo F, Sancho M, Marcos A, Nakamura A, Maestú F (2015) Influence of the APOE ε4 allele and mild cognitive impairment diagnosis in the disruption of the MEG resting state functional connectivity in sources space. J Alzheimers Dis 44(2):493–505

Dai Y, Zhang W, Dickens DL, He B (2012) Source connectivity analysis from MEG and its application to epilepsy source localization. Brain Topogr 25(2):157–166

De Haan W, van der Flier WM, Koene T, Smits LL, Scheltens P, Stam CJ (2012a) Disrupted modular brain dynamics reflect cognitive dysfunction in Alzheimer's disease. Neuroimage 59 (4):3085–3093

De Haan W, van der Flier WM, Wang H, Van Mieghem PF, Scheltens P, Stam CJ (2012b) Disruption of functional brain networks in Alzheimer's disease: what can we learn from graph spectral analysis of resting-state magnetoencephalography? Brain Connect 2(2):45–55

De Haan W, Mott K, van Straaten EC, Scheltens P, Stam CJ (2012c) Activity dependent degeneration explains hub vulnerability in Alzheimer's disease. PLoS Comput Biol 8(8), e1002582. doi:10.1371/journal.pcbi.1002582

Delbeuck X, Van der Linden M, Collette F (2003) Alzheimer's disease as a disconnection syndrome? Neuropsychol Rev 13:79–92

Di Martino A, Ross K, Uddin LQ, Sklar AB, Castellanos FX, Milham MP (2009) Functional brain correlates of social and nonsocial processes in autism spectrum disorders: an activation likelihood estimation meta-analysis. Biol Psychiatry 65(1):63–74

Doesburg SM, Vidal J, Taylor MJ (2013) Reduced theta connectivity during set-shifting in children with autism. Front Hum Neurosci 7:785

Douw L, de Groot M, van Dellen E, Heimans JJ, Ronner HE, Stam CJ, Reijneveld JC (2010) Functional connectivity is a sensitive predictor of epilepsy diagnosis after the first seizure. PLoS One 5(5), e10839

Drevets WC, Price JL, Furey ML (2008) Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. Brain Struct Funct 213 (1–2):93–118

Fisher RS, van Emde BW, Blume W, Elger C, Genton P, Lee P, Engel J Jr (2005) Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia 46(4):470–472

Franciotti R, Iacono D, Della Penna S, Pizzella V, Torquati K, Onofrj M, Romani GL (2006) Cortical rhythms reactivity in AD, LBD and normal subjects: a quantitative MEG study. Neurobiol Aging 27(8):1100–1109

Garcés P, Angel Pineda-Pardo J, Canuet L, Aurtenetxe S, López ME, Marcos A, Yus M, Llanero-Luque M, Del-Pozo F, Sancho M, Maestú F (2014) The default mode network is functionally and structurally disrupted in amnestic mild cognitive impairment—a bimodal MEG-DTI study. Neuroimage Clin 6:214–221

Geschwind N (1965) Disconnexion syndromes in animals and man: I. Brain 88(2):237–294

He Y, Wang J, Wang L, Chen ZJ, Yan C, Yang H, Tang H, Zhu C, Gong Q, Zang Y, Evans AC (2009) Uncovering intrinsic modular organization of spontaneous brain activity in humans. PLoS One 4(4), e5226

Higashima M, Takeda T, Kikuchi M, Nagasawa T, Hirao N, Oka T, Nakamura M, Koshino Y (2007) State-dependent changes in intrahemispheric EEG coherence for patients with acute exacerbation of schizophrenia. Psychiatry Res 149(1–3):41–47

Honaga E, Ishii R, Kurimoto R, Canuet L, Ikezawa K, Takahashi H, Nakahachi T, Iwase M, Mizuta I, Yoshimine T, Takeda M (2010) Post-movement beta rebound abnormality as indicator of mirror neuron system dysfunction in autistic spectrum disorder: an MEG study. Neurosci Lett 478(3):141–145

Hsiao FJ, Yu HY, Chen WT, Kwan SY, Chen C, Yen DJ, Yiu CH, Shih YH, Lin YY (2015) Increased intrinsic connectivity of the default mode network in temporal lobe epilepsy: evidence from resting-state MEG recordings. PLoS One 10(6), e0128787

Jeong W, Jin SH, Kim M, Kim JS, Chung CK (2014) Abnormal functional brain network in epilepsy patients with focal cortical dysplasia. Epilepsy Res 108(9):1618–1626

Jessen F, Amariglio RE, van Boxtel M, Breteler M, Ceccaldi M, Chételat G, Dubois B, Dufouil C, Ellis KA, van der Flier WM, Glodzik L, van Harten AC, de Leon MJ, McHugh P, Mielke MM, Molinuevo JL, Mosconi L, Osorio RS, Perrotin A, Petersen RC, Rabin LA, Rami L, Reisberg B, Rentz DM, Sachdev PS, de la Sayette V, Saykin AJ, Scheltens P, Shulman MB, Slavin MJ, Sperling RA, Stewart R, Uspenskaya O, Vellas B, Visser PJ, Wagner M, Subjective Cognitive Decline Initiative (SCD-I) Working Group (2014) A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. Alzheimers Dement 10(6):844–852

Kennedy DP, Courchesne E (2008a) Functional abnormalities of the default network during self- and other-reflection in autism. Soc Cogn Affect Neurosci 3(2):177–190

Kennedy DP, Courchesne E (2008b) The intrinsic functional organization of the brain is altered in autism. Neuroimage 39(4):1877–1885

Kennedy DP, Redcay E, Courchesne E (2006) Failing to deactivate: resting functional abnormalities in autism. Proc Natl Acad Sci USA 103(21):8275–8280

Kikuchi M, Yoshimura Y, Hiraishi H, Munesue T, Hashimoto T, Tsubokawa T, Takahashi T, Suzuki M, Higashida H, Minabe Y (2015) Reduced long-range functional connectivity in young children with autism spectrum disorder. Soc Cogn Affect Neurosci 10(2):248–254

Kim H (2012) A dual-subsystem model of the brain's default network: self-referential processing, memory retrieval processes, and autobiographical memory retrieval. Neuroimage 61 (4):966–977. doi:10.1016/j.neuroimage.2012.03.025

Koechlin E, Summerfield C (2007) An information theoretical approach to prefrontal executive function. Trends Cogn Sci 11(6):229–235

Krishnan B, Vlachos I, Wang ZI, Mosher J, Najm I, Burgess R, Iasemidis L, Alexopoulos AV (2015) Epileptic focus localization based on resting state interictal MEG recordings is feasible irrespective of the presence or absence of spikes. Clin Neurophysiol 126(4):667–674

Lemieux L, Daunizeau J, Walker MC (2011) Concepts of connectivity and human epileptic activity. Front Syst Neurosci 5:12

Li CT, Chen LF, Tu PC, Wang SJ, Chen MH, Su TP, Hsieh JC (2013) Impaired prefronto-thalamic functional connectivity as a key feature of treatment-resistant depression: a combined MEG, PET and rTMS study. PLoS One 8(8), e70089

Li Q, Cao W, Liao X, Chen Z, Yang T, Gong Q, Zhou D, Luo C, Yao D (2015) Altered resting state functional network connectivity in children absence epilepsy. J Neurol Sci 354(1–2):79–85

López ME, Bruña R, Aurtenetxe S, Pineda-Pardo JÁ, Marcos A, Arrazola J, Reinoso AI, Montejo P, Bajo R, Maestú F (2014) Alpha-band hypersynchronization in progressive mild cognitive impairment: a magnetoencephalography study. J Neurosci 34(44):14551–14559

Lu Q, Bi K, Liu C, Luo G, Tang H, Yao Z (2013) Predicting depression based on dynamic regional connectivity: a windowed Granger causality analysis of MEG recordings. Brain Res 1535:52–60

Maestú F, Yubero R, Moratti S, Campo P, Gil-Gregorio P, Paul N, Solesio E, del Pozo F, Nevado A (2011) Brain activity patterns in stable and progressive mild cognitive impairment during working memory as evidenced by magnetoencephalography. J Clin Neurophysiol 28 (2):202–209

Maestú F, Peña JM, Garcés P, González S, Bajo R, Bagic A, Cuesta P, Funke M, Mäkelä JP, Menasalvas E, Nakamura A, Parkkonen L, López ME, Del Pozo F, Sudre G, Zamrini E, Pekkonen E, Henson RN, Becker JT, Magnetoencephalography International Consortium of Alzheimer's Disease (2015) A multicenter study of the early detection of synaptic dysfunction in Mild Cognitive Impairment using Magnetoencephalography-derived functional connectivity. Neurol Clin 1(9):103–109

Menon V (2011) Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cogn Sci 15(10):483–506, Review

Morrison JH, Scherr S, Lewis DA, Campbell MJ, Bloom FE, Rogers J, Benoit R (1986) The laminar and regional distribution of neocortical somatostatin and neuritic plaques: implications for Alzheimer's disease as a global neocortical disconnection syndrome. The Biological Substrates of Alzheimer's Disease. Academic, Orlando, pp 115–131

Mulert C, Kirsch V, Pascual-Marqui R, McCarley RW, Spencer KM (2011) Long-range synchrony of γ oscillations and auditory hallucination symptoms in schizophrenia. Int J Psychophysiol 79(1):55–63

Myers N, Pasquini L, Göttler J, Grimmer T, Koch K et al (2014) Within-patient correspondence of amyloid-β and intrinsic network connectivity in Alzheimer's Disease. Brain 1:1–13

Nath S, Agholme L, Kurudenkandy FR, Granseth B, Marcusson J (2012) Spreading of neurodegenrative pathology via neuron-to-neuron transmission of β–amyloid. J Neurosci 32 (26):8767–8777

Niso G, Carrasco S, Gudín M, Maestú F, Del-Pozo F, Pereda E (2015) What graph theory actually tells us about resting state interictal MEG epileptic activity. Neurol Clin 8:503–515

O'Muircheartaigh J, Vollmar C, Barker GJ, Kumari V, Symms MR, Thompson P, Duncan JS, Koepp MJ, Richardson MP (2012) Abnormal thalamocortical structural and functional connectivity in juvenile myoclonic epilepsy. Brain 135(12):3635–3644

Osipova D, Ahveninen J, Kaakkola S, Jääskeläinen IP, Huttunen J, Pekkonen E (2003) Effects of scopolamine on MEG spectral power and coherence in elderly subjects. Clin Neurophysiol 114 (10):1902–1907

Pascual-Marqui RD, Lehmann D, Koukkou M, Kochi K, Anderer P, Saletu B, Tanaka H, Hirata K, John ER, Prichep L, Biscay-Lirio R, Kinoshita T (2011) Assessing interactions in the brain with exact low-resolution electromagnetic tomography. Philos Trans A Math Phys Eng Sci 369 (1952):3768–3784

Pineda-Pardo JA, Bruña R, Woolrich M, Marcos A, Nobre AC, Maestú F, Vidaurre D (2014a) Guiding functional connectivity estimation by structural connectivity in MEG: an application to discrimination of conditions of mild cognitive impairment. Neuroimage 101:765–777

Pineda-Pardo JA, Garcés P, López ME, Aurtenetxe S, Cuesta P, Marcos A, Montejo P, Yus M, Hernández-Tamames JA, Del-Pozo F, Becker JT, Maestu F (2014b) White matter damage disorganizes brain functional networks in amnestic mild cognitive impairment. Brain Connect 4(5):312–322

Pittau F, Vulliemoz S (2015) Functional brain networks in epilepsy: recent advances in noninvasive mapping. Curr Opin Neurol 28(4):338–343

Raichle ME (2011) The restless brain. Brain Connect 1(1):3–12

Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL (2001) A default mode of brain function. Proc Natl Acad Sci USA 98(2):676–682

Rotarska-Jagiela A, van de Ven V, Oertel-Knöchel V, Uhlhaas PJ, Vogeley K, Linden DE (2010) Resting-state functional network correlates of psychotic symptoms in schizophrenia. Schizophr Res 117(1):21–30

Sargolzaei S, Cabrerizo M, Goryawala M, Eddin AS, Adjouadi M (2015) Scalp EEG brain functional connectivity networks in pediatric epilepsy. Comput Biol Med 56:158–166

Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss AL, Greicius MD (2007) Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci 27(9):2349–2356

Sestieri C, Corbetta M, Romani GL, Shulman GL (2011) Episodic memory retrieval, parietal cortex, and the default mode network: functional and topographic analyses. J Neurosci 31 (12):4407–4420

Sommer IE, Clos M, Meijering AL, Diederen KM, Eickhoff SB (2012) Resting state functional connectivity in patients with chronic hallucinations. PLoS One 7(9), e43516

Spreng RN, Mar RA, Kim AS (2009) The common neural basis of autobiographical memory, prospection, navigation, theory of mind, and the default mode: a quantitative meta-analysis. J Cogn Neurosci 21(3):489–510. doi:10.1162/jocn.2008.21029

Sridharan D, Levitin DJ, Menon V (2008) A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. Proc Natl Acad Sci USA 105 (34):12569–12574

Stam CJ, van Cappellen van Walsum AM, Pijnenburg YA, Berendse HW, de Munck JC, Scheltens P et al (2002) Generalized synchronization of MEG recordings in Alzheimer's Disease: evidence for involvement of the gamma band. J Clin Neurophysiol 19(6):562–574

Stam CJ, Jones BF, Manshanden I, van Cappellen van Walsum AM, Montez T, Verbunt JP, de Munck JC, van Dijk BW, Berendse HW, Scheltens P (2006) Magnetoencephalographic evaluation of resting-state functional connectivity in Alzheimer's disease. Neuroimage 32 (3):1335–1344

Stam CJ, de Haan W, Daffertshofer A, Jones BF, Manshanden I, van Cappellen van Walsum AM, Montez T, Verbunt JP, de Munck JC, van Dijk BW, Berendse HW, Scheltens P (2009) Graph theoretical analysis of magnetoencephalographic functional connectivity in Alzheimer's disease. Brain 132(Pt 1):213–224

Stefan H, Lopes da Silva FH (2013) Epileptic neuronal networks: methods of identification and clinical relevance. Front Neurol 4:8

Tsiaras V, Simos PG, Rezaie R, Sheth BR, Garyfallidis E, Castillo EM, Papanicolaou AC (2011) Extracting biomarkers of autism from MEG resting-state functional connectivity networks. Comput Biol Med 41(12):1166–1177

Uddin LQ, Kelly AM, Biswal BB, Castellanos FX, Milham MP (2009) Functional connectivity of default mode network components: correlation, anticorrelation, and causality. Hum Brain Mapp 30(2):625–637

Uhlhaas PJ, Linden DE, Singer W, Haenschel C, Lindner M, Maurer K, Rodriguez E (2006) Dysfunctional long-range coordination of neural activity during Gestalt perception in schizophrenia. J Neurosci 26(31):8168–8175 van Lutterveld R, Hillebrand A, Diederen KM, Daalman K, Kahn RS, Stam CJ, Sommer IE (2012) Oscillatory cortical network involved in auditory verbal hallucinations in schizophrenia. PLoS One 7(7), e41149

Varotto G, Tassi L, Franceschetti S, Spreafico R, Panzica F (2012) Epileptogenic networks of type II focal cortical dysplasia: a stereo-EEG study. Neuroimage 61(3):591–598

Wei HL, An J, Zeng LL, Shen H, Qiu SJ, Hu DW (2015) Altered functional connectivity among default, attention, and control networks in idiopathic generalized epilepsy. Epilepsy Behav 46:118–125

Wotruba D, Michels L, Buechler R, Metzler S, Theodoridou A, Gerstenberg M, Walitza S, Kollias S, Rössler W, Heekeren K (2014) Aberrant coupling within and across the default mode, task-positive, and salience network in subjects at risk for psychosis. Schizophr Bull 40 (5):1095–1104

Wu T, Ge S, Zhang R, Liu H, Chen Q, Zhao R, Yin Y, Lv X, Jiang T (2014) Neuromagnetic coherence of epileptic activity: an MEG study. Seizure 23(6):417–423

Xiao F, Lei D, An D, Li L, Chen S, Chen F, Yang T, Ren J, Huang X, Gong Q, Zhou D (2015a) Functional brain connectome and sensorimotor networks in rolandic epilepsy. Epilepsy Res 113:113–125

Xiao F, Li L, An D, Lei D, Tang Y, Yang T, Ren J, Chen S, Huang X, Gong Q, Zhou D (2015b) Altered attention networks in benign childhood epilepsy with centrotemporal spikes (BECTS): a resting-state fMRI study. Epilepsy Behav 45:234–241