

Original Research

A new look at gamma? High- (>60 Hz) γ -band activity in cortical networks: Function, mechanisms and impairment

Peter J. Uhlhaas^{a,*}, Gordon Pipa^{a,b,c}, Sergio Neuenschwander^a, Michael Wibral^d, Wolf Singer^{a,c}

^aDepartment of Neurophysiology, Max-Planck Institute for Brain Research, Deutschordenstr. 46, Frankfurt am Main 60528, Germany

^bDepartment for Neuroinformatics, Institute of Cognitive Science, University of Osnabrueck, Osnabrueck 49069, Germany

^cFrankfurt Institute for Advanced Studies, Johann Wolfgang Goethe-Universität, Max-von-Laue-Str. 1, Frankfurt am Main 60438, Germany

^dMEG-Unit, Brain Imaging Centre Frankfurt, Johann Wolfgang Goethe-Universität, Heinrich Hoffmann Strasse 10, Frankfurt am Main 60528, Germany

ARTICLE INFO

Article history:

Available online 27 October 2010

Keywords:

Oscillations
Synchrony
Gamma
Cognition
Psychiatry

ABSTRACT

γ -band oscillations are thought to play a crucial role in information processing in cortical networks. In addition to oscillatory activity between 30 and 60 Hz, current evidence from electro- and magnetoencephalography (EEG/MEG) and local-field potentials (LFPs) has consistently shown oscillations >60 Hz (high γ -band) whose function and generating mechanisms are unclear. In the present paper, we summarize data that highlights the importance of high γ -band activity for cortical computations through establishing correlations between the modulation of oscillations in the 60–200 Hz frequency and specific cognitive functions. Moreover, we will suggest that high γ -band activity is impaired in neuropsychiatric disorders, such as schizophrenia and epilepsy. In the final part of the paper, we will review physiological mechanisms underlying the generation of high γ -band oscillations and discuss the functional implications of low vs. high γ -band activity patterns in cortical networks.

© 2010 Published by Elsevier Ltd.

1. Introduction: neural oscillations and brain functions

Research into neural oscillations in nervous systems has received increasing interest in recent years due to their fundamental role in the coding and transmission of information (Uhlhaas et al., 2009; Buzsaki, 2006; Fries, 2009). Oscillations in the low (δ , θ , α) and high (β , γ) frequency bands are thought to play a fundamental role in basic aspects of information processing during sensory processing and higher cognitive functions as well as for synaptic plasticity and development of cortical networks (Buzsaki, 2006; Buzsaki and Draguhn, 2004; Uhlhaas et al., 2009, 2010). Moreover, computational and physiological work has uncovered neurotransmitter systems and anatomical correlates of patterned, rhythmic activity (Engel et al., 1991; Rodriguez et al., 2004; Traub et al., 2004; Wang and Buzsaki, 1996) that offer important links from basic science to clinical applications for translation research (Uhlhaas and Singer, 2010).

* Corresponding author. Department of Neurophysiology, Max-Planck Institute for Brain Research, Deutschordenstr. 46, Frankfurt am Main 60590, Germany. Tel.: +49 69 6301 7643; fax: +49 69 6301 83783.

E-mail address: uhlhaas@mpih-frankfurt.mpg.de (P.J. Uhlhaas).

¹ In addition to oscillations >1 Hz, there is also evidence for rhythmic activity <0.1 Hz as measured in EEG and fMRI data which may have a role in cortical processes (Monto et al., 2008; Fox and Raichle, 2007).

Of particular interest for the neural coding of information are neural oscillations in the γ -band range. Initial descriptions were provided by Adrian and colleagues in the 1940s (Adrian, 1950). They recorded LFPs from the olfactory bulb of anesthetized cats, rabbits and hedgehogs and observed oscillations in the 40–60 Hz frequency range. Similarly, in a series of studies Freeman and colleagues (Bressler and Freeman, 1980; Freeman and Skarda, 1985) reported oscillations between 35 and 85 Hz with pronounced amplitude ~40 Hz in the olfactory bulb of cats, rabbits and rats. Systematic correlations between olfactory perception and modulation of 40 Hz activity led to the proposal that spatial and amplitude modulation of γ -waves is related to the coding of information in the olfactory system (Freeman, 1991).

Crucial evidence for a role of γ -band oscillations in cortical computations was reported by Gray et al. (1989). They investigated the relations between stimulus-induced synchronization of γ -band oscillations and feature binding in cat primary visual cortex (V1). The data demonstrated a correlation between oscillatory activity ~40 Hz and global properties of the stimulus. This finding led to the binding-by-synchrony hypothesis, stating that synchronised γ -oscillations serve as a mechanism to coordinate distributed neuronal responses (Singer, 1999; Singer and Gray, 1995).

In the following years, numerous studies identified close relations between oscillations ~40 Hz and a variety of cognitive and executive functions, comprising feature binding, polymodal

integration, working memory, motor-planning, attention and access to consciousness (for a review see, Fries, 2009; Jensen et al., 2007; Singer, 1999; Tallon-Baudry and Bertrand, 1999; Herrmann et al., 2004; Uhlhaas et al., 2009). Such high-frequency oscillations are particularly effective to precisely time the occurrence of neuronal discharges (Fries et al., 2001a) which is a necessary prerequisite for synchronization of activity and for the generation of temporal codes. In general, there is a correlation between the distance over which synchronization is observed and the frequency of the synchronised oscillations. Short distance synchronization tends to occur at higher frequencies (in the γ -band range) than long-distance synchronization, which often manifests itself in the β – but also in the θ - and α -frequency range (Kopell et al., 2000, von Stein et al., 2000).

In addition to γ -band activity ~ 40 Hz, recent studies based on MEG and Electroencephalography (EEG) have also reported γ -band oscillations >60 Hz that can reach up to 200 Hz (for reviews see Crone et al., 2006; Jerbi et al., 2009). These so called “high γ -band oscillations” have been identified previously in animal experiments in the retina and cortex and referred to as Ω -oscillations (Munk and Neuenschwander, 2000) (for a taxonomy of different γ -bands see Fig. 1).

In the following paper we aim to provide a comprehensive perspective on high γ -band activity in cortical networks by summarising data from recent studies in our laboratory and other groups. We shall review some of the early studies with EEG and MEG on low γ -band activity that highlighted the importance of oscillations in the 30–60 Hz frequency range for normal cognitive functions as well as for brain disorders, such as schizophrenia. Subsequently, we shall discuss the data from LFPs, electrocorticographical (ECoG) and MEG-studies which have consistently shown high γ -band oscillations in the context of a range of cognitive and perceptual processes. Finally, we shall provide an overview of the physiological mechanisms underlying the generation of high γ -band activity and discuss the implication of these findings for research into neural oscillations.

2. Low (30–60 Hz) γ -band oscillations and brain function

2.1. Low (30–60 Hz) γ -band oscillations in EEG- and MEG-data

The hypothesis that synchronised 40 Hz oscillations are related to the binding of stimulus elements in visual perception triggered a series of studies with EEG and MEG. Tallon-Baudry and colleagues carried out a series of seminal studies that provided important support for this hypothesis. In the first experiment (Tallon-Baudry et al., 1996) the authors presented illusory triangles (Kanizsa squares) to human observers in two conditions: 1) two coherent stimuli (a Kanizsa and a real triangle) and a non-coherent stimulus (no-triangle stimulus). EEG-data were obtained and analysed for the frequency content of both phase-locked (evoked) and non-phase-locked (induced) oscillatory activity. The results showed oscillatory activity predominantly in the 40 Hz frequency range. An early evoked 40 Hz response did not vary with stimulation condition whereas the induced activity with a latency ~ 280 ms was only apparent in response to coherent triangles. In a second study (Tallon-Baudry et al., 1997a) performed with the same paradigm but with MEG-recordings, evoked but not induced 40 Hz activity could be identified.

Further evidence for the role of 40 Hz induced oscillations in the construction of coherent object representations was obtained with a visual search task (Tallon-Baudry et al., 1997b). Participants were required to detect a hidden Dalmatian dog vs. a neutral stimulus in which no Gestalt was perceived. Perception of the Dalmatian resulted in a selective enhancement of induced

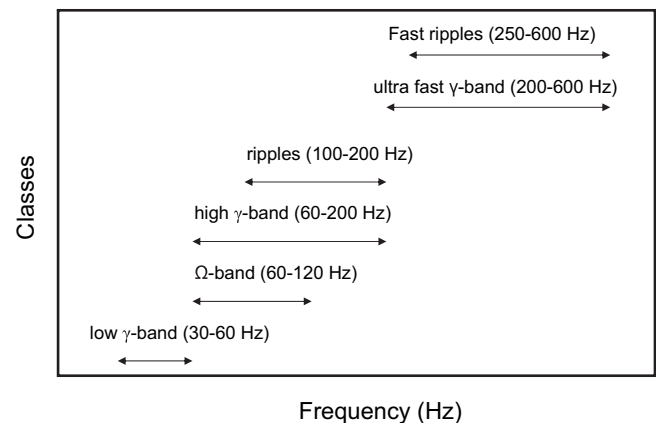


Fig. 1. Taxonomy of γ -band activity. γ -Band oscillations cover a frequency range from 30 to 600 Hz and can be differentiated into: 1) low γ -band oscillations (e.g., Gray et al., 1989; Tallon-Baudry et al., 1996); 2) Ω -band oscillations (60–120 Hz) originate in the retina and propagate along the geniculo-cortical pathway (Munk and Neuenschwander, 2000); 3) high γ -band oscillations as observed in ECoG, LFP and MEG-Data (Colgin et al., 2009; Crone et al., 1998; Gruetner et al., 2010); 4) so called “ripples”, short-lasting oscillatory phenomena covering a frequency range between 100–200 Hz (Bragin et al., 2010; Buzsáki et al., 1992); 5) ultra fast γ -band oscillations reach frequencies up to 600 Hz and have been reported during sensory processing (e.g., Curio, 2000). 6) Finally, ripples can also occur between 250–600 Hz. These oscillations frequently reflect hypersynchronous activity in epileptogenic regions (Bragin et al., 2010).

EEG-activity ~ 40 Hz. Similarly, induced rhythmic activity around 40 Hz over occipitotemporal and frontal electrodes was also present during the delay period of a working memory task (Tallon-Baudry et al., 1998, for studies extending the relationship between γ -band oscillations and long-term memory see Gruber and Müller, 2006).

These and other findings by Tallon-Baudry and colleagues led to the proposal that induced γ -band activity is related to the construction of coherent object representations and the maintenance of information in working memory. In contrast, evoked 40 Hz oscillations were considered unrelated to higher cognitive functions (Tallon-Baudry and Bertrand, 1999). Several studies, however, have demonstrated in the meantime that evoked oscillations are strongly influenced by top-down factors, such as attention (Tiitinen et al., 1993) and task instructions (Herrmann et al., 1999) (for a review see Herrmann et al., 2004).

Further evidence for the role of synchronised 40 Hz oscillations in the large-scale coordination of distributed neural responses was reported in a study by Rodriguez et al. (1999). The authors applied a novel method to examine the stability of phase relations across experimental trials of induced oscillations to obtain an estimate of the precision of synchrony independently of oscillation amplitude (Lachaux et al., 1999). EEG-data were obtained during the perception of Mooney faces. These consist of degraded pictures of human faces where all shades of grey are removed, the shadows rendered in black and the highlights in white. In these experiments, amplitude and synchrony of 40 Hz oscillations were found to correlate with the construction of coherent object representations. Oscillations ~ 40 Hz were characterised by enhanced long-range synchronization between temporal and parietal electrodes, suggesting that phase-synchronization of γ -band activity serves as a mechanism for the large-scale integration of distributed neuronal responses (Varela et al., 2001).

Close relations between long-range synchronization in the γ -band and conscious perception were demonstrated in a study by Melloni et al. (2007). Participants had to detect and identify a briefly exposed word (33 ms) presented between masking

stimuli. EEG signals were analysed for spectral power and precision of phase synchrony over a wide frequency range and for event-related potentials. The first electrophysiological event that distinguished seen from unseen words was an early and transient burst of long-distance synchronization observed in the low γ -band. In contrast, regional distributions of γ -spectral power revealed no significant differences between conditions, suggesting that access to conscious perception is reflected in an early transient global increase of phase synchrony of oscillatory activity in the γ -frequency range.

2.2. Low (30–60 Hz) γ -band oscillations in psychiatric disorders

Aberrant γ -band activity in the 30–60 Hz range has received increasing attention as a pathophysiological mechanism in neuropsychiatric disorders (see Uhlhaas and Singer, 2006, for a review). Numerous studies have revealed that γ -band activity is abnormal in schizophrenia, autism and Alzheimer's disease (Koenig et al., 2005; Wilson et al., 2007). The option to examine the mechanisms underlying synchronised γ -band oscillations in animal models and in in-vitro preparations makes it now possible to identify pathophysiological mechanisms and to develop targeted pharmacological interventions (Roopun et al., 2008a).

Deficits in the amplitude and synchrony of γ -band oscillations in the 30–60 Hz range have been a particular focus in schizophrenia research (for reviews see Uhlhaas et al., 2008; Uhlhaas and Singer, 2010). Several reports (Kwon et al., 1999; Spencer et al., 2008) demonstrated robust impairments in the auditory steady state response (ASSR) to 40 Hz stimulation in patients with schizophrenia. Steady-state responses (SSRs) are a basic neural response to a temporally modulated stimulus to which SSRs are synchronised in frequency and phase. Thus, they probe the ability of neuronal networks to generate and maintain oscillatory activity in different frequency bands.

In addition, there is evidence for reductions in the amplitude of evoked and induced γ -band oscillations. Consistent with the evidence that early sensory processes are impaired (Uhlhaas et al., 2006a; Silverstein et al., 2006), several studies have also demonstrated abnormalities in stimulus-locked oscillations \sim 40 Hz during auditory and visual processing (Johannessen et al., 2008; Spencer et al., 2003). Schizophrenia is furthermore associated with reductions in the amplitude and synchrony of self-generated, rhythmic activity in the 30–60 Hz frequency range in a number of cortical regions (Haenschel et al., 2009; Spencer et al., 2003; Uhlhaas et al., 2006b). Several studies have shown, for example, reduced phase-synchronization of oscillations in the γ -band but also at β -frequency during perceptual organisation (Spencer et al., 2003; Uhlhaas et al., 2006b). These findings suggest that impaired synchronization of induced oscillations could underlie the hypothesized functional dysconnectivity of cortical networks in schizophrenia (Friston, 1999).

The neuronal mechanisms responsible for the generation of oscillations and synchrony in the 30–60 Hz frequency range have been studied extensively both in vivo and in-vitro (see section 4). This allows in some instances to establish links between anatomical deficits and abnormalities in neurotransmitter systems in schizophrenia that may underlie abnormalities seen in EEG and MEG studies. Specifically, the finding that γ -band oscillations are dependent upon Gamma-aminobutyric acid (GABA)ergic interneurons is compatible with a large body of evidence suggesting alterations in GABAergic neurotransmission in schizophrenia, including a reduction in the messenger RNA (mRNA) of glutamic acid decarboxylase (GAD) 67 and deficits in Parvalbumin-positive (PV) interneurons (for a review see Lewis et al., 2005).

2.3. Low (30–60 Hz) γ -band oscillations in EEG-data and microsaccades

Recently, the validity of many EEG studies that reported induced 40 Hz activity has been questioned by Yuval-Greenberg et al. (2008). Their critique was based on the observation that artefacts from muscular activity related to microsaccades exhibit a spectral profile similar to that of 40 Hz activity reported previously. As the frequency of microsaccade occurrence is influenced by stimulation but microsaccades do not occur precisely time-locked to the stimulus event, these artefacts are easily misinterpreted as stimulus-induced 40 Hz activity. In the study of Yuval-Greenberg and colleagues, stimulus-induced power changes in the 40 Hz range were in fact almost exclusively related to artefacts from microsaccades.

It is important to note that these artefacts can be most easily confounded with brain-derived 40 Hz activity when the analysis of EEG-data is performed in a nose reference system. In contrast, these artefacts appear with an eye-centered topography when analysed in average reference as pointed out by Melloni et al. (2009) and can therefore be identified and excluded.

Unfortunately several (but not all) studies on 40 Hz activity in the EEG literature have been performed using the nose reference system (i.e. Rodriguez et al., 1999; Tallon-Baudry et al., 1996, 1998). Another confound is saccade related corollary activity that originates in the brain and may give rise to true oscillations in the gamma frequency range (Melloni et al., 2009). It is therefore a topic of future reanalysis and research to validate or disprove these specific reports on 40 Hz activity in the EEG.

3. High (60–200 Hz) γ -band oscillations and brain function

3.1. High γ -band oscillations in invasive electrophysiology

Data obtained from simultaneous recordings from the retina, lateral geniculate (LGN) and cortex showed that rhythms above 60 Hz are present in the retina and that this fast oscillatory patterning of responses propagates through the visual pathways by a feedforward mechanism (Castelo-Branco et al., 1998; Laufer and Verzeano, 1967; Neuenschwander et al., 2003; Neuenschwander and Singer, 1996). Retinal ganglion cells exhibit precise oscillatory activity patterns from recurrent local inhibitory interactions, which become synchronous over large distances by means of electrical coupling via gap junctions (Vaney, 1994). Synchronous oscillations in the retina are dependent on stimulus size and contrast (Neuenschwander et al., 1999), but also on stimulus-continuity (Neuenschwander and Singer, 1996), suggesting that they may convey global information about the image (Stephens et al., 2006). Since the fast oscillations originating in the retina propagate along the geniculate-cortical pathway (Castelo-Branco et al., 1998), they may entrain target circuits in the cortex, reducing input spike variability (Kenyon et al., 2004). In accordance with this suggestion, it has been shown that neurons in both the LGN and the cortex respond preferentially to synchronous spikes (Alonso et al., 1996), indicating that synchronous oscillatory inputs may be particularly salient for cortical neurons.

The entrainment of cortical activity by fast oscillatory inputs seems to depend on the level of central activation. Experiments in the anesthetized cat where cortical state transitions were induced by electrical stimulation of the mesencephalic reticular formation (Herculano-Houzel et al., 1999; Munk and Neuenschwander, 2000) have shown that the temporal characteristics of the responses in the visual cortex may change drastically depending on the activation of modulatory projections. At intermediate levels of cortical activation (characterised by high amplitude delta fluctuations in

the EEG), the responses are dominated by high γ -band inputs (70–105 Hz), which were shown to originate in the retina (Castelo-Branco et al., 1998). During activated states (high γ -band components in the EEG), on the other hand, the cortical responses exhibit the classical low γ -band rhythms (20–65 Hz). It is still unclear whether and how fast oscillatory inputs (e.g., fast retinal oscillations) entrain or interact with other cortical rhythms.

Electrophysiological studies in monkeys have shown that high γ -band activity may also be involved in higher cognitive functions such as working memory and movement planning and are tightly related to the behavioural task (Pesaran et al., 2002; Pipa et al., 2009; Wu et al., 2008). Pipa et al. (2009) showed that LFPs recorded in the prefrontal cortex of rhesus monkeys expressed sustained and stimulus specific high γ -band oscillations during the memory phase of a visual short-term memory paradigm. This highlights that the high γ -band oscillatory pattern can be both stimulus induced but also intrinsically generated (Fig. 2).

Clear evidence that distinct γ -band frequencies may be related to different mechanisms comes from studies in the hippocampus. γ -band oscillations in CA1 occupy separate frequency bands, one ranging from 25 to 50 Hz and the other from 65 to 140 Hz. These distinct rhythms have different origins: high γ -band oscillations are entrained by the entorhinal cortex, while the low γ -band oscillations are generated intrinsically within the hippocampal network (Bragin et al., 1995; Csicsvari et al., 2003). Recently, Colgin et al. (2009) have shown in the rat that during periods of low γ -band activity in CA1, neuronal synchronization is particularly strong (measured as coherence) between CA1 and CA3. Conversely, during periods of high γ -band oscillations, CA1 activity is entrained by the high-frequency entorhinal oscillations.

3.2. High γ -band activity in ECoG-data

ECoG recordings with surgically implanted electrodes allow the direct recording of brain activity that is particularly suited for the examination of low-amplitude high γ -band oscillations (for reviews see Crone et al., 2006; Engel et al., 2005). Measurements with ECoG are restricted to patients who undergo functional mapping and seizure localisation with subdural electrodes prior to surgical treatment for epilepsy. These studies have consistently reported γ -band oscillations at frequencies >60 Hz during a wide range of cognitive tasks (for a reviews see Crone et al., 2006; Jerbi et al., 2009) but also at lower γ -band frequencies (Axmacher et al., 2010; Howard et al., 2003).

One of the first studies to demonstrate high γ -band activity was reported by Crone et al. (1998). They recorded ECoG-signals from 5 patients during a visuo-motor task in which participants were required to make a sustained voluntary muscle contraction in response to a visual stimulus. Event-related γ -band synchronization occurred in a low (35–50 Hz) and in a higher γ -band range (75–100 Hz) which differed with respect to temporal and spatial characteristics. High γ -band oscillations were transient and increased during the motor response. In contrast, low γ -band activity began after the onset of the motor response and was characterised by a sustained response, suggesting independent functions and mechanisms.

High γ -band responses have also been consistently reported during visual and auditory processing. Edwards et al. (2005) recorded ECoG-signals from left frontal and temporal cortex during an auditory mismatch negativity paradigm (MMN). Deviant tones generated an N100-response that was localised in anterior auditory

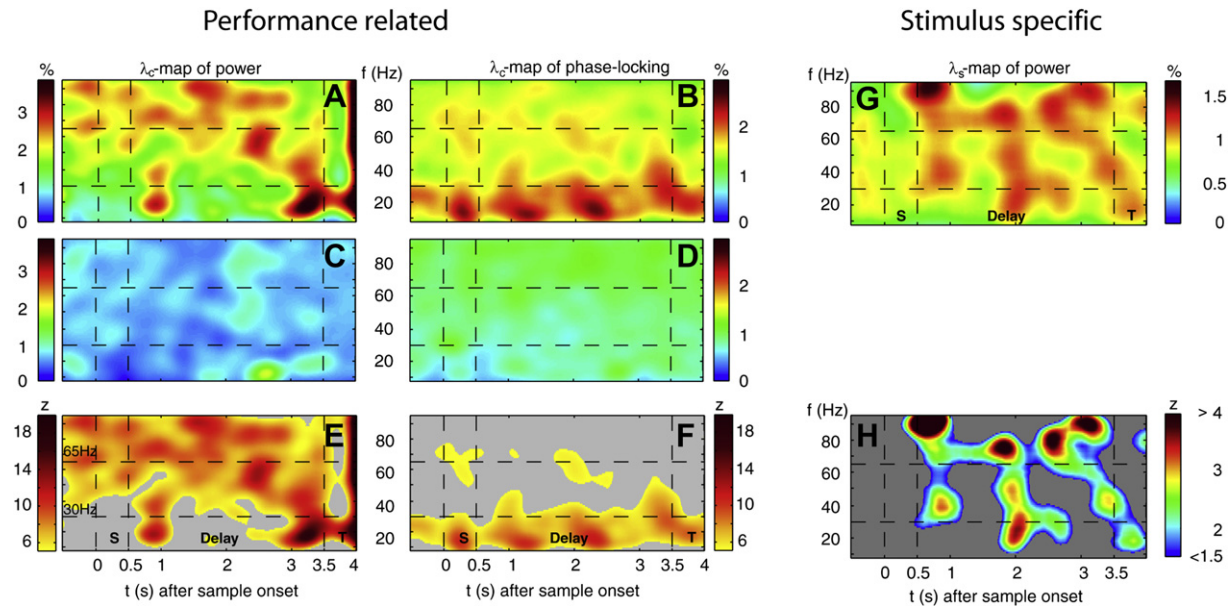


Fig. 2. γ -Band activity in prefrontal LFP during a working memory task. Performance-dependent and stimulus-specific oscillations and their phase-locking in prefrontal field potentials. (A, B) Time-frequency λ_c -maps for a visual memory task. After sample stimulus presentation for 0.5 s, the information of the sample has to be maintained for 3 s and compared to the test stimulus. A λ_c -map provides the percentage of sites/pairs with significant increases of power/phase-locking in trials with correct responses. Abscissa and ordinate represent peri-stimulus time aligned to the onset of sample stimuli and signal frequency, respectively. Color codes provide the percentage of sites/pairs with significant changes ('S', 'T': Sample and Test stimulus presentation, 'Delay': during delay the information of the sample has to be maintained). The left column provides maps for power and the middle column maps for phase-locking. (C, D) Shows the same as A and B but for scrambled (λ^{chance}) trials to destroy any existing performance effect. Hence, λ^{chance} -maps show the amount of modulation of λ_c for power in C and for phase-locking in D that can be expected purely by chance. (E, F) The same modulation of λ_c -maps as shown in A and B but expressed as a z-score in relation to the mean and standard deviation of purely random modulation of the λ^{chance} -maps shown in A and B ($Z_\lambda = (\lambda_c - \bar{\lambda}^{\text{chance}})/\sigma_{\lambda^{\text{chance}}}$). The critical z-score ($Z_{\text{crit}} = 4.19$) for a two sided modulation and a test level 1% has been Bonferroni corrected for 24 non-overlapping sliding windows during pre-sample, sample, delay, and test and 16 non-overlapping frequency bands between 7 and 95 Hz. Especially during the delay period, high gamma oscillations dominate the performance related modulation, while other frequencies are not affected by the behavioural performance. In G, the stimulus-selective responses are shown based on time-frequency λ_s -map. Color codes provide the percentage of sites with significant differences in power across different stimuli. (H) Modulations of the $\lambda_s(P)$ -map expressed as z-score in respect to baseline (-0.5 to 0 s). Stimulus-specific oscillations occur in the classical and high γ -band activity with frequencies up to 90 Hz (adapted from Pipa et al., 2009).

cortices, the superior temporal pole (STP) and the superior temporal gyrus (STG). In addition, time-frequency analyses of induced and evoked oscillations revealed both low and high γ -band activity. Similarly to the results of Crone et al. (1998), low and high γ -band activity was characterised by distinct localisations and temporal profiles. In a second study, high γ -band activity was also enhanced during selective attention in an auditory task (Ray et al., 2008a).

Lachaux et al. (2005) examined oscillatory activity in ECoG-data with Mooney faces in 4 epileptic patients. The pattern of γ -band activity revealed a different spectral profile than reported with scalp-recorded EEG-data (Rodriguez et al., 1999). ECoG-data showed an increase of γ -band oscillations between 50–150 Hz and a concurrent decrease in the lower γ -band. High γ -band activity was recorded in the fusiform gyrus, the lateral occipital gyrus and the intra-parietal sulcus. Occipitotemporal sites were the first to be activated, closely followed by the parietal sites, while portions of the primary visual cortex seemed to deactivate temporarily. Comparison between face vs. no-face responses revealed significantly stronger high γ -band activity (50–150 Hz) in the lateral occipital gyrus.

High γ -band activity has also been linked to higher cognitive functions, such as working memory and language processing. Mainy et al. (2008) analysed ECoG-data in mesiotemporal structures during the encoding of a series of 10 letters. High γ -band activity (50–150 Hz) was found in regions associated with the phonological loop, including Broca's area and auditory cortex, in the prefrontal cortex as well as in the fusiform gyrus and hippocampus. This activity increased with the number of items to be encoded.

Finally, low and high γ -band oscillations have also been observed in human cortex during sleep. Le Van Quyen et al. (2010) examined γ -band oscillations during polysomnographically defined sleep–wake states using large-scale microelectrode recordings in epilepsy patients. Two distinct γ -band frequencies, one in the lower (~ 40 Hz) and another in the higher (80–120 Hz) frequency range, were expressed during slow-wave sleep (SWS) and correlated with positive potentials in the EEG. In contrast to the conditions encountered during the awake state, low and high γ -band oscillations were characterised by a similar temporal profile.

3.3. High gamma-band oscillations in MEG-data

Support for the existence and functional relevance of high γ -band activity comes from a series of MEG-experiments that parallel the findings from ECoG-experiments.

In a recent study (Gruetzner et al., 2010; Fig. 3), we used Mooney faces stimuli and performed a time-frequency analysis to investigate the relationship between perceptual closure and high γ -band activity. Sensor-data revealed sustained high γ -band activity between 60–100 Hz associated with the processing of Mooney stimuli while low γ -band oscillations decreased. Closure-related γ -band activity was observed between 200 and 300 ms over occipitotemporal channels between 60–100 Hz. Time-resolved source reconstruction revealed an early (0–200 ms) coactivation of caudal inferior temporal gyrus (cITG) and regions in posterior parietal cortex (PPC) that was larger for perceived faces. At the time of perceptual closure (200–400 ms), this activation in the cITG extended to the fusiform gyrus. Our data are in agreement with the findings by Lachaux et al. (2005) with ECoG-data that show that the network underlying the perceptual closure of Mooney faces operates mainly in the high γ -band range.

High γ -band activity has also been observed during memory processes. Jokisch and Jensen (2007) recorded MEG-signals while participants performed a delayed-match-to-sample task. Participants were instructed to remember either the identity or the spatial

orientation of briefly presented faces. Maintenance of visual information in the orientation condition resulted in significantly enhanced high γ -band activity ~ 80 Hz over occipito-parietal sensors. A beamforming approach localised the high γ -band activity to sources in the occipital lobe. In a second study, Osipova et al. (2006) demonstrated that high γ -band activity in visual cortex during the encoding period of a declarative memory task is also predictive for the later retrieval of information.

Additional data from MEG-studies implicating high γ -band activity in auditory working memory has been reported by Kaiser et al. (2008). The authors examined stimulus-specific γ -band components during auditory spatial short-term memory. Participants were presented with right- or left-lateralized sounds that differed in their lateralization angles. γ -band patterns in different frequency ranges (59 Hz, 62 Hz, 68 Hz, 72 Hz) were found for each sample stimulus over parieto-occipital cortex during the middle 200–300 ms of the delay phase, suggesting a role of distinct γ -bands in the maintenance of auditory information. The same group also reported high γ -band activity during the perception of Kanizsa squares (Kaiser et al., 2004). Previous work by Tallon-Baudry et al. (1997a) failed to find evidence for induced γ -band activity during perceptual grouping in MEG-data. In contrast, Kaiser et al. (2004) observed that the perception of illusory triangles was correlated with an increase of γ -band activity ~ 70 Hz peaking at 240 ms over occipital sensors.

Recent evidence from MEG also suggests that synchronization in the high γ -band oscillations and their synchronization enhances the processing of attended stimuli and facilitates attentional selection. Siegel et al. (2008) examined oscillations in the 5–100 Hz frequency range in a spatially cued motion discrimination task. Participants were required to detect motion of a dynamic random dot pattern that was preceded by a small dot in either the left or right hemifield that led to a covert attentional shift. The onset of the dynamic dot patterns was followed by transient high gamma-band response (50–100 Hz) over posterior sensors while oscillatory activity below 50 Hz decreased. A beamforming source localisation revealed a differential attentional effect for different frequencies in several cortical regions along the dorsal visual pathway. Finally, attentional modulation caused an increase in the synchronization between source-related activity in the alpha, beta, low and high γ -frequency range.

Differential modulation of low and high gamma-band activity as reported in ECoG and other invasive electrophysiological studies has also been observed in several MEG-recordings. Hoogenboom et al. (2006) presented sine wave grating at fixation and participants had to indicate via a button press whether a change in the acceleration of the grating occurred. The visual stimulation triggered a consistent pattern of induced γ -band oscillations at two frequencies in the calcarine sulcus: 1) A lower frequency oscillation at 40 Hz and 2) an increase between 70–80 Hz that was maximal in the calcarine sulcus.

Further evidence for the role of low and high γ -band activity comes from studies that examined the relationship between specific cognitive processes and differential modulations of γ -band oscillation frequency. Vidal et al. (2006) examined the influence of visual grouping and attention-related information processing during a delayed-match-to-sample task. In the encoding phase, the display was either homogeneous (grouping condition) or items differed in color (attention condition). Thus, attention could be either focussed on a subset of items or distributed on the whole display. Grouping-related γ -band oscillations were present in all conditions but modulated by the grouping properties of the stimulus (one or two groups) in the high γ -band (70–120 Hz) at central occipital locations. Attention-related γ -band oscillations appeared as an additional component whenever attentional focusing was

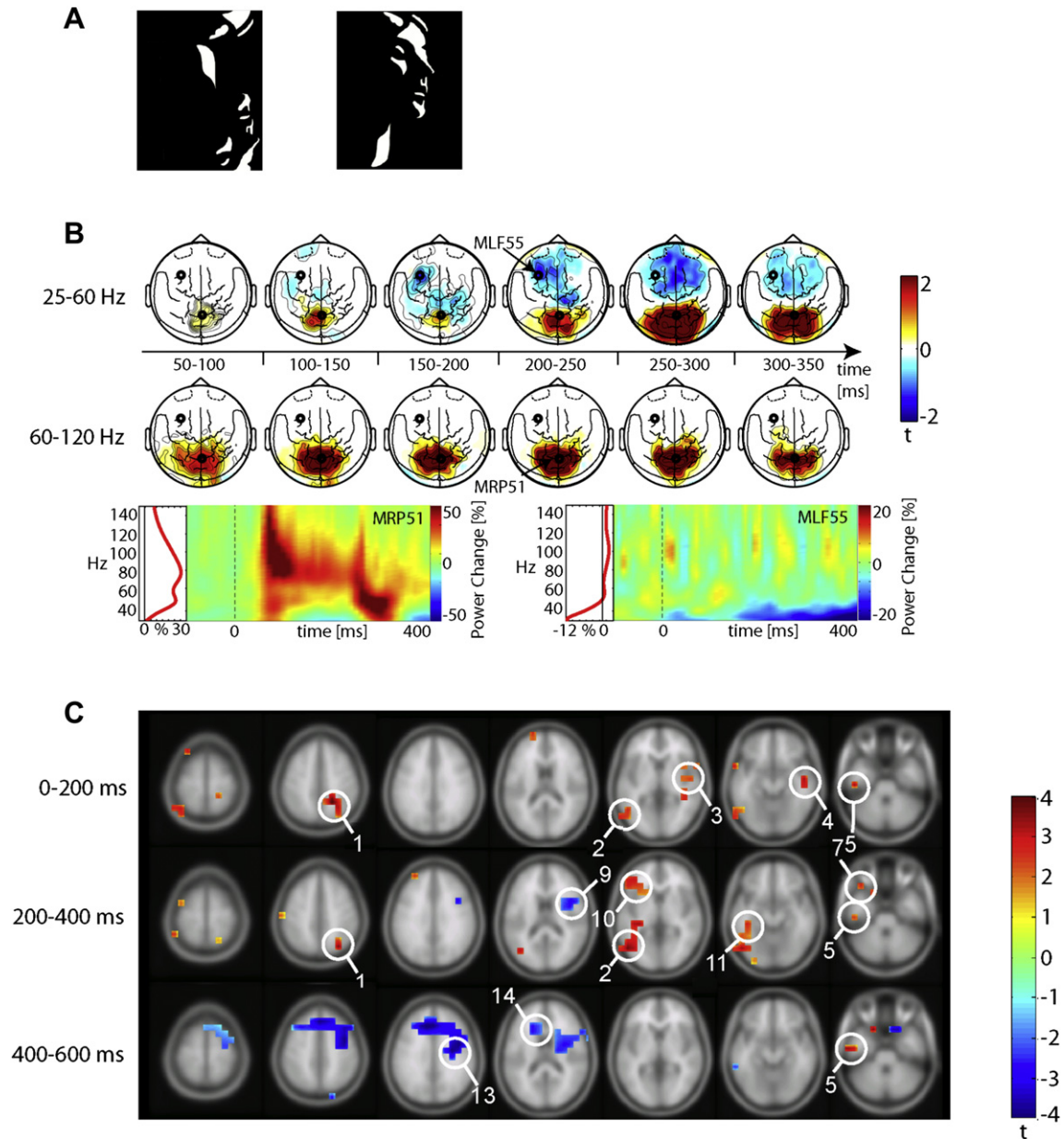


Fig. 3. High γ -band activity during perceptual closure in MEG-data. a) Examples of a inverted-scrambled (left) and upright Mooney face. b) Statistical analysis of power changes in response to upright Mooney faces. All data represent grand averages or statistical analysis across all subjects. The top part of the panel shows the temporal evolution of the topography of the statistical analysis; the bottom panel contains power spectra and time-frequency representations (TFRs) for specific sensors. c) Differences in source power at 80 Hz between the face and the non-face condition (t values masked by $p < 0.01$, corrected). Time intervals are plotted from top to bottom, and consecutive brain slices are plotted from left to right for each time interval (slice distance, 20 mm) in neurological convention. Each cluster is marked on one slice per time interval, with the circles representing the center of each cluster (1–14). Red clusters represent stronger source power for faces; blue clusters represent stronger source power for non-faces (t values masked by $p < 0.01$, not corrected). 1, Superior parietal lobe; 2, caudal inferior temporal gyrus (cITG); 3, superior temporal gyrus; 4, right anterior inferotemporal cortex (aIT); 5, left aIT; 6, angular/supramarginal gyrus; 7, orbitofrontal cortex; 8, middle frontal gyrus (MiFG); 9, right inferior frontal gyrus (IFG); 10, left IFG; 11, fusiform face area (FFA); 12, primary visual cortex; 13, premotor cortex; 14, cingulate gyrus (adapted from Gruetzner et al., 2010).

requested in the low γ -band (44–66 Hz) at parietal locations. These findings suggest that different visuo-perceptual processes (perceptual grouping vs. attentional focusing) correlate robustly with high and low γ -band activity respectively, suggesting a functional specialisation of the two frequencies in cortical processing.

Distinct correlations between the frequency of γ -band oscillations and cognitive processes were reported by the same group in a second study (Wyart and Tallon-Baudry, 2008). MEG-signals were recorded while participants attended toward or away from faint stimuli that were reported as consciously seen only half of the time.

The analysis of induced oscillations revealed distinct and independent neural correlates of visual awareness and spatial attention in the low and high γ -band. Thus, both attended and unattended consciously seen stimuli induced increased activity in the 50–110 Hz range over occipital sensors. Spatial attention on the other hand led to an enhanced high (76–90 Hz) γ -band activity over parieto-occipital regions to both consciously seen and unseen stimuli whereas the awareness related effect correlated with activity modulation in the low (54–64 Hz) γ -band range over occipital sensors.

3.4. High γ -band oscillations in psychiatric and neurological disorders

Abnormal high γ -band activity has been consistently associated with epilepsy in the EEG before and during epileptic events (for a review see Ramppp and Stefan, 2006; Bragin et al., 2010). Specifically, high-frequency oscillations above 100 Hz (ripples) have been proposed as a biomarker for epilepsy (Bragin et al., 2010).

Ripples are a feature of the rodent, cat and human brain that occur predominantly in the hippocampus and cortex and are short-lasting oscillatory phenomena that reach up to frequencies of 200 Hz. During normal brain functioning, ripples occur during sensory stimulation, SWS and memory consolidation (Buzsáki et al., 1992). In addition, there is also evidence that ripples above 200 Hz, so called fast ripples, reflect pathological hypersynchrony of neuronal clusters that can be recorded in patients with medial temporal lobe epilepsy as well as in rodent models (Bragin et al., 2010). Fast ripples can reach frequencies up to 600 Hz but a differentiation between pathological vs. normal ripple activity on the basis of frequency alone is not possible as oscillations in the 200–600 Hz frequency range have also been recorded in normal neocortex (e.g., Curio, 2000).

Recent evidence points also to a role of dysfunction in high γ -band oscillations in the pathophysiology of cognitive dysfunctions in schizophrenia. Haenschel et al. (2009) investigated the relationship between impairments in oscillatory activity in a broad frequency range (3–100 Hz) and working memory (WM) in a delayed-match-to-sample paradigm in 14 patients with early-onset schizophrenia and 14 matched control participants. During the early retention period, patients with schizophrenia showed a WM-dependent increase in induced alpha and γ -band activity that was comparable to controls. In contrast, during the later maintenance phase, patients showed a shift in the peak of induced γ -band activity to lower WM-load conditions over anterior electrodes. In addition, high γ -band activity was reduced in patients during the retrieval period.

We recently examined with MEG high γ -band activity in chronic as well as in unmedicated, first episode (FE) patients with schizophrenia (Tillmann et al., 2008). In chronic schizophrenia patients, impaired task performance during the perception of Mooney faces was accompanied by a widespread deficit in the power of γ -band oscillations between 60 and 120 Hz in a time window of 50–300 ms after stimulus onset. Analysis of source-related activity with a beamforming approach revealed pronounced reductions in γ -band activity in the right temporal lobe. In addition, analyses of MEG-responses from the FE-sample revealed that the reductions in high gamma-band activity were also present at the onset of the disorder, suggesting that these abnormalities in γ -band activity are not an artefact of medication.

4. Physiological correlates of low and high γ -band activity

Given the potential importance of high γ -band oscillations for cortical processes, the precise nature and generating mechanisms are crucial for the interpretation of physiological signals. Indeed, recent studies have questioned whether high γ -band activity is reflecting an oscillatory process and not simply spiking activity (Ray et al., 2008b).

In order to address these issues, we will now discuss mechanisms that can induce synchronised oscillations in the low and high γ -band. To distinguish between different mechanisms, we will also discuss the features of the oscillations and their power spectra. Specifically we are going to propose that the width of the spectra, i.e. narrow banded oscillations vs. broad banded oscillations, may be an important criterion to distinguish γ -band activity generated

by an oscillatory process from γ -band modulations caused by spiking activity.

4.1. Gamma oscillations induced by mutual inhibition, excitation, recurrent inhibition and gap-junction coupling

Mutual inhibition, mutual excitation and recurrent inhibition emerge from the interaction of elements in a network. It is important to note that emergent oscillations can be very different from the dynamical patterns of the isolated individual neurons. Experimental and theoretical studies highlighted the importance and stability of recurrent inhibition for all three mechanisms (Van Vreeswijk et al., 1994; Uhlhaas et al., 2009; Kopell and Ermentrout, 2004; Vicente et al., 2008).

Recurrent inhibition generates the oscillation and synchronizes the population by the delayed interplay of excitation and inhibition. Especially for the biologically relevant case of coupling by-delay and heterogeneous networks, recurrent inhibition between excitatory and inhibitory sub-networks was found to stabilize and induce zero phase synchronization reliably and quickly (Kopell et al., 2000; Van Vreeswijk et al., 1994; Vicente et al., 2008). In addition, synchronization via recurrent inhibition can synchronize neuronal activity without changing the overall firing rate of neurons (Tiesinga and Sejnowski, 2004; Buia and Tiesinga, 2006).

The frequency of oscillations emerging from recurrent inhibition can be determined by several parameters, including driving strength, synaptic strength, and synaptic decay time (White et al., 1998). For regimes in which parameters other than the synaptic decay dominate the network frequency, even small heterogeneity across the neurons and conduction delays can destabilize oscillatory firing pattern and synchronization in the network (White et al., 1998). This makes the synaptic dynamics, i.e. the synaptic decay, the most important parameter that determines oscillation frequency. Chow et al. found that oscillation frequency for a simple model is proportional to the synaptic decay time and depends much less on the drive to the cells. This fact gives rise to a major restriction in the maximum oscillation frequency that can be generated by recurrent inhibition. Given typical decay times of chemical synapses, the oscillation frequency generated by recurrent inhibition seems to be limited to frequencies up to 80 Hz.

Recent experimental studies showed that both low and high γ -band activity are paced by synaptic inhibition. Oke et al. (2010) examined kainate and carbachol induced oscillations in slices of rat visual cortex. Current source density analysis showed that high γ -band oscillations (peak frequency \sim 80 Hz) and low γ -band activity (peak frequency \sim 37 Hz) co-existed albeit with important differences in regards to localisation and pharmacological profile. High γ -band oscillations occurred in layer II while low γ -band activity was found predominantly in layer V. In addition, pharmacological manipulation showed that γ -band activity is depended on AMPA receptor-mediated excitation, GABA-A receptor-mediated inhibition and gap junctions, indicating that high γ -band oscillations are generated by rhythmic recurrent synaptic excitation and inhibition in layer III, similar to the γ -band oscillation in the entorhinal cortex (Cunningham et al., 2003) and somatosensory cortex (Buhl et al., 1998).

Van der Meer and Redish (2009) examined LFP-data in the ventral striatum of rats during a spatial decision task and showed a systematic relationship between low and high γ -band oscillations and fast-spiking interneurons (FSI). The authors reported prominent low γ -band activity (45–55 Hz) as well as high γ -band oscillations (70–85 Hz) that were characterised by distinct relationships to behavior, task events, and spiking activity. Specifically, both γ -band frequencies showed different phase, firing rate, and coherence relationships with FSI.

Current models and electrophysiological evidence suggests that oscillations >80 Hz are gap-junction mediated (Whittington et al., 2000). Gap-junction coupling is nearly instantaneous and therefore makes the decay time of the synaptic currents become less important for the stability of the synchronization among the neurons of a homogenous, i.e. either purely excitatory or inhibitory, population or subpopulation (Bartos et al., 2007). Gap junctions act as a diffusive coupling mechanism and therefore homogenize the membrane fluctuation of the neurons in the network (Kopell et al., 2000). This in turn stabilizes high-frequency oscillatory synchrony arising by recurrent excitation and mutual inhibition and therefore allows for stable frequencies up to 200 Hz (Buzsaki and Draguhn, 2004). The importance of gap-junction mediated oscillatory synchrony was highlighted in experimental studies that demonstrated that fast oscillations with up to 200 Hz can be observed even if chemical synaptic transmission is blocked (Buzsaki and Draguhn, 2004).

4.2. Network gamma oscillations induced by clustering

Another mechanism that can induce high γ -band activity, even in networks without gap-junction coupling, is based on an effect that is called clustering (Friedrich and Kinzel, 2009; Jin et al., 2009; Kitajima and Kurths, 2009) or phase coding (O'Keefe and Recce, 1993; Buzsaki, 2002). Clustering describes the effect when different subpopulations of a larger network fire with the same frequency but have systematic phase relation between them (Fig. 4a1 and a2). A simple example of clustering is a larger network separated into two clusters. All clusters fire with the same frequency f but are shifted in phase, i.e. shift by $2\pi/3$ leading. In principle, a more complicated phase relations between more than two populations can occur, i.e. N clusters with each a phase offset of

$2\pi/N$ (Fig. 4a1 and b1). In general, clustering leads to additional frequency components at the frequencies $2f, 3f, \dots, Nf$. Whether all frequencies ($2f, 3f, \dots, Nf$) are induced depends on the exact phase relations but is independent of the dominant frequency f of each individual oscillation (Fig. 4a2, a3, b2 and b3).

To distinguish phase coding from other mechanisms that induce additional frequency peaks in the spectra at the harmonics of the carrier frequency, one can study the spiking activities of individual neurons in relation to the dominant carrier oscillation with frequency f . In case of clustered networks spikes of individual neurons in the network should occur preferentially at certain phases of the oscillation. Using this strategy clustering was confirmed experimentally for example in the hippocampus of rats (O'Keefe and Recce, 1993; Buzsaki, 2002) and in the prefrontal cortex of monkeys (Siegel et al., 2009). In both cases the relative phase of an individual cluster, i.e. sub network, was associated with behaviourally relevant information.

4.3. Entrainment and non-linear mixing of high γ -band activity

Both entrainment and non-linear mixing can induce high γ -band activity but the mechanisms are very different from mechanisms such as recurrent inhibition. While recurrent inhibition leads to oscillatory synchrony that emerges by the interplay of different elements of the network, both entrainment and non-linear mixing are fully determined by the properties of individual elements of the network and not by their mutual interaction.

The basic idea of entrainment is that an oscillation from a rhythm generator is transferred to larger populations via synchronization. Maybe the simplest mechanism of such synchronization is entrainment via common drive from a single source (Huang and Pipa, 2007), i.e. from other cortical and sub-cortical areas (Steriade

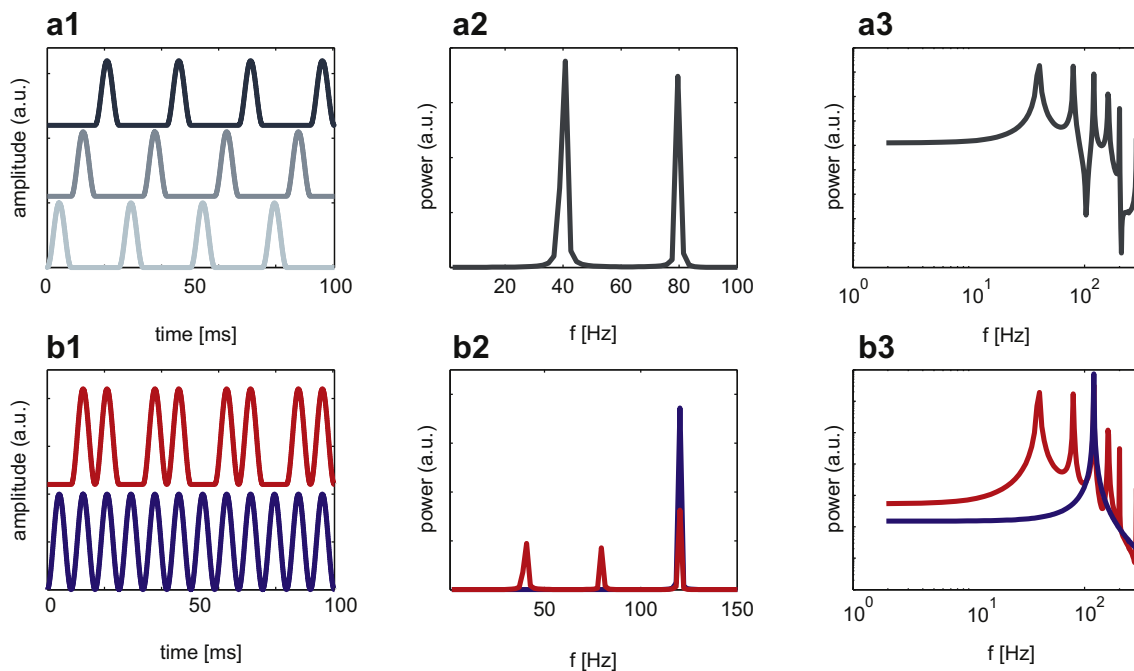


Fig. 4. Phase coding and clustering. The principle of phase coding and clustering is that different sub-processes are phase-locked to a common carrier frequency. The carrier frequency is 40 Hz. The principle is demonstrated for three different sub-processes in a1. Each of the sub-processes is oscillatory with a frequency of 40 Hz. The relative phase alignment to the carrier wave is different for each of the sub-processes. b1 demonstrates the superposition of subsets of the processes from a1. The red process is composed of the first and second processes from figure a1. The blue process in b1 is composed of all three processes from a1. Since each spindle in a1 was modeled by a sinusoidal the resulting blue process is a purely sinusoidal wave with a frequency of 120 Hz. a2, a3 show the power spectra of the processes shown in a1. The power spectrum is identical for all three processes. b2 and b3 show the power spectra of the compound processes shown in b1. The red compound process has a 40 Hz component and corresponding harmonics. The strongest power occurs at 120 Hz. The purely sinusoidal blue curve has a single power component at 120 Hz.

et al., 1993), that synchronizes the respective target cells. In local networks, pacemaker cells with intrinsic oscillatory activity can entrain the network activity in a certain frequency range, e.g., chattering cells or fast-rhythmic bursting cells that have been discussed to be involved in generating stimulus driven gamma oscillations (Gray and McCormick, 1996; Steriade et al., 1998). It is important to note that entrainment determines both the rhythm and the synchronization among the target population. The oscillation frequency of such an entrained network is determined by the frequency of the generator and the properties of the network elements that are entrained. If the firing frequency of individual neurons is high, the rhythmic activity of such entrained oscillation can reach γ -band frequencies.

Another mechanism that leads to narrow band high-frequency oscillations is non-linear mixing of at least two oscillations (Priestley, 1983). When two signals with frequency f_1 and f_2 are mixed linearly, it is well known that the resulting signal is just the linear superposition, and that the power spectrum of the composed signal is the sum of the two individual spectral profiles. However, when signals are mixed non-linearly the resulting spectral profile can be different and contain other frequencies than the frequencies of the mixed signals themselves (Priestley, 1983). Experimental evidence for non-linear mixing was found across different species, modalities, and types of neuronal activity (Kleinfeld and Mehta, 2006).

4.4. Broad band high γ -band activity induced by synaptic currents

γ -band spectra >60 Hz can also be the result of the superposition of non-oscillatory activity. Thus, it had been hypothesized that broad band high γ -band could reflect multi unit activity of non-synchronised local neuronal population (e.g., Ray et al., 2008b; Miller et al., 2009).

The assumption is that the measured signal results from the superposition of a very large number of synaptic currents in a local population (Fig. 5c1). The spectral profile of each of the synaptic currents is determined by the spectral profile (Fig. 5b2 and b3) of the incoming spike trains (Fig. 5b1), and in addition by the temporal characteristics of each synapse (Fig. 5a1). In a simple linear model the temporal activation of the synapse can be modeled as a filter (Fig. 5a2 and a3) acting on the spectrum of the point process. Since spike trains are very transient signals, their spectral profile usually contains high-frequency and broad band components (Fig. 5b2 and b3).

These findings can be generalized also for other types of point processes, i.e. renewal processes that describe the incoming spiking activity. Renewal processes are for example spike trains that are defined by just the inter spike interval distribution. The typical differences between the power spectrum of an arbitrary renewal process and a Poisson process (Fig. 5b2 and b3) are restricted to frequency components lower than the spiking frequency (Pipa et al., submitted for publication; Lindner, 2006). In contrast, high-frequency spectral components of the spike trains are mainly determined by the spike wave form and are therefore rather independent of the temporal structure of the firing (Fig. 5b2 and b3).

This allows us to easily generalize the findings by Miller et al. (2009). Deviation from Poisson statistics basically introduces a low frequency structure in the spectral profile of the spike train (Fig. 5c2 and c3). For γ -band processes, for example, the spectral profile of the spike train and the synaptic currents have a dominant frequency equal to the expected spike rate (Pipa et al., submitted for publication; Lindner, 2006). With other words, if the spiking activity is not Poissonian but slightly structured such as in the example of regular γ -processes, the peak frequency in the power spectrum scales linearly with the firing frequency. For frequencies

higher than the firing frequency the relevant $1/f^2$ scaling is expected to be rather independent of the exact temporal structure of the spike train. These arguments support the idea that broad band high γ -band spectral profiles can be used to estimate the spike rate of an underlying population.

Finally, broad-band γ frequency components (Fig. 5f2 and f3) can also result from short lasting (Fig. 5f1, red) and jagged oscillation spindles (Fig. 5f1, blue). Short lasting jagged oscillation spindles are patterns that are periodic or quasi periodic and last for an interval of just a few oscillation cycles. Any spectral analysis tool will transform such a jagged short lasting spindle into broad-band spectra with peaks at harmonic frequencies (Fig. 5f2 and f3).

5. High γ -band oscillations in cortical networks

While earlier studies with invasive and non-invasive electrophysiological methods have concentrated on γ -band oscillations between 30 and 60 Hz, the current data highlight the relevance of high γ -band activity for cortical computations. Data from LFP-, EEG- and MEG-recordings show that γ -band oscillations occur frequently up to 100 Hz and in some cases even up to 200 Hz and above and are closely related to a range of cognitive and perceptual functions. In addition, preliminary evidence suggests that abnormalities in high γ -band activity may also be involved in psychiatric and neurological disorders, such as schizophrenia and epilepsy. In the following section, we will discuss some of the implications of these findings for the understanding of γ -band oscillations as well as provide some considerations in regards to the measurement and analysis of high γ -band activity (Fig. 6).

5.1. Diversity of high γ -band oscillations

Our review indicates that high γ -band oscillations are diverse in regards to the generating mechanisms and functions. Thus, oscillatory activity >60 Hz comprises the fast oscillatory patterning of responses in the retina that propagates through visual pathways (Ω -oscillations) (Munk and Neuenschwander, 2000), induced rhythmic activity during cognitive and perceptual tasks between 60 and 200 Hz (i.e. Colgin et al., 2009; Gruetzner et al., 2010; Ray et al., 2008a) as well as ripples that can reach in certain cases frequencies up to 600 Hz (Bragin et al., 2010). Clearly, these examples of high γ -band oscillations are distinct, suggesting that frequency alone is not sufficient to allow for a differentiation between different oscillatory phenomena. Instead, these data call for a close integration between invasive electrophysiology and non-invasive EEG- and MEG-approaches that allow the characterization of high γ -band activity and their respective generating mechanisms.

5.2. Low vs. high γ -band activity: a valid distinction?

Although γ -band oscillations >60 Hz can be reliably measured with several techniques, questions remain regarding the validity of this distinction. In several studies (e.g., Axmacher et al., 2010; Pesaran et al., 2002; Uhlhaas et al., 2006), γ -band oscillations do not follow strictly the separation into a low and high γ -band rhythm and involve frequency modulation in both bands.

In addition, shifts in the frequency of γ -band oscillations have been observed as a result of changes in stimulus characteristics. In the visual cortex, it is well documented that oscillation frequency depends on stimulus parameters, such as speed (Gray et al., 1990; Gray and Viana Di Prisco, 1997; Friedman-Hill et al., 2000; Lima et al., 2010) and spatial frequency (Hadjipapas et al., 2007). γ -band oscillations may also exhibit considerable shifts in frequency in response to complex stimuli, such as moving plaids,

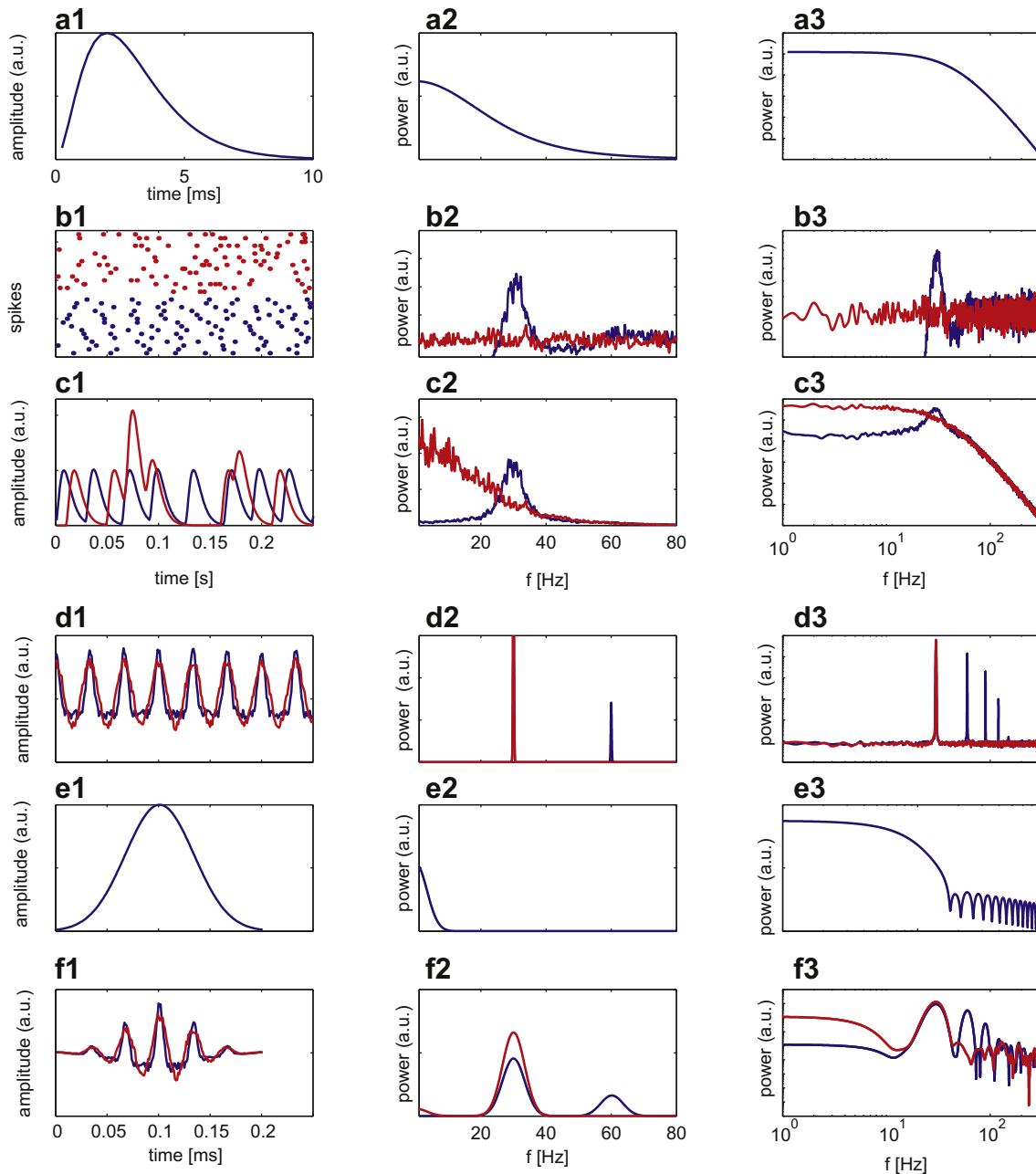


Fig. 5. Mechanisms of high γ -band activity. Illustration of two mechanisms that can generate high γ -band activity. The first half of the figure (rows a–c) demonstrates how spiking activity, that is completely uncorrelated, can induce high γ -band activity. a1 shows the temporal activation of synaptic currents. It is modeled by an alpha function with a polynomial rise and an exponential decay. b1 shows two types of spike trains with at a rate of 30 Hz. Red spikes are generated by a Poisson process, blue spikes by a gamma process with a shape factor of 15. c1 shows the synaptic currents, derived by a convolution of the kernel from a1 with the spikes train in b1. a2, b2, and c2 show the power spectrum of the respective signals shown in a1, a2, and a3. The peak frequency of the γ spike train is directly determined by the firing frequency of the process (here 30 Hz). For fast firing neurons also much higher frequencies are possible. The decay of spectral power for large frequencies is mainly determined by the filter response in a2. a3, b3, and c3 show the same as a2, b2, and c2 but with logarithmic scales for both the x and y axis. The second half of the figure (rows d–f) shows high γ -band activity based on short lasting oscillation spindles. a1 shows two oscillatory signals with a frequency of 30 Hz and with a small noise component (white noise, SNR 10). The first signal (red) is a pure sinusoidal signal. The second signal is non-sinusoidal ($2(\sin(2\pi ft)^{10} - 0.5)$) and therefore induces harmonics in the spectrum (see d2 and d3). e1 shows a windowing function, here Gaussian. f1 shows the signals from d1 windowed with the function in e1. d2–f2 and d3–f3 show the corresponding power spectra for the signal and window function.

probably because they induce fundamentally different patterns of activation in the cortex (Lima et al., 2010).

However, there is also consistent evidence that distinctions between low and high γ -band oscillations may be heuristically useful because they reflect distinct physiological processes. This view is supported by the following evidence: 1) several studies (e.g., Colgin et al., 2009; Crone et al., 1998; Hoogenboom et al., 2006) have clearly demonstrated both low and high γ -band oscillations that

undergo distinct and non-overlapping frequency modulations. 2) Low and high γ -band oscillations can be correlated with different cognitive processes (Vidal et al., 2006; Wyart and Tallon-Baudry, 2008). 3) Both low and high γ -band oscillations can be generated by recurrent inhibition but differ in their relationship to spiking activity of PV-interneurons, their pharmacological modulation profiles as well as their layer specificity (Oke et al., 2010; van der Meer and Redish, 2009).

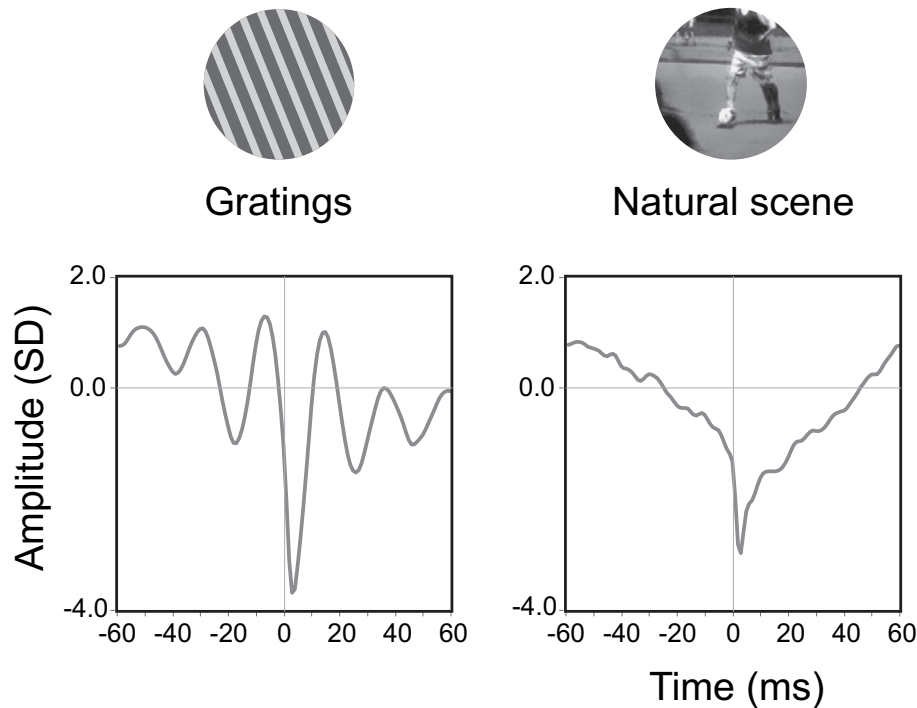


Fig. 6. Spiking activity and high γ -band oscillations in LFP-data. Normalized spike-triggered averages of the LFP for responses to gratings and natural scenes. Recordings were obtained from the same electrode in the primary visual cortex of a macaque monkey. In response to gratings (left), the LFP showed strong γ -band oscillations (47 Hz) precisely locked to the spiking responses. These oscillatory patterns were absent in the responses to natural scenes (right). Notice, however, that despite the absence of oscillations a precise phase relationship between the spiking events and fast negative fluctuations in the LFP (jagged oscillations) persisted. Controls showed that these features in the LFP were not due to filtering leakage artifacts of spikes into the LFP. Plots express units of standard deviation (SD) of the LFP voltage.

5.3. Low vs. high γ -band activity: selective routing of information

The close association between the modulation of both low and high γ -band activity and cognitive processes suggests that different γ -band frequencies are recruited for the dynamic formation of distinct assemblies that underlie a specific behavioural or cognitive function. Separation of frequency bands could enhance the selectivity of information exchange between population of neurons. It would allow for precise synchrony within assemblies and segregation of different assemblies (Fries, 2005). Accordingly, both low and high γ -band activity could provide a framework for multiplexing that facilitates parallel processing in cortical networks at multiple temporal scales (Roopun et al., 2008b; Wyart and Tallon-Baudry, 2008).

Support for this hypothesis was reported by Colgin et al. (2009). They showed that through differential modulation of low and high γ -band activity, selective routing of information between the entorhinal cortex and hippocampus was established. Thus, high- γ -band oscillations synchronised with high- γ -band in CA1, whereas oscillations in the 25–50 Hz frequency range were coherent between CA1 and CA3.

Selective routing of information has also been correlated with attentional processes. In a series of studies in monkey area V4, Fries and collaborators (Fries, 2009; Fries et al., 2001b, 2008) have put forward an appealing hypothesis in which selective attention is achieved through routing of information within neuronal populations oscillating coherently at the same γ -band frequency (Fries et al., 2001b, Womelsdorf et al., 2007; Fries, 2009).

Interestingly, it has been recently shown that the frontal eye field (FEF) initiates synchronization of γ -band responses in a spatial attention task in area V4 at a narrow frequency band (from 40 to 60 Hz), even though cells in the FEF oscillated within a much broader frequency band up to 150 Hz (Gregoriou et al., 2009).

Although not shown in this study, it is conceivable that high γ -band oscillations in the FEF activity serve selective communication with areas other than V4 while they are at the same time phase-locked with V4 at lower frequencies. In this case, coordination of activity relevant for an attentional task would involve multiplexing of functional sub-networks operating in distinct γ -bands, as it has been shown in the hippocampus (Tort et al., 2010, 2008).

5.4. Individual differences and high and low γ -band oscillations

Further evidence for the possible relevance of distinct γ -band oscillations comes from studies which have examined individual differences.

Hoogenboom et al. (2006) examined the variability of high and low γ -band activity in MEG-data. Comparison between participants revealed that some individuals exhibited clearly separated spectral bands (\sim 40 Hz and between 70 and 80 Hz) whereas others did not. In addition, the distribution of low and high γ -band activity remained highly stable after a second measurement, suggesting that the two γ -band frequencies may reflect a trait marker of cortical processing. Data reported by Edden et al. (2009) suggests that differences in the frequency of γ -band oscillations may reflect differences in GABA-neurotransmission.

Results from a recent study by Lima et al. (2010) support the variability of γ -band oscillations. Comparisons of LFP responses in the visual cortex of monkeys revealed surprisingly high interindividual variability in γ -bands frequency. In response to the same stimulus (moving gratings at the preferred direction with comparable size, spatial frequency and speed), oscillation frequency could vary two-fold across the individuals (from 30 to 65 Hz). Interestingly, when comparisons were made for the two hemispheres of the same monkey, the frequency distributions were very similar. As shown in Fig. 7, these results indicate that different individuals

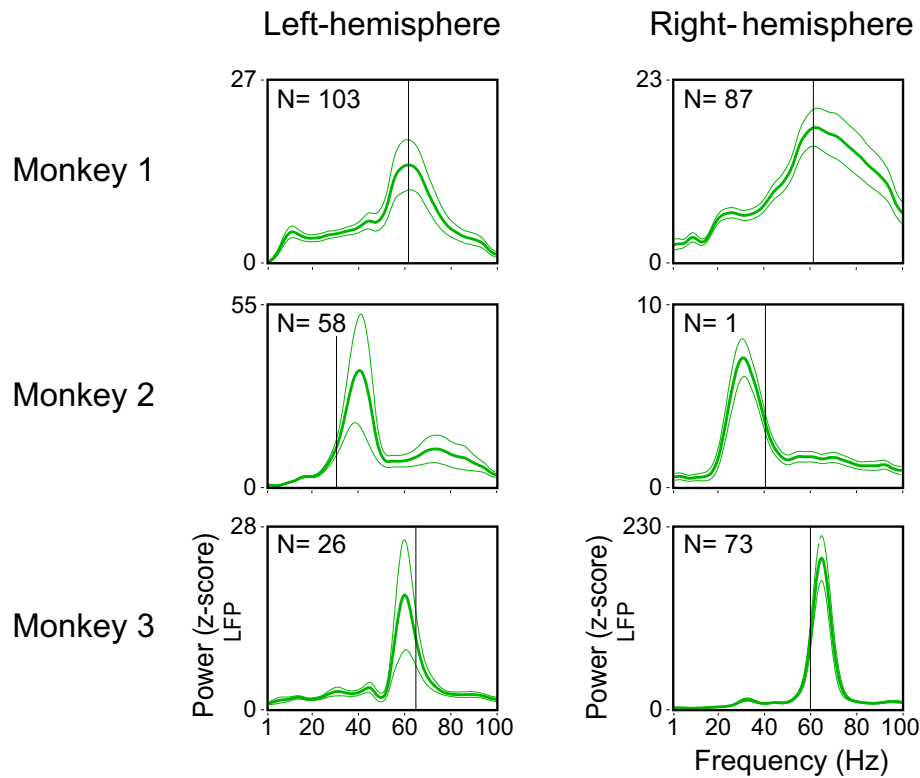


Fig. 7. Spectral signatures of low and high γ -band oscillations. Comparisons across monkeys for LFP responses to moving gratings in V1. Although the stimuli used in all tests were physically similar, each individual has a characteristic spectral signature. Notice that the spectral profiles are similar across the two hemispheres of the same individual. Each curve is the average of N recordings sites. The thinner traces enclose the 95% confidence interval of the mean. Vertical guide lines were positioned to help localize the induced γ -band frequency for the corresponding stimulus in the opposite hemisphere (modified from Lima et al., 2010).

differ significantly with respect to the dominant γ -band frequencies. Thus, there appear to exist a spectral signature reflecting the differences in the functional architecture of the cortex.

5.5. High γ -band activity and low frequency oscillations

Neural oscillations occur over a wide range of frequencies and recent evidence suggests that different frequency bands are linked through cross-frequency interactions (Jensen and Colgin, 2007; Palva and Palva, 2005).

Canolty et al. (2006) demonstrated a similar relationship for the modulation of high γ -band activity through the phase of θ -band oscillations. The authors analysed EcoG-signals in frontal and temporal cortices from five patients undergoing neurosurgical treatment for epilepsy. The authors observed a strong increase of oscillatory activity between 20 and 200 Hz, during an auditory working memory task. In addition, the amplitude of γ -band oscillations between 80 and 150 Hz was significantly correlated with the phase of the θ -rhythm, suggesting that coupling between these two frequencies supports higher cognitive functions.

Similarly, Colgin et al. (2009) showed that high γ -band activity was phase-locked to the hippocampal θ -rhythm. Interestingly, low and high γ -band activity occurred at different phases of the CA1 θ rhythm. Oscillations in the 60–140 Hz band were associated with the trough of the θ -cycle whereas low γ -band activity was maximal near the peak.

These data on the relationship between high γ -band activity and the phase of the θ -cycle are consistent with a large body of evidence that has linked low γ -band activity with θ oscillations. Several authors (e.g., Lisman and Buzsáki, 2008) have proposed that the combination of γ - with θ -oscillations provides a neural mechanism

for the recall of items from long-term memory as well as for the maintenance of information in working memory. The findings by Colgin et al. (2009) and Canolty et al. (2006) suggest that this mechanism utilizes frequencies in the high γ -band range as well.

5.6. High γ -band activity: relationship to BOLD signals and EEG-data

High γ -band oscillations may also be related to other indexes of neural activity, such as the BOLD signal. Evidence for a close relationship between high γ -band oscillations and changes in the hemodynamic signal was reported by Niessing et al. (2005). The authors examined simultaneously recorded electrical (LFP) signals and hemodynamic responses with optical imaging in the cat visual cortex. Correlations between the amplitude of LFPs across a wide frequency range and changes in the hemodynamic response to different visual stimulation conditions showed a consistent relationship between the modulation of high γ -band oscillations and hemodynamic responses. Increases in the hemodynamic response were significantly correlated with high γ -band activity but not with low γ -band oscillations or activity in the θ -, α -, and β -band. In addition, the hemodynamic response was only loosely coupled to action potential frequency suggesting that BOLD signals may reflect high γ -band oscillations and the underlying physiological mechanisms.

While there is a good convergence between data from recent MEG- and ECoG-studies on the relationship between high γ -band oscillations and cognitive processes, oscillations >60 Hz have been rarely observed in the scalp-recorded EEG-data. Reasons for the differences between the two recording techniques could be the higher sensitivity of MEG to tangential as opposed to radial sources. In addition, it has been argued that the skull acts as a low-pass filter

(Pfurtscheller and Cooper, 1975), leading to diminished signal strength at higher frequencies in the EEG, whereas MEG-signals are not influenced by different tissue conductances.

However, preliminary evidence suggests that high γ -band oscillations can also be recorded in the EEG. In a recent study, we (Best et al., submitted for publication) employed a contour integration paradigm (Field et al., 1993) that allows precise control over grouping parameters. Subjects were presented with contours among noise elements for 200 ms. Task difficulty was varied in three conditions by modifying the density ratio of signal to noise elements and by changing the degree to which the signal elements were adapted to the ideal contour. EEG signals showed that grouping-related γ -band oscillations occurred mainly in the 60–120 Hz frequency range that correlated systematically with stimulus properties. These data suggest that high γ -band activity can be measured in scalp-recorded EEG signals. However, further studies are necessary that investigate the limits of measuring high γ -band activity in EEG-data.

6. Summary

The current evidence suggests that γ -band oscillations >60 Hz represent a robust phenomenon in electrophysiological recordings that may be crucial for the understanding of neural oscillations and synchrony in cortical networks. Our review suggests systematic correlations between modulation of high γ -band activity and a wide range of cognitive and perceptual processes that parallel findings obtained for low γ -band oscillations. In addition, preliminary evidence suggests that high γ -band oscillations may also be relevant for the understanding of psychiatric and neurological conditions, such as schizophrenia and epilepsy. Finally, correlations with other indices of neurophysiological activity, such as BOLD, highlight the potential importance of high γ -band activity as a fundamental aspect of brain functioning.

Yet, several issues remain to be addressed in future research that will be crucial for the progress in this field. Our review suggests that the mechanisms generating oscillations >60 Hz remain unclear and that oscillations between 60 and 200 Hz can be generated by diverse synaptic and non-synaptic processes. Specifically, the questions to what extent broad band modulations of γ -band activity, for example, reflect spiking activity is of central importance for the interpretation of neurophysiological signals in LFP and ECoG-data. Accordingly, further research will be required that spans multiple levels, including in-vitro models and computational work, that allows the integration of macroscopic signals with cellular and synaptic physiology.

In conclusion, high γ -band activity may become a fundamental aspect of temporal coding in cortical networks through supporting precise spiking activity in local cortical circuits. Given the involvement of high γ -band oscillations in a wide range of cognitive processes and basic physiological mechanisms, it may hold crucial insights for the understanding of normal and abnormal brain functioning.

Funding/support

This work was supported by the Max Planck Society. Partly supported (GP) by the Frankfurt Institute of Advanced Studies, the Hertie Foundation and project PHOCUS. The project PHOCUS acknowledges the financial support of the Future and Emerging Technologies (FET) programme within the Seventh Framework Programme for Research of the European Commission, under FET-Open grant number: 240763.

References

Adrian, E.D., 1950. The electrical activity of the mammalian olfactory bulb. *Electroencephalogr. Clin. Neurophysiol.* 2, 377–388.

- Alonso, J.M., Usrey, W.M., Reid, R.C., 1996. Precisely correlated firing in cells of the lateral geniculate nucleus. *Nature* 383, 815–819.
- Axmacher, N., Henseler, M.M., Jensen, O., Weinreich, I., Elger, C.E., Fell, J., 2010. Cross-frequency coupling supports multi-item working memory in the hippocampus. *Proc. Natl. Acad. Sci. U. S. A.* 107, 3228–3233.
- Bartos, M., Vida, I., Jonas, P., 2007. Synaptic mechanisms of synchronized gamma oscillations in inhibitory interneuron networks. *Nat. Rev. Neurosci.* 8, 45–56.
- Best, M., Rodriguez, E., Lovell, P.G., Singer, W., Uhlhaas, P.J. Neural synchrony as the electrophysiological correlate of contour integration in the human EEG, submitted for publication.
- Bragin, A., Engel Jr., J., Staba, R.J., 2010. High-frequency oscillations in epileptic brain. *Curr. Opin. Neurol.* 23, 151–156.
- Bragin, A., Jandó, G., Nádasdy, Z., Hetke, J., Wise, K., Buzsáki, G., 1995. Gamma (40–100 Hz) oscillation in the hippocampus of the behaving rat. *J. Neurosci.* 15, 47–60.
- Bressler, S.L., Freeman, W.J., 1980. Frequency analysis of olfactory system EEG in cat, rabbit, and rat. *Electroencephalogr. Clin. Neurophysiol.* 50, 19–24.
- Buhl, E.H., Tamás, G., Fisahn, A., 1998. Cholinergic activation and tonic excitation induce persistent gamma oscillations in mouse somatosensory cortex in vitro. *J. Physiol. (Lond.)* 513, 117–126.
- Buia, C., Tiesinga, P., 2006. Attentional modulation of firing rate and synchrony in a model cortical network. *J. Comput. Neurosci.* 20, 247–264.
- Buzsáki, G., 2002. Theta oscillations in the hippocampus. *Neuron* 33, 325–340.
- Buzsáki, G., 2006. *Rhythms of the Brain*. Oxford University Press, New York.
- Buzsáki, G., Draguhn, A., 2004. Neuronal oscillations in cortical networks. *Science* 304, 1926–1929.
- Buzsáki, G., Horváth, Z., Urioste, R., Hetke, J., Wise, K., 1992. High-frequency network oscillation in the hippocampus. *Science* 256, 1025–1027.
- Canolty, R.T., Edwards, E., Dalal, S.S., Soltani, M., Nagarajan, S.S., Kirsch, H.E., Berger, M.S., Barbaro, N.M., Knight, R.T., 2006. High gamma power is phase-locked to theta oscillations in human neocortex. *Science* 313, 1626–1628.
- Castelo-Branco, M., Neuenchwander, S., Singer, W., 1998. Synchronization of visual responses between the cortex, lateral geniculate nucleus, and retina in the anesthetized cat. *J. Neurosci.* 18, 6395–6410.
- Colgin, L.L., Denninger, T., Fyhn, M., Hafting, T., Bonnevie, T., Jensen, O., Moser, M.-B., Moser, E.I., 2009. Frequency of gamma oscillations routes flow of information in the hippocampus. *Nature* 462, 353–357.
- Crone, N.E., Sinai, A., Korzeniewska, A., 2006. High-frequency gamma oscillations and human brain mapping with electrocorticography. *Prog. Brain Res.* 159, 275–295.
- Csicsvari, J., Jamieson, B., Wise, K.D., Buzsáki, G., 2003. Mechanisms of gamma oscillations in the hippocampus of the behaving rat. *Neuron* 37, 311–322.
- Crone, N.E., Miglioretti, D.L., Gordon, B., Lesser, R.P., 1998. Functional mapping of human sensorimotor cortex with electrocorticographic spectral analysis. II. Event-related synchronization in the gamma band. *Brain* 121, 2301–2315.
- Cunningham, M.O., Davies, C.H., Buhl, E.H., Kopell, N., Whittington, M.A., 2003. Gamma oscillations induced by kainate receptor activation in the entorhinal cortex in vitro. *J. Neurosci.* 23, 9761–9769.
- Curio, G., 2000. Linking 600-Hz “spikelike” EEG/MEG wavelets (“sigma-bursts”) to cellular substrates: concepts and caveats. *J. Clin. Neurophysiol.* 17, 377–396.
- Edden, R.A., Muthukumaraswamy, S.D., Freeman, T.C., Singh, K.D., 2009. Orientation discrimination performance is predicted by GABA concentration and gamma oscillation frequency in human primary visual cortex. *J. Neurosci.* 29, 15721–15726.
- Edwards, E., Soltani, M., Deouell, L.Y., Berger, M.S., Knight, R.T., 2005. High gamma activity in response to deviant auditory stimuli recorded directly from human cortex. *J. Neurophysiol.* 94, 4269–4280.
- Engel, A.K., Konig, P., Kreiter, A.K., Singer, W., 1991. Interhemispheric synchronization of oscillatory neuronal responses in cat visual cortex. *Science* 252, 1177–1179.
- Engel, A.K., Moll, C.K., Fried, I., Ojemann, G.A., 2005. Invasive recordings from the human brain: clinical insights and beyond. *Nat. Rev. Neurosci.* 6, 35–47.
- Field, D.J., Hayes, A., Hess, R.F., 1993. Contour integration by the human visual system: evidence for a local ‘association field’. *Vis. Res.* 33, 173–193.
- Fox, M.D., Raichle, M.E., 2007. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat. Rev. Neurosci.* 8, 700–711.
- Freeman, W.J., 1991. The physiology of perception. *Sci. Am.* 264, 78–85.
- Freeman, W.J., Skarda, C.A., 1985. Spatial EEG patterns, non-linear dynamics and perception: the neo-Sherringtonian view. *Brain Res.* 357, 147–175.
- Friedrich, J., Kinzel, W., 2009. Dynamics of recurrent neural networks with delayed unreliable synapses: metastable clustering. *J. Comput. Neurosci.* 27, 65–80.
- Friedman-Hill, S., Maldonado, P.E., Gray, C.M., 2000. Dynamics of striate cortical activity in the alert macaque: I. Incidence and stimulus-dependence of gamma-band neuronal oscillations. *Cereb. Cortex* 10, 1105–1116.
- 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.
- Fries, P., Neuenchwander, S., Engel, A.K., Goebel, R., Singer, W., 2001a. Rapid feature selective neuronal synchronization through correlated latency shifting. *Nat. Neurosci.* 4, 194–200.
- Fries, P., Reynolds, J.H., Rorie, A.E., Desimone, R., 2001b. Modulation of oscillatory neuronal synchronization by selective visual attention. *Science* 291, 1560–1563.
- Fries, P., Womelsdorf, T., Oostenveld, R., Desimone, R., 2008. The effects of visual stimulation and selective visual attention on rhythmic neuronal synchronization in macaque area V4. *J. Neurosci.* 28, 4823–4835.

- Friston, K.J., 1999. The disconnection hypothesis. *Schizophr. Res.* 30, 115–125.
- Gray, C.M., Engel, A.K., König, P., Singer, W., 1990. Stimulus-dependent neuronal oscillations in cat visual cortex: receptive field properties and feature dependence. *Eur. J. Neurosci.* 2, 607–619.
- Gray, C.M., Koenig, P., Engel, A.K., Singer, W., 1989. Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties. *Nature* 23, 334–337.
- Gray, C.M., McCormick, D.A., 1996. Chattering cells: superficial pyramidal neurons contributing to the generation of synchronous oscillations in the visual cortex. *Science* 274, 109–113.
- Gray, C.M., Viana Di Prisco, G., 1997. Stimulus-dependent neuronal oscillations and local synchronization in striate cortex of the alert cat. *J. Neurosci.* 17, 3239–3253.
- Gregoriou, G.G., Gotts, S.J., Zhou, H., Desimone, R., 2009. High-frequency, long-range coupling between prefrontal and visual cortex during attention. *Science* 324, 1207–1210.
- Gruber, T., Müller, M.M., 2006. Oscillatory brain activity in the human EEG during indirect and direct memory tasks. *Brain Res.* 1097, 194–204.
- Gruetzner, C., Uhlhaas, P.J., Genc, E., Kohler, A., Singer, W., Wibral, M., 2010. Neuroelectromagnetic correlates of perceptual closure processes. *J. Neurosci.* 30, 8342–8352.
- Hadjipapas, A., Adjarian, P., Swettenham, J.B., Holliday, I.E., Barnes, G.R., 2007. Stimuli of varying spatial scale induce gamma activity with distinct temporal characteristics in human visual cortex. *Neuroimage* 35, 518–530.
- Haenschel, C., Bittner, R.A., Waltz, J., Haertling, F., Wibral, M., Singer, W., Linden, D.E., Rodriguez, E., 2009. Cortical oscillatory activity is critical for working memory as revealed by deficits in early onset schizophrenia. *J. Neurosci.* 29, 9481–9489.
- Herculano-Houzel, S., Munk, M.H., Neunschwander, S., Singer, W., 1999. Precisely synchronized oscillatory firing patterns require electroencephalographic activation. *J. Neurosci.* 19, 3992–4010.
- Herrmann, C.S., Mecklinger, A., Pfeiffer, E., 1999. Gamma responses and ERPs in a visual classification task. *Clin. Neurophysiol.* 110, 636–642.
- Herrmann, C.S., Munk, M.H.J., Engel, A.K., 2004. Cognitive functions of gamma-band activity: memory match and utilization. *Trends Cogn. Sci.* 8, 347–355.
- Hoogenboom, N., Schoffelen, J.-M., Oostenveld, R., Parkes, L.M., Fries, P., 2006. Localizing human visual gamma-band activity in frequency, time and space. *Neuroimage* 29, 764–773.
- Howard, M.W., Rizzuto, D.S., Caplan, J.B., Madsen, J.R., Lisman, J., Aschenbrenner-Scheibe, R., Schulze-Bonhage, A., Kahana, M.J., 2003. Gamma oscillations correlate with working memory load in humans. *Cereb. Cortex* 13, 1369–1374.
- Huang, D., Pipa, G., 2007. Achieving synchronization of networks by an auxiliary hub. *Europhys. Lett.* 77, 1–5. 50010.
- Jensen, O., Colgin, L.L., 2007. Cross-frequency coupling between neuronal oscillations. *Trends Cogn. Sci.* 11, 267–269.
- Jensen, O., Kaiser, J., Lachaux, J.P., 2007. Human gamma-frequency oscillations associated with attention and memory. *Trends Neurosci.* 30, 317–324.
- Jokisch, D., Jensen, O., 2007. Modulation of gamma and alpha activity during a working memory task engaging the dorsal or ventral stream. *J. Neurosci.* 27, 3244–3251.
- Jerbi, K., Ossandón, T., Hamamé, C.M., Senova, S., Dalal, S.S., Jung, J., Minotti, L., Bertrand, O., Berthoz, A., Kahane, P., Lachaux, J.P., 2009. Task-related gamma-band dynamics from an intracerebral perspective: review and implications for surface EEG and MEG. *Hum. Brain Mapp.* 30, 1758–1771.
- Jin, T., Jin, X.L., Chen, G.R., Huang, Z.L., 2009. Karhunen-Loeve decomposition approach to analyzing complex network synchronization. *J. Phys. Math. Theor.* 32, 13.
- Johannesen, J.K., Bodkins, M., O'Donnell, B.F., Shekhar, A., Hetrick, W.P., 2008. Perceptual anomalies in schizophrenia co-occur with selective impairments in the gamma frequency component of midlatency auditory ERPs. *J. Abnorm. Psychol.* 117, 106–118.
- Kaiser, J., Böhler, M., Lutzenberger, W., 2004. Magnetoencephalographic gamma-band responses to illusory triangles in humans. *NeuroImage* 23, 551–560.
- Kaiser, J., Heidegger, T., Wibral, M., Altmann, C.F., Lutzenberger, W., 2008. Distinct gamma-band components reflect the short-term memory maintenance of different sound lateralization angles. *Cereb. Cortex* 18, 2286–2295.
- Kitajima, H., Kurths, J., 2009. Bifurcation in neuronal networks with hub structure. *Physica A Stat. Mech. Appl.* 388 (20), 4499–4508.
- Kenyon, G.T., Theiler, J., George, J.S., Travis, B.J., Marshak, D.W., 2004. Correlated firing improves stimulus discrimination in a retinal model. *Neural Comput.* 16, 2261–2291.
- Kleinfeld, D., Mehta, S.B., 2006. Spectral mixing in nervous systems: experimental evidence and biologically plausible circuits. *Progr. Theor. Phys. Suppl.* 161, 86–98.
- Koenig, T., Prichep, L., Dierks, T., Hubl, D., Wahlund, L.O., John, E.R., Jelic, V., 2005. Decreased EEG synchronization in Alzheimer's disease and mild cognitive impairment. *Neurobiol. Aging* 26, 165–171.
- Kopell, N., Ermentrout, B., 2004. Chemical and electrical synapses perform complementary roles in the synchronization of interneuronal networks. *Proc. Natl. Acad. Sci. U. S. A.* 101, 15482–15487.
- Kopell, N., Ermentrout, G.B., Whittington, M.A., Traub, R.D., 2000. Gamma rhythms and beta rhythms have different synchronization properties. *Proc. Natl. Acad. Sci. U. S. A.* 97, 1867–1872.
- Kwon, J.S., O'Donnell, B.F., Wallenstein, G.V., Greene, R.W., Hirayasu, Y., Nestor, P.G., Hasselmo, M.E., Potts, G.F., Shenton, M.E., McCarley, R.W., 1999. Gamma frequency-range abnormalities to auditory stimulation in schizophrenia. *Arch. Gen. Psychiatry* 56, 1001–1005.
- Lachaux, J.P., George, N., Tallon-Baudry, C., Martinerie, J., Hugueville, L., Minotti, L., Kahane, P., Renault, B., 2005. The many faces of the gamma band response to complex visual stimuli. *Neuroimage* 25, 491–501.
- Lachaux, J.P., Rodriguez, E., Martinerie, J., Varela, F.J., 1999. Measuring phase synchrony in brain signals. *Hum. Brain Mapp.* 8, 194–208.
- Laufer, M., Verzeano, M., 1967. Periodic activity in the visual system of the cat. *Vis. Res.* 7, 215–229.
- Le Van Quyen, M., Staba, R., Bragin, A., Dickson, C., Valderrama, M., Fried, I., Engel, J., 2010. Large-scale microelectrode recordings of high-frequency gamma oscillations in human cortex during sleep. *J. Neurosci.* 30, 7770–7782.
- Lewis, D.A., Hashimoto, T., Volk, D.W., 2005. Cortical inhibitory neurons and schizophrenia. *Nat. Rev. Neurosci.* 6, 312–324.
- Lima, B., Singer, W., Chen, N., Neunschwander, S., 2010. Synchronization dynamics in response to plaid stimuli in monkey V1. *Cereb. Cortex* 20, 1556–1573.
- Lindner, B., 2006. Superposition of many independent spike trains is generally not a Poisson process. *Phys. Rev. E* 73, 22–901.
- Lisman, J., Buzsáki, G., 2008. A neural coding scheme formed by the combined function of gamma and theta oscillations. *Schizophr. Bull.* 34, 974–980.
- Mainy, N., Jung, J., Baciú, M., Kahane, P., Schoendorff, B., Minotti, L., Hoffmann, D., Bertrand, O., Lachaux, J.P., 2008. Cortical dynamics of word recognition. *Hum. Brain Mapp.* 29, 1215–1230.
- 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.
- Melloni, L., Schwiedrzik, C.M., Rodriguez, E., Singer, W., 2009. (Micro)saccades, corollary activity and cortical oscillations. *Trends Cogn. Sci.* 13, 239–245.
- Miller, K.J., Sorensen, L.B., Ojemann, J.G., den Nijs, M., 2009. Power-law scaling in the brain surface electric potential. *PLoS Comput. Biol.* 5, 12.
- Monto, S., Palva, S., Voipio, J., Palva, J.M., 2008. Very slow EEG fluctuations predict the dynamics of stimulus detection and oscillation amplitudes in humans. *J. Neurosci.* 28, 8268–8272.
- Munk, M.H., Neunschwander, S., 2000. High-frequency oscillations (20 to 120 Hz) and their role in visual processing. *J. Clin. Neurophysiol.* 17, 341–360.
- Neunschwander, S., Castelo-Branco, M., Baron, J., Singer, W., 2003. Feed-forward synchronization: propagation of temporal patterns along the retinothalamic pathway. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 357, 1869–1876.
- Neunschwander, S., Castelo-Branco, M., Singer, W., 1999. Synchronous oscillations in the cat retina. *Vis. Res.* 39, 2485–2497.
- Neunschwander, S., Singer, W., 1996. Long-range synchronization of oscillatory light responses in the cat retina and lateral geniculate nucleus. *Nature* 379, 728–732.
- Niessing, J., Ebisch, B., Schmidt, K.E., Niessing, M., Singer, W., Galuske, R.A.W., 2005. Hemodynamic signals correlate tightly with synchronized gamma oscillations. *Science* 309, 948–951.
- Oke, O.O., Magony, A., Anver, H., Ward, P.D., Jiruska, P., Jefferys, J.G., Vreugdenhil, M., 2010. High-frequency gamma oscillations coexist with low-frequency gamma oscillations in the rat visual cortex in vitro. *Eur. J. Neurosci.* 31, 1435–1445.
- O'Keefe, J., Recce, M.L., 1993. Phase relationship between hippocampal place units and the EEG theta rhythm. *Hippocampus* 3, 317–330.
- Osipova, D., Takashima, A., Oostenveld, R., Fernández, G., Maris, E., Jensen, O., 2006. Theta and gamma oscillations predict encoding and retrieval of declarative memory. *J. Neurosci.* 26, 7523–7531.
- Palva, J.M., Palva, S., Kaila, K., 2005. Phase synchrony among neuronal oscillations in the human cortex. *J. Neurosci.* 25, 3962–3972.
- Pesaran, B., Pezaris, J.S., Sahani, M., Mitra, P.P., Andersen, R.A., 2002. Temporal structure in neuronal activity during working memory in macaque parietal cortex. *Nat. Neurosci.* 5, 805–811.
- Pfurtscheller, G., Cooper, R., 1975. Frequency dependence of the transmission of the EEG from cortex to scalp. *Electroencephalogr. Clin. Neurophysiol.* 38, 93–96.
- Pipa, G., Städtler, E.S., Rodriguez, E.F., Waltz, J.A., Muckli, L.F., Singer, W., Goebel, R., Munk, M.H.J., 2009. Performance- and stimulus-dependent oscillations in monkey prefrontal cortex during short-term memory. *Front. Integr. Neurosci.* 3, 25.
- Pipa, G., Gruen, S., van Vreeswijk, C. Impact of spike-train auto-structure on probability distribution of joint-spike events, submitted for publication.
- Priestley, M., 1983. *Spectral Analysis and Time Series*, vols. 1 and 2. Academic Press, London.
- Ramp, S., Stefan, H., 2006. Fast activity as a surrogate marker of epileptic network function? *Clin. Neurophysiol.* 117, 2111–2117.
- Ray, S., Niebur, E., Hsiao, S.S., Sinai, A., Crone, N.E., 2008a. High-frequency gamma activity (80–150 Hz) is increased in human cortex during selective attention. *Clin. Neurophysiol.* 119, 116–133.
- Ray, S., Crone, N.E., Niebur, E., Franzczuk, P.J., Hsiao, S.S., 2008b. Neural correlates of high-gamma oscillations (60–200 Hz) in macaque local field potentials and their potential implications in electrocorticography. *J. Neurosci.* 28, 11526–11536.
- Rodriguez, E., George, N., Lachaux, J.P., Martinerie, J., Renault, B., Varela, F.J., 1999. Perception's shadow: long-distance synchronization of human brain activity. *Nature* 397, 430–433.
- Rodriguez, R., Kallenbach, U., Singer, W., Munk, M.H.J., 2004. Short- and long-term effects of cholinergic modulation on gamma oscillations and response synchronization in the visual cortex. *J. Neurosci.* 24, 10369–10378.
- Roopun, A.K., Cunningham, M.O., Racca, C., Alter, K., Traub, R.D., Whittington, M.A., 2008a. Region-specific changes in gamma and beta2 rhythms in NMDA receptor dysfunction models of schizophrenia. *Schizophr. Bull.* 34, 962–973.
- Roopun, A.K., Kramer, M.A., Carracedo, L.M., Kaiser, M., Davies, C.H., Traub, R.D., Kopell, N.J., Whittington, M.A., 2008b. Period concatenation underlies interactions between gamma and beta rhythms in neocortex. *Front. Cell. Neurosci.* 2, 1.
- Siegel, M., Donner, T.H., Oostenveld, R., Fries, P., Engel, A.K., 2008. Neuronal synchronization along the dorsal visual pathway reflects the focus of spatial attention. *Neuron* 6, 709–719.

- Siegel, M., Warden, M.R., Miller, E.K., 2009. Phase-dependent neuronal coding of objects in short-term memory. *Proc. Natl. Acad. Sci. U. S. A.* 06, 21341–21346.
- Silverstein, S.M., Wong, M.H., Schenkel, L.S., Kovasz, I., Feher, A., Smith, T.E., Goicoechea, C., Uhlhaas, P.J., Carpiello, K., Savitz, A., 2006. Reduced top-down influences in contour detection in schizophrenia. *Cogn. Neuropsychiatry* 11, 112–132.
- Singer, W., 1999. Neuronal synchrony: a versatile code for the definition of relations? *Neuron* 24 (49–65), 111–125.
- Singer, W., Gray, C.M., 1995. Visual feature integration and the temporal correlation hypothesis. *Annu. Rev. Neurosci.* 18, 555–586.
- Spencer, K.M., Nestor, P.G., Niznikiewicz, M.A., Salisbury, D.F., Shenton, M.E., McCarley, R.W., 2003. Abnormal neural synchrony in schizophrenia. *J. Neurosci.* 23, 7407–7411.
- Spencer, K.M., Salisbury, D.F., Shenton, M.E., McCarley, R.W., 2008. Gamma-band auditory steady-state responses are impaired in first episode psychosis. *Biol. Psychiatry* 64, 369–375.
- Stephens, G.J., Neuenschwander, S., George, J.S., Singer, W., Kenyon, G.T., 2006. See globally, spike locally: oscillations in a retinal model encode large visual features. *Biol. Cybern.* 95, 327–348.
- Steriade, M., McCormick, D.A., Sejnowski, T.J., 1993. Thalamocortical oscillations in the sleeping and aroused brain. *Science* 262, 679–685.
- Steriade, M., Timofeev, I., Dürmüller, N., Grenier, F., 1998. Dynamic properties of corticothalamic neurons and local cortical interneurons generating fast rhythmic (30–40 Hz) spike bursts. *J. Neurophysiol.* 79, 483–490.
- 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, 42–49.
- Tallon-Baudry, C., Bertrand, O., Wienbruch, C., Ross, B., Pantev, C., 1997a. Combined EEG and MEG recordings of visual 40 Hz responses to illusory triangles in human. *Neuroreport* 8, 1103–1107.
- Tallon-Baudry, C., Bertrand, O., Delpuech, C., Pernier, J., 1997b. 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.
- Tallon-Baudry, C., Bertrand, O., 1999. Oscillatory gamma activity in humans and its role in object representation. *Trends Cognit. Sci.* 3, 151–162.
- Tiesinga, P.H., Sejnowski, T.J., 2004. Rapid temporal modulation of synchrony by competition in cortical interneuron networks. *Neural Comput.* 16, 251–275.
- Tiitinen, H., Sinkkonen, J., Reinikainen, K., Alho, K., Lavikainen, J., Näätänen, R., 1993. Selective attention enhances the auditory 40-Hz transient response in humans. *Nature* 364, 59–60.
- Tillmann, C., Wibral, M., Leweke, M., Kohler, A., Singer, W., Koethe, D., Kranaster, L., Maurer, K., Uhlhaas, P.J., 2008. High-frequency Gamma-band Oscillations during Perceptual Organisation in Chronic and First-episode Schizophrenia Patients. *Soc. Neurosci. Abstr.* 54, 2. Society for Neuroscience 38th Annual Meeting, Washington, D.C., USA.
- Tort, A.B.L., Komorowski, R., Eichenbaum, H., Kopell, N.J., 2010. Measuring phase-amplitude coupling between neuronal oscillations of different frequencies. *J. Neurophysiol.* 104, 1195–1210.
- Tort, A.B.L., Kramer, M.A., Thorn, C., Gibson, D.J., Kubota, Y., Graybiel, A.M., Kopell, N.J., 2008. Dynamic cross-frequency couplings of local field potential oscillations in rat striatum and hippocampus during performance of a T-maze task. *Proc. Natl. Acad. Sci. U. S. A.* 105, 20517–20522.
- Traub, R.D., Bibbig, A., LeBeau, F.E., Buhl, E.H., Whittington, M.A., 2004. Cellular mechanisms of neuronal population oscillations in the hippocampus in vitro. *Annu. Rev. Neurosci.* 27, 247–278.
- Uhlhaas, P.J., Haenschel, C., Nikolic, D., Singer, W., 2008. The role of oscillations and synchrony in cortical networks and their putative relevance for the pathophysiology of schizophrenia. *Schizophr. Bull.* 34, 927–943 (6.59).
- Uhlhaas, P.J., Linden, D.E.J., Singer, W., Haenschel, C., Lindner, M., Maurer, K., Rodriguez, E., 2006b. Dysfunctional long-range coordination of neural activity during gestalt perception in schizophrenia. *J. Neurosci.* 26, 8168–8175.
- Uhlhaas, P.J., Phillips, W.A., Schenkel, L., Silverstein, S.M., 2006a. Theory of mind and perceptual context-processing in schizophrenia. *Cogn. Neuropsychiatry* 11, 416–436.
- Uhlhaas, P.J., Roux, R., Rotarska-Jagiela, A., Rodriguez, E., Singer, W., 2010. Neural synchrony and the development of cortical networks. *Trends Cogn. Sci.* 14, 72–80.
- Uhlhaas, P.J., Singer, W., 2006. Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. *Neuron* 52, 155–168.
- Uhlhaas, P.J., Singer, W., 2010. Abnormal neural oscillations and synchrony in schizophrenia. *Nat. Rev. Neurosci.* 11, 100–114.
- Uhlhaas, P.J., Pipa, G., Lima, B., Melloni, L., Neuenschwander, S., Nikolić, D., Singer, W., 2009. Neural synchrony in cortical networks: history, concept and current status. *Front. Integr. Neurosci.* 3, 17.
- van der Meer, M.A., Redish, A.D., 2009. Low and high gamma oscillations in rat ventral striatum have distinct relationships to behavior, reward, and spiking activity on a learned spatial decision task. *Front. Integr. Neurosci.* 3, 9.
- Van Vreeswijk, C., Abbott, L.F., Ermentrout, G.B., 1994. When inhibition not excitation synchronizes neural firing. *J. Comput. Neurosci.* 1, 313–321.
- Vaney, D.L., 1994. Patterns of neuronal coupling in the retina. *Prog. Retin. Eye Res.* 13, 301–355.
- Varela, F., Lachaux, J.P., Rodriguez, E., Martinerie, J., 2001. The brain web: phase synchronization and large-scale integration. *Nat. Rev. Neurosci.* 2, 229–239.
- Vicente, R., Gollo, L.L., Mirasso, C.R., Fischer, I., Pipa, G., 2008. Dynamical relaying can yield zero time lag neuronal synchrony despite long conduction delays. *Proc. Natl. Acad. Sci. U. S. A.* 105, 17157–17162.
- Vidal, J.R., Chaumon, M., O'Regan, J.K., Tallon-Baudry, C., 2006. Visual grouping and the focusing of attention induce gamma-band oscillations at different frequencies in human magnetoencephalogram signals. *J. Cogn. Neurosci.* 18, 1850–1862.
- von Stein, A., Chiang, C., Konig, P., 2000. Top-down processing mediated by inter-areal synchronization. *Proc. Natl. Acad. Sci. U. S. A.* 97, 14748–14753.
- Wang, X.J., Buzsáki, G., 1996. Gamma oscillation by synaptic inhibition in a hippocampal interneuronal network model. *J. Neurosci.* 16, 6402–6413.
- White, J.A., Chow, C.C., Ritt, J., Kopell, N., 1998. Frequency control in synchronized networks of inhibitory neurons. *J. Comput. Neurosci.* 5.
- Whittington, M.A., Traub, R.D., Kopell, N., Ermentrout, B., Buhl, E.B., 2000. Inhibition-based rhythms: experimental and mathematical observations on network dynamics. *Int. J. Psychophysiol.* 38, 315–336.
- Wilson, T.W., Rojas, D.C., Reite, M.L., Teale, P.D., Rogers, S.J., 2007. Children and adolescents with autism exhibit reduced MEG steady-state gamma responses. *Biol. Psychiatry* 62, 192–197.
- Womelsdorf, T., Schoffelen, J.-M., Oostenveld, R., Singer, W., Desimone, R., Engel, A.K., Fries, P., 2007. Modulation of neuronal interactions through neuronal synchronization. *Science* 316, 1609–1612.
- Wu, W., Wheeler, D.W., Staedtler, E.S., Munk, M.H., Pipa, G., 2008. Behavioral performance modulates spike field coherence in monkey prefrontal cortex. *Neuroreport* 19, 235–238.
- Wyart, V., Tallon-Baudry, C., 2008. Neural dissociation between visual awareness and spatial attention. *J. Neurosci.* 28, 2667–2679.
- Yuval-Greenberg, S., Tomer, O., Keren, A.S., Nelken, I., Deouell, L.Y., 2008. Transient induced gamma-band response in EEG as a manifestation of miniature saccades. *Neuron* 58, 429–441.