Clinical Neurophysiology 116 (2005) 2719–2733

www.elsevier.com/locate/clinph

Invited review

Human EEG gamma oscillations in neuropsychiatric disorders

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Accepted 15 July 2005
Available online 25 October 2005

Abstract

Due to their small amplitude, the importance of high-frequency EEG oscillations with respect to cognitive functions and disorders is often underestimated as compared to slower oscillations. This article reviews the literature on the alterations of gamma oscillations (about 30–80 Hz) during the course of neuropsychiatric disorders and relates them to a model for the functional role of these oscillations for memory matching. The synchronous firing of neurons in the gamma-band has been proposed to bind multiple features of an object, which are coded in a distributed manner in the brain, and is modulated by cognitive processes such as attention and memory. In certain neuropsychiatric disorders the gamma activity shows significant changes. In schizophrenic patients, negative symptoms correlate with a decrease of gamma responses, whereas a significant increase in gamma amplitudes is observed during positive symptoms such as hallucinations. A reduction is also observed in Alzheimer's Disease (AD), whereas an increase is found in epileptic patients, probably reflecting both cortical excitation and perceptual distortions such as déjà vu phenomena frequently observed in epilepsy. ADHD patients also exhibit increased gamma amplitudes. A hypothesis of a gamma axis of these disorders mainly based on the significance of gamma oscillations for memory matching is formulated.
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Keywords: ADHD; Alzheimer's Disease; Epilepsy; Gamma; Memory; Schizophrenia

1. Introduction

1.1. From slow to fast oscillations

Since the discovery of the electroencephalogram (EEG) by Hans Berger, 1929, oscillatory patterns can be observed in the brain electrical activity (Berger, 1929). The most prominent oscillation in the spontaneous EEG exists in a frequency band of 8–12 Hz, which was considered by Berger as the basic rhythm and was named α-rhythm. Alpha oscillations appear with well noticeable amplitudes between 10 and 50 μV and have multiple cognitive correlates (Basar et al., 1997). The chronologically next identified frequency range between 12 and 30 Hz was named by Berger consequently with the Greek letter β. Faster oscillations in the human EEG between 30 and 80 Hz could later be identified and were named as gamma activity (Chatrian et al., 1960). The slower waves below the alpha range were first named as δ and afterwards were divided into the delta (0–4 Hz) and theta (4–8 Hz) ranges. Since the amplitudes of the EEG oscillations decrease with increasing frequencies (Fig. 1), higher frequency bands such as the omega range (80–120 Hz) were identified later. Today it is known that oscillations with frequencies up to 600 Hz exist in the EEG (Curio et al., 1994).

The functional significance of brain activity in the alpha, theta and delta frequency bands and event-related oscillations within this frequency range were discovered relatively early, because these slow waves can easily be observed in the EEG (Basar, 1980; Basar et al., 1997; Demiralp and Basar, 1992; Steriade et al., 1990). Oscillations in the beta band and in higher frequency bands could, however, be revealed adequately only with the use of special amplifiers and analysis techniques due to their small amplitudes.

An important property of brain oscillations in the brain is that they can show phase relations either in terms of a phase synchronisation among various oscillators or

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doi:10.1016/j.clinph.2005.07.007

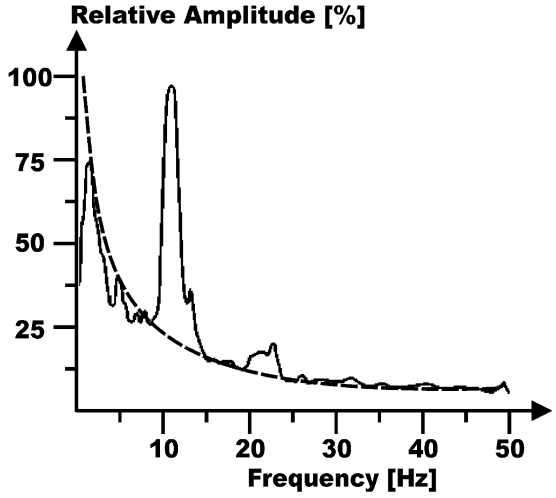

Fig. 1. Relationship between the amplitude and the frequency of brain electrical oscillations. High frequency EEG oscillations have smaller amplitudes compared with the lower frequencies. In general, the relationship between the amplitude (A) and frequency (F) is given as $A \sim 1/F$. A theoretical $1/F$ curve is shown (dashed line) in comparison to a real EEG spectrum (continuous line). Some resonance frequencies can be observed around 10 and 20 Hz, at which the EEG amplitudes are higher than the $1/F$ curve. However, the principal similarity between the theoretical and the real curve is easy to mark.

a phase-coupling to a transient event. The discussion of these properties is important for understanding possible functional meanings of oscillatory activity in the brain (Varela et al., 2001). Within this framework, three types of phase synchrony can be described for brain electrical signals: inter-neuronal, inter-electrode and inter-trial.

The inter-neuronal phase synchronisation represents a local synchronisation among neurons in a relatively small area of some millimeters, such that their membrane potentials oscillate in phase and/or they fire synchronously with each other. This type of synchrony can be investigated by measuring either the membrane potentials of a number of single cells simultaneously or by measuring multiunit activity and local field potentials using electrodes in close proximity. On the other hand, this type of synchrony is very basic for the generation of the EEG, because only synchronous activity of a large set of neurons can reach the skull and therefore, each EEG electrode records the spatial sum of such synchronous activity of a large number of oscillating neurons or neural circuits (Basar, 1980; Steriade et al., 1990). Therefore, EEG oscillations result from brain activity with high inter-neuronal synchrony. However, either more neurons with the same degree of inter-neuronal synchrony or the same number of neurons with a higher degree of inter-neuronal synchrony may lead to increased EEG amplitudes.

On the other hand, phase synchrony may also exist on a larger scale, and the electrical signals from distant electrodes may contain coherent oscillations with 0 or constant phase shift (Varela et al., 2001). Such synchronous activity among distant parts of the brain yields high values (close to 1) in the coherence function. This type of synchrony is important in the detection of anatomically distant, however, functionally closely related brain structures that are interacting either through simultaneous communication with the same sub-cortical structure (0 phase shift) or among each other through long cortico-cortical connections (constant phase shift). It is called inter-electrode synchrony and measured via coherence functions.

The third type of phase synchronisation, inter-trial synchrony, is especially important in the analysis of event-related oscillations, which can only be analyzed through statistical approaches on the data when the same event is repeated a number of times (trials). In this case, two different types of oscillatory responses can be obtained (Basar, 1980; Herrmann et al., 2005). The so-called 'evoked' oscillations are phase-coupled to the triggering event, hence start within a preferred range of phase angles after the external event. This type of responses result in clear oscillations in the average of the trials, even if no amplitude enhancement is present in single trials. A second type of event-related oscillations that are termed 'induced' responses show an amplitude increase in single trials, however, do not occur with a constant phase lag after the triggering event. Therefore, they are not observable in the averaged response, in case many trials have been averaged. However, they can be quantified by transforming the single trials into the frequency domain first, and then averaging the transformed data after removing the phase information. Due to their different temporal dynamics, both types of event-related oscillations may correspond to different functions, although their generation might depend on the same or similar circuits.

1.2. Gamma-activity

In recent years, a special interest for oscillations in the gamma frequency range has emerged in the neurosciences (Basar-Eroglu et al., 1996). The interest for these oscillations depends on the fact that gamma activity is closely correlated with cognitive functions (Engel et al., 2001).

Various gamma phenomena can be grouped into the following categories (Galambos, 1992): *Spontaneous gamma oscillations*, that contribute a fraction of the total EEG/MEG power at any given moment have been explained by thalamocortical resonant synaptic interactions (Llinas and Ribary, 1992) and have been assumed to reflect the consciousness level. On the other hand, a number of studies based on multiunit activity or field potential measurements in sensory cortices of various species showed *induced gamma oscillations* that follow a sensory stimulus, but are not phase-locked to the stimulus (Engel et al., 1992), i.e. do not show any inter-trial phase synchronisation. Induced gamma activity has been interpreted to reflect feature-binding processes and to generate a neural representation of the stimulus by integrating the different features encoded in

different neuronal maps. However, not only the features that are represented by synchronously firing neurons are integrated to a coherent object, but also object representations and related motor activity are integrated by the gamma oscillations (Roelfsema et al., 1997). *Evoked gamma responses* that are most consistently recorded from human scalp are occurring in an earlier time window than induced gamma oscillations and are phase-locked to the stimulus, i.e. show inter-trial phase synchrony. It has also been demonstrated that simple sensory stimuli evoke such gamma responses in the cortex and subcortical structures of the animal brain (Basar, 1980; Demiralp et al., 1996). *Steady-state gamma oscillations* are the driven electrical responses, of the brain obtained by the application of repetitive stimuli like clicks, tone pips or an amplitude modulated tone which reach their maximum at repetition rates around 40 Hz (Galambos et al., 1981). Later, Pantev et al. (1991) used magnetoencephalographic measurements to reveal that the generators of the steady-state gamma response (SSR) and the transient gamma band response overlap and concluded that the SSR to auditory stimuli is essentially the overlapping sum of the successive transient gamma band responses.

Spontaneous gamma activity is recorded without any task for the subjects/patients. In order to record steady-state responses, a repetitive stimulation (e.g. visual or auditory) needs to be supplied, which repeats at the frequency of interest, i.e. 40 Hz. Evoked and induced gamma oscillations occur as transient event-related oscillations (EROs) in experimental paradigms exploring cognition, which at the same time evoke event-related potentials (ERPs, cf. Fig. 2).

While occurring within different contexts and with different temporal dynamics and relations to sensory and cognitive events, there is evidence that spontaneous, steady-state, evoked and induced gamma oscillations might be generated by the same neural circuits (Basar, 1980; Herrmann, 2001; Pantev et al., 1991). Basar (1980) used intracranial measurements of field potentials to demonstrate that brain structures respond to transient stimuli with enhancement of oscillations within those frequency ranges, which are present in the power spectrum of the spontaneous electrical activity of that brain structure. This phenomenon, which the author calls response susceptibility, shows a close relationship between the generators of spontaneous and evoked or induced oscillations. Later, Herrmann (2001) demonstrated that resonance phenomena existed in visual steady-state responses at the same frequencies where evoked oscillations usually occur. Additionally, the sources of auditory steady-state responses were located in primary auditory cortex (Gutschalk et al., 1999; Herdman et al., 2002), which is also true for the sources of event-related gamma activity revealed by intracranial recordings in monkeys (Brosch et al., 2002) and humans (Crone et al., 2001). Along the same lines, visual steady-state responses were located in human visual cortex (Hillyard et al., 1997; Müller et al., 1997), where also event-related gamma activity was found in intracranial recordings in monkeys (Fries et al., 2001; Rols et al., 2001) as well as in humans (Tallon-Baudry et al., 2005). Furthermore, the cognitive correlates of evoked and induced gamma responses generally overlap (Debener et al., 2003; Engel et al., 2001; Fries et al., 2001; Herrmann et al., 2004a; b; Tiitinen et al., 1993; Yordanova et al., 1997a; b). Therefore, it seems plausible to assume that similar generation mechanisms are responsible for both types of gamma activity. On this basis, we will not separate the different measurement modalities and review the different types of gamma oscillations within a general frame.

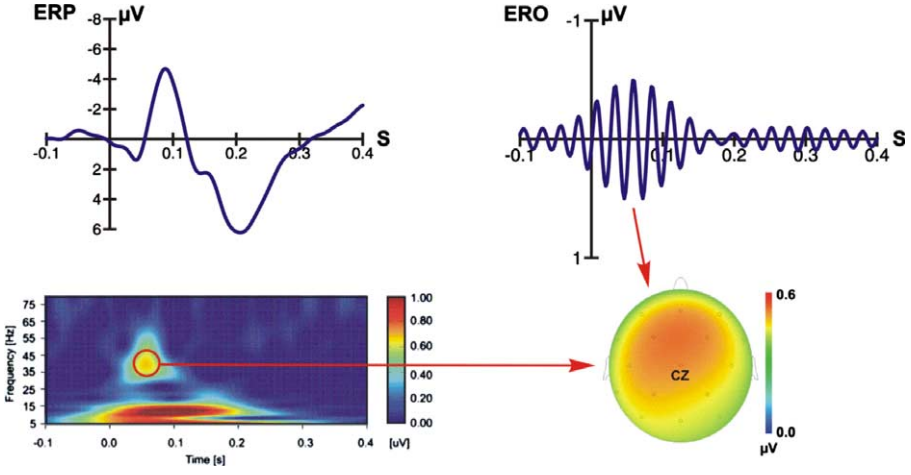

Fig. 2. ERPs and EROs are generated simultaneously and can be differentiated by filtering or frequency transformation. Filtering the ERP response of an auditory stimulus (upper left panel) with a band-pass of 35–45 Hz yields the ERO in the gamma-band (upper right panel). The 40 Hz oscillations, that are already present before the stimulus, are enhanced significantly by the stimulus. Please note that the amplitudes of less than 1 μV are much smaller than those of the alpha oscillations that can be in a range of 10–50 μV. In order to see the temporal behaviour of slow and fast oscillations simultaneously, the ERP can be transformed to the time–frequency domain (lower left panel). The gamma-band ERO is visible as a short burst of 40 Hz activity around 50 ms after stimulus onset. The scalp topography of this auditory gamma-band response is illustrated in the lower right panel.

2. Gamma activity reflects memory matching

A number of studies have shown that gamma oscillations are modulated by a variety of cognitive processes such as attention, object recognition, and working memory (Debener et al., 2003; Fries et al., 2001; Herrmann and Mecklinger, 2001; Herrmann et al., 2004a; b; Tiitinen et al., 1993; Yordanova et al., 1997a; b). Therefore, gamma activity is assumed to reflect an integration mechanisms of the brain (Herrmann et al., 2004; b).

Neurons in the brain can be connected to each other either via very strong or rather weak connections. These connections constitute the basis of human memory. If, for example, a neuron in early visual cortex, which reacts to horizontal contours, is coupled with a strong connection to a neuron of a higher visual area, which reacts to faces, then both neurons belong to the memory representation of the face. The strong connection has been learned through the frequent presence of the horizontal contours (e.g. mouth) in faces. Therefore, the neurons of the lower visual areas are coupled to the neurons of the higher visual areas, whenever the brain perceives a known object. This leads to a feedback, because these connections are regularly bidirectional. This feedback then results in a ‘stronger‘ gamma activity than it is the case for unknown objects, for which no such feedback or only a significantly weaker feedback occurs due to the missing memory representations (Herrmann et al., 2004a; b). This match and utilization model (MUM) is mainly based on perceptual forms of memory and it is not clear, whether it can also apply to other forms such as episodic or implicit memory.

MUM offers the advantage to explain many findings of stronger or weaker gamma activity observed in various experimental conditions. On one hand, the findings in terms of stronger gamma oscillations for existing memory representations (Tallon-Baudry et al., 1998; Gruber et al., 2002; Gruber and Müller, 2005; Kaiser et al., 2003) can surely be explained by this integration mechanism. Other studies have shown that words induce higher gamma activity than pseudo-words (Pulvermüller et al., 1995), known faces more than non-recognizable rotated faces (Keil et al., 1999), and identifiable objects more than random dot patterns (Revonsuo et al., 1997). Because memory representations exist for words, faces, and objects, but not for pseudo-words, rotated faces and random dot patterns, the former ones lead to more gamma activity than latter ones.

While it has been demonstrated very vividly that EEG gamma activity is related to memory processes, these oscillations probably reflect low-level processes of perceptual memory residing mainly in sensory cortices. If however, the contribution of higher association areas is required as in the example of working memory, memory consolidation via the hippocampus or retention of contents from memory, then slower frequency ranges such as theta and alpha seem to come into play (Basar et al., 2000; Klimesch, 1999). During the retention period of delayed-matching-to-sample-tasks, for example, the total alpha activity increases with increasing memory load (Busch and Herrmann, 2003; Herrmann et al., 2004; c; Jensen et al., 2002; Schack and Klimesch, 2002). Theta activity, which is believed to result from hippocampal neurons (Buzsaki, 2002; O’Keefe, 1993; O’Keefe and Burgess, 1999; Tesche and Karhu, 2000), is often found during the recall of memory items (Klimesch et al., 2001) and is higher for known/recognized/old items than for unknown/unrecognized/new ones (Burgess and Gruzelier, 1997; Klimesch et al., 2000; van Strien et al., 2005). It has been demonstrated that these slower rhythms have a phase correlation with gamma activity (Burgess and Ali, 2002; Fell et al., 2003; Schack et al., 2002) indicating that both types of oscillations probably need to interact in a specific way for proper memory function. According to Varela et al. (2001), these slower rhythms could provide the temporal framing for successive cognitive moments of synchronous assemblies, within which beta and gamma rhythms operate. However, how exactly this interaction might occur is still under debate.

3. Changes in gamma activity in neuropsychiatric disorders

As these high frequency oscillations with small amplitudes can be better registered with modern technology, they were intensively investigated only recently. It turned out, that there are significant interindividual deviations in gamma activity that correlate with cognitive parameters (Strüber et al., 2000). Additionally, it was demonstrated that an excess or deficiency of this ‘cognitive‘ activity is characteristic for certain pathological conditions. Both phenomena were to be expected, if gamma activity is relevant for cognition.

There have been a number of results relating gamma activity to neuropsychiatric diseases such as epilepsy, schizophrenia, attention deficit hyperactivity disorder (ADHD), dementia, traumatic brain injury, autism, Williams syndrome, migraine and stroke. These studies are listed in Table 1 with a short explanation of the measurement modalities of gamma oscillations and the results obtained. In this review, we want to focus on pathological conditions, in which the increase or decrease of gamma activity relates to MUM and where the symptoms go in line with predictions of MUM for changed gamma oscillations. These will be epilepsy, schizophrenia, ADHD and Alzheimer’s disease.

Gamma activity is, of course, not the only electrophysiological indicator of these disorders. Many studies reported EEG findings relevant to these diseases also in other frequency bands. However, this review will focus only on the correlations of changes of gamma oscillations with these disorders.

Table 1
Summary of the studies on changes of the gamma oscillations under pathological conditions

Disorder	Measurement modality	γ	Articles
Epilepsy	Human spontaneous EEG	↑	Fisher et al. (1992); Alarcon et al. (1995); Willoughby et al. (2003); Worrell et al. (2004); Wendling et al. (2002); Kobayashi et al. (2004)
	Human EEG (intermittent photic stimulation)	↑	Kalitzin et al. (2002); Parra et al. (2003, 2005)
	Rat EEG (kainic acid)	↑	Medvedev et al. (2000, 2001, 2002)
	Rat EEG (electrical stimulation of CA1)	↑	Ma and Leung (2002)
	Hippocampal slice (electrical stimulation)	↑	Köhling et al. (2000); Traub et al. (2005); Khazipov and Holmes (2003)
	Hippocampal slice (kainic acid)	↑	Fisahn (2005)
ADHD	Evoked	↑	Yordanova et al. (2001)
Hallucinations	Spontaneous EEG	↑	Baldeweg et al. (1998)
	Phase-locking	↑	Spencer et al. (2004)
Schizophrenia	Sleep EEG	↑	Tekell et al. (2005)
	Spontaneous MEG	↓	Kissler et al. (2000)
	Evoked	?	Clementz et al. (1997)
		–	Clementz and Blumenfeld (2001)
		↓	Haig et al. (2000); Spencer et al. (2003); Gallinat et al. (2004); Green et al. (2003)
	Synchrony (positive symptoms)	↑	Lee et al. (2003a,b); Spencer et al. (2004)
	Synchrony (negative symptoms)	↓	Lee et al. (2003a,b); Spencer et al. (2004)
	Synchrony (first episode)	↓	Symond et al. (2005)
	Steady-state	↓	Kwon et al. (1999); Hong et al. (2004); Krishnan et al. (2005)
Alzheimer's Disease	Spontaneous EEG or MEG	↓	Ribary et al. (1991); Stam et al. (2002); Koenig et al. (2005)
	Spontaneous EEG	–	Babiloni et al. (2004)
	EEG + photic stimulation (Down syndrome)	↓	Politoff et al. (1996)
Aging	Evoked	↓	Böttger et al. (2002)
	Hippocampal slices (carbachol or kainate induced)	↓	Vreugdenhil and Toescu (2005)
Autism and Williams synd.	Induced	↓	Grice et al. (2001)
Migraine	Spontaneous EEG	↓	Hall et al. (2004)
Stroke	Spontaneous EEG	↓	Molnar et al. (1997)
Brain injury	Spontaneous EEG	↓	Thornton (1999)
	Evoked	↓	Slewa-Younan et al. (2002)

4. Gamma oscillations in epilepsy

Epilepsy is a functional disorder of the brain due to excessive neuronal discharges. In ICD-10 (International Classification of Diseases, 10th Revision, Geneva: World Health Organization, 1992) this disorder is classified under the disorders of the nervous system (G40). Epilepsy is often accompanied by psychiatric symptoms (Bruton et al., 1994; Mace, 1993; Mendez et al., 1993). Epilepsy can be differentiated from other seizure-like disorders through the use of the EEG. During a seizure the EEG reveals epileptiform waves, which are mainly sharp waves (of 80–200 ms duration) and spikes (of 20–80 ms duration) that may also appear as spike-wave complexes in combination with the slow waves. In focal epilepsy, at the start of a seizure (ictus) epileptiform potentials are recorded in electrodes close to the focus, and in the case of a secondary generalization they spread consequentially to all electrode locations. In a primary generalized seizure, they start with the same amplitudes at all electrodes at the same time. However, epileptiform potentials can also be registered during the seizure-free period between two seizures, which is called the inter-ictal period.

The formation of an epileptic seizure has been investigated widely in animal models. Two mechanisms seem to be of primary importance: On the one hand, the decrease of neuronal inhibition mediated by the GABAergic chloride channels may lead to an excessive firing of neurons (Treiman, 2001). On the other hand, a hyper-excitation due to excessive activation of the glutamatergic system could

also result in the same effect. For example the glutamate agonist cainic acid, a substance that binds to the glutamate receptors and stimulates them stronger than glutamate itself, induces an epileptic seizure in rats (Pisa et al., 1980). This procedure at the same time yields an increase in gamma activity in the rat brain (Medvedev et al., 2000). The administration of the indirect dopamine agonist amphetamine also triggers an epileptic seizure in rats. If, however, a glutamate antagonist is administrated before amphetamine, it can suppress both the generation of gamma activity and the seizure-like motor hyperactivity in freely behaving rats (Ma and Leung, 2002).

During the inter-ictal phase between two epileptic seizures, spontaneous gamma activity in patients with primary generalized epilepsy has been shown to be 7–10 times higher in amplitude compared with healthy subjects (Willoughby et al., 2003). Intracranial recordings in patients with implanted subdural electrode grids have additionally shown that especially before the start of an epileptic seizure high frequency oscillations occur in the electrocorticogram (Fisher et al., 1992). Shortly before a seizure, the authors observed a twofold increase in the amplitude of the frequency range between 40 and 50 Hz and a fivefold increase in the frequency range between 80 and 120 Hz compared with a reference period long before the seizure. A later study reported similar results in the frequency range of 20–80 Hz (Alarcon et al., 1995).

The fact that the high frequency oscillations mainly occur around the epileptic focus in patients with neocortical epilepsy has been interpreted as a cue for their fundamental role in epilepsy (Worrell et al., 2004). Furthermore, the presence of gamma activity in human EEG during epileptic seizures whenever a muscle spasm occurs was evaluated as further evidence for this functional coupling (Kobayashi et al., 2004). A review article about the occurrence of gamma activity in epilepsy proposes that the epileptic brain activity is a direct response to an excessive increase in gamma activity (Medvedev, 2002).

5. Gamma oscillations in ADHD

ICD-10 lists ADHD as a hyperkinetic disorder (F90) and it is characterized by usually starting within the first 5 years of life. Patients often exhibit a deficiency in persevering for occupations that require a cognitive effort. Additionally, the patients have a tendency to change from one activity to another without finishing any of them. DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Washington: American Psychiatric Association, 1994) divides ADHD into predominantly non-attentive (314.00) and predominantly hyperactive-impulsive types (314.01).

In an attention deficit, one could surely first assume the presence of a deficit of neuronal activity that is necessary or responsible for attention. However, the hyperactivity, which often accompanies the attention deficit, indicates that a neuronal hyper-excitation could also be responsible for this deficit.

Yordanova et al. (2001) investigated the gamma activity in ADHD-children. In healthy subjects, visual target stimuli evoke significantly higher gamma activity than standard stimuli, because the targets are processed more attentively (Herrmann, 2001). Also auditory target stimuli demonstrate such an effect (Debener et al., 2003). The analysis of the phase of the gamma activity additionally showed that target stimuli synchronize the phase of gamma oscillations (Yordanova et al., 1997a; b). To investigate attention-related gamma activity in ADHD, a paradigm with targets was carried out in ADHD-children. The analysis of auditory targets lead to the result that evoked gamma activity and the synchrony of its phase were significantly stronger than in controls, when stimuli were delivered to the right ear (Yordanova et al., 2001). This lateralization was probably due to the required reaction to targets with the right hand while no reaction was required for standards. Target tones presented to the right ear are processed in the left hemisphere where also the required reaction with the right hand is prepared while target tones presented to the left ear are processed in the right hemisphere where no motor preparation takes place. The integration of both processes in one hemisphere, i.e. analyzing target tones and preparing a motor response, probably resulted in the lateralized effect.

6. Gamma oscillations in Schizophrenia

Schizophrenia (DSM-IV: 295.x, ICD-10: F20.x) is generally characterized by a disturbance of perception (illusions and hallucinations), disorganized thoughts, and ‘blunted’ or ‘flat’ affects (McCarley et al., 1993). One of the central deficits in this disease is considered to be a lack of the integration of sensory input with the information stored in memory (Gray, 1998). This integration disorder gets especially evident, when the patients suffer from hallucinations, during which the lack of a sensory input from the environment is not correctly integrated with top-down information (expectancies, thoughts, memories) and for example ‘alien voices’ are heard. A similar disturbance of integration probably underlies the disorganized thoughts that appear as strange associations and non-coherent ideas.

The schizophrenic symptoms can be divided into positive and negative components depending on whether they also appear in healthy subjects (Kay et al., 1987). Positive symptoms are those, which occur in schizophrenic patients but not in healthy people. The illusions and hallucinations or thought disturbances belong to this category. Negative symptoms are those that do not appear in schizophrenic patients or to a lesser degree than in healthy subjects. Flat affect, apathy and attention disturbances of the patients belong to this category.

After it was found that the gamma activity is relevant for the integration of neuronal activations, it was asked whether

schizophrenic patients might suffer from a deficiency in gamma oscillations. The first group of researchers, who investigated this hypothesis, was a group of psychologists from San Diego (Clementz et al., 1997). They used the P50-paradigm (double-click paradigm) for their investigation, in which two auditory stimuli follow each other rapidly. In healthy subjects each of the two stimuli evoke a positive component in the event-related potentials (ERP), that appears approximately 50 ms after the stimulus and is therefore called P50. However, the P50 amplitude after the second stimulus is significantly suppressed in comparison to the first response. This phenomenon is called P50-suppression. Schizophrenic patients lack this P50-suppression (Boutros et al., 1991; Freedman et al., 1983). The group of Brett Clementz could demonstrate in a combined EEG and magnetoencephalography (MEG) study that two magnetic gamma responses evoked by the two stimuli also revealed a lack of suppression (Clementz et al., 1997). This could either be due to an increased gamma response to the second stimulus or due to a reduced gamma response to the first stimulus (Clementz et al., 2001). However, in their later study, the authors could not replicate a lack of gamma suppression.

Subsequently, a further study investigated, how evoked steady-state oscillations in the gamma band react in schizophrenia (Kwon et al., 1999). This rhythmic driving response of the human EEG is routinely investigated in the clinics for frequencies between 3 and 20 Hz, and can also be obtained with frequencies of up to 80 Hz and higher (Herrmann, 2001). Various studies could show that the rhythmic driving response is different in schizophrenics compared with the normal population (Clementz et al., 2004; Wada et al., 1995). However, in those studies the 40 Hz frequency range was not specifically investigated. Kwon et al. have explicitly investigated the 40-Hz steady-state response and showed through a continuous stimulation with auditory stimuli of different frequencies (20, 30, and 40 Hz), that the schizophrenics responded with reduced steady-state oscillations as compared to healthy subjects (Kwon et al., 1999). This was interpreted to reflect a degenerative change in early sensory cortices.

Event-related gamma activity has also been investigated in relation with the attention processes and has been found to be higher when a stimulus is processed attentively (Fries et al., 2001; Gruber et al., 1999; Tiitinen et al., 1993). Especially, in a target detection task target stimuli evoke more gamma oscillations than standard stimuli, when the target stimuli have to be identified (Debener et al., 2003; Herrmann and Mecklinger, 2001). Haig et al. (2000) demonstrated that for auditory standard stimuli there was a reduction of the evoked gamma response in schizophrenic patients. The same was true for target responses over the dominant left hemisphere. However, the effect reversed over the right hemisphere.

Kissler et al. (2000) have further shown that mental arithmetic induces an increase in gamma activity in the left hemisphere of healthy subjects. However, schizophrenic patients did not demonstrate such an increase of left-sided gamma activity during mental arithmetic. Gamma activity has also been correlated with the correct binding of individual features to a coherent object (Tallon et al., 1995; Tallon-Baudry et al., 1997). Therefore, Spencer et al. (2003, 2004) investigated, whether this binding function and related gamma activity is intact in schizophrenia. The authors found that illusory Kanizsa figures, in which the inducing elements should be bound to a figure, induce less gamma activity in schizophrenics than in healthy subjects.

Because the medications for the management of schizophrenia may also have an influence on the electrophysiological responses of the patients, recently unmedicated schizophrenic patients were investigated with an oddball-paradigm using double-clicks as standard stimuli and 1000 Hz sine tones as target stimuli (oddballs). This study also showed that auditory targets evoke less gamma oscillations in schizophrenic patients than in healthy subjects, whereas no differences were found for gamma responses to task-irrelevant double-clicks (Gallinat et al., 2004). In a recent review, van der Stelt et al. (2004) have summarized these findings.

Most studies reviewed up to this point demonstrated a reduction of gamma activity in schizophrenic patients, which is well in line with the memory and attention deficits observed in schizophrenia (Lussier and Stip, 2001). However, another study on gamma activity has shown that somatosensory hallucinations induce increased gamma oscillations (Baldeweg et al., 1998). In line with that result, Spencer et al. (2004) revealed that schizophrenic patients with hallucinations showed increased high-frequency oscillations. However, while these high-frequency oscillations had a frequency of about 40 Hz in controls, it was reduced to around 30 Hz in schizophrenic subjects. The studies cited above did not divide their patients according to whether they predominantly showed positive or negative symptoms. In a more recent study, the schizophrenic patients were divided into various categories according to their positive and negative symptom scores (Lee et al., 2003b). This study reported that a reduction of the gamma activity was correlated mainly with negative symptoms. For predominantly positive symptoms, however, the gamma activity showed a significant increase compared with a healthy group. These findings were previously summarized in a review on the gamma activity in schizophrenia (Lee et al., 2003a).

7. Gamma oscillations in Alzheimer's disease

Alzheimer's disease (AD) is the most frequent type of primary degenerative dementias affecting 5–10% of the population above the age of 65 (ICD-10: F.00). Amnesia is the earliest, most frequent and severe symptom in AD. Clinically, the disease is characterized by progressive amnesia, which is followed by a slow decline in all

cognitive domains resulting in global dementia (DSM-IV, 294.1x). AD is caused by the degeneration of nerve-cells in the brain and their replacement by elements known as neurofibrillary tangles and senile plaques, which start in the entorhinal cortex and limbic areas during the early stage of the disease and then spread out to other parts of the cortex. Postmortem studies have enabled correlation of the numbers of these elements with the degree of mental impairment during life.

Since gamma activity has been linked to memory access (Gruber et al., 2002; Gruber and Müller, 2005; Herrmann et al., 2004a,b; Kaiser et al., 2003), a study of AD investigated spontaneous gamma activity during an eyes-closed condition without a task for the subjects (Stam et al., 2002). The authors demonstrated that the synchronization in this frequency range was suppressed as compared to controls. Similar results were reported earlier by Ribary et al. (1991). Politoff et al. (1996) analyzed EEG abnormalities in subjects with Down syndrome (DS), who develop Alzheimer's disease (AD) histopathology before they develop dementia, and found that beta and gamma power were significantly decreased in EEG during photic stimulation and interpreted this result to indicate decreased responsiveness to photic stimulation as in AD. However, it should be noted, that other authors failed to find similar results in AD (Babiloni et al., 2004).

The fact that gamma oscillations decrease with increasing age in the mouse hippocampus (Vreugdenhil and Toescu, 2005) and in human frontal cortex (Böttger et al., 2002) demonstrate that gamma activity is already affected by normal aging processes supporting the notion that it might be relevant for AD. The age-dependent loss of dopamine D2 receptors (Li et al., 2001) might be the cause of this decrease in gamma oscillations during aging, since there is a positive correlation between dopamine and gamma activity (see below).

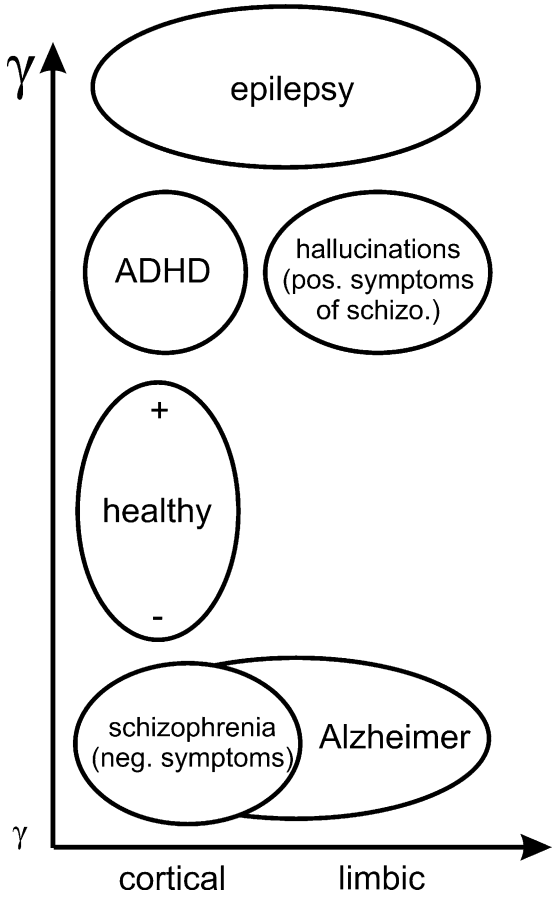

Fig. 3. Hypothetical relationship between gamma activity, brain regions and pathology. Even in healthy subjects, gamma activity shows a significant interindividual variation that correlates with cognitive parameters. In ADHD patients, it is slightly higher. For schizophrenia a subgrouping in positive and negative symptoms is well documented, and it has been suggested that both groups can be differentiated by increased (positive symptoms, especially hallucinations) or reduced (negative symptoms) gamma activity. Alzheimer's disease is accompanied with a reduction of gamma synchronization. An extremely high level of gamma activity may lead to epileptic seizures through the hyper-excitation of the cortex. Accordingly, states with higher gamma activity contain a risk for such seizures.

8. The hypothesis of a gamma-axis of neuropsychiatric disorders

While the data reported above reflects the state of the art without any integrative interpretation, we will now suggest a hypothesis that integrates these findings in a speculative but functionally meaningful manner. For the understanding of neuropsychiatric disorders, it is important to have a model of the correctly working cognitive functions and their changes during pathology (Gordon, 2001).

The above-mentioned results demonstrate vividly that the significance of gamma activity in neuropsychiatric disorders should not be underestimated. Particularly, we can summarize that negative schizophrenic symptoms, which result from hypoactivity of the mesocortical dopamine system are accompanied rather by a suppression of gamma activity. However, positive symptoms, which result from hyperactivation of the mesolimbic system, are accompanied by an increase in gamma activity. Further, ADHD, for which prefrontal cortex plays a crucial role, is associated with a mild increase of gamma oscillations. A further increase of gamma activity seems to trigger epileptic seizures, which can result from cortical as well as limbic overexcitation. Finally, Alzheimer's disease resulting from pathological changes starting in the limbic area and leading to a progressive amnesia yields suppressed gamma synchronization. The reduced gamma activity in this disorder fits well with the observed memory deficits as predicted by MUM. In Fig. 3, this 'gamma axis' of these disorders is presented and compared with the gamma activity of healthy subjects, which varies intra- and inter-individually depending on various parameters (Busch et al., 2004; Karakas et al., 2003; Strüber et al., 2000). It is

suppressed during sleep (Llinas and Ribary, 1993) and during anesthesia (John and Prichep, 2005; Keller et al., 1990; Madler et al., 1991), whereas in active, attentive states it is increased compared with less 'active' states, as indicated by many cognitive experiments.

The hypothesis of a gamma axis for the above mentioned disorders is supported by a series of further findings. While gamma activity is generated through the interaction of the glutamatergic pyramidal cells and GABAergic interneurons (Traub et al., 1999), dopamine can modulate the gamma activity significantly. For example, Schütt and Basar (1992) showed that dopamine enhanced evoked gamma oscillations in the visceral ganglia of the helix pomatia. Furthermore, gamma activity in rat hippocampus is significantly enhanced by phenylcyclidin that increases the dopaminergic activity by inhibiting dopamine re-uptake (Ma and Leung, 2000). In contrast, the dopamine antagonist haloperidol suppresses the gamma activity in humans (Ahveninen et al., 2000). Hence, a positive correlation exists between the dopamine level and gamma activity. This might depend on the fact that dopamine can modulate both GABAergic (Wang et al., 2002) and glutamatergic (Price and Pittman, 2001) transmission in slices of rat brain and thus could have an effect on the generation of gamma activity.

These findings together with the dopamine hypothesis of schizophrenia support the hypothesis of a gamma axis. Dopamine plays a significant role in schizophrenia. Neuroleptics as effective medications against positive schizophrenic symptoms, block the dopamine D2 receptor (Creese et al., 1976). Other drugs such as amphetamine, cocaine and methylphenidate (Ritalin) that act as dopamine agonists trigger symptoms that are similar to the positive symptoms of schizophrenia (Laruelle et al., 1996). Administration of L-DOPA in Parkinson patients may also result in psychotic symptoms (Missale et al., 1998). Hence, an excessive increase of dopamine seems to lead to both higher gamma activity as well as to positive symptoms, which can be explained by the neuronal causes of the schizophrenic symptoms: An increased dopaminergic activity in the mesolimbic system projecting from the ventral tegmentum to the limbic system leads to the occurrence of positive symptoms (Epstein et al., 1999). Since limbic structures are strongly interconnected with the frontal cortex (Jodo et al., 2005), the changes of the limbic activity can have influences on the frontal cortex activity (Izaki et al., 2003). This might explain the increased gamma oscillations during positive symptoms.

The finding that reduced gamma activity in some studies correlates with negative symptoms of schizophrenia (Lee et al., 2003b) is also in accordance with our hypothesis. Negative symptoms result from a reduced activity of dopaminergic neurons in the mesocortical system, which projects from the ventral tegmentum of the mesencephalon to the cortex (Knable and Weinberger, 1997). This reduced activity could directly lead to decreased amplitudes of gamma oscillations. It is especially plausible for the study with unmedicated schizophrenics (Gallinat et al., 2004), because they were investigated in an early stage during the course of the disease and it is known that approximately 70% of all schizophrenics predominantly demonstrate negative symptoms in the first years of the disease (Hafner et al., 1993).

The close relationship between increased gamma activity and the occurrence of primary epilepsies can be well understood by considering the neuronal mechanisms of cortical excitation. Glutamatergic pyramidal cells are the source of EEG gamma activity in the rat hippocampus and the glutamatergic stimulation in rats leads to the appearance of gamma activity in vivo (Martin, 2001) and in vitro (Whittington et al., 1995). On the other hand, glutamate is also considered to be responsible for epileptic seizures due to its excitatory effect on cortical tissue (Meldrum, 1995; Rogawski, 1992). Hence, we assume that an increase of cortical excitation is reflected by an increase of gamma activity leading to epileptic seizures in extreme cases. This increase can be regulated by dopamine. Therefore, one would expect a positive correlation between dopamine and the occurrence of epileptic seizures, which has actually been demonstrated (Starr, 1996).

Also the relationship between ADHD and gamma activity can be explained by dopamine. It is well described in the literature that dopamine plays an important role in ADHD (Madras et al., 2002). However, it is still debated whether a hypo- or hyper-activation of the dopamine system is to be made responsible (Viggiano et al., 2003). The gamma-hypothesis of ADHD formulated here proposes that an excess of gamma activity is responsible for ADHD, and therefore an increased activity of the dopamine system is the reason. This would lead to the assumption that ADHD children should have a higher tendency for epileptic seizures due to their increased gamma activity. A correlative relationship between ADHD and epilepsy is already documented in the literature. ADHD symptoms were more frequent among children with epileptic seizures (Dunn et al., 2003; Hesdorffer et al., 2004; Thome-Souza et al., 2004). This effect appeared also then, when recently diagnosed epileptic children were investigated (Hesdorffer et al., 2004). Some authors even describe ADHD as 'cognitive epilepsy' (Laporte et al., 2002).

The relationship between neuropsychiatric disorders and the level of gamma activity may be explained by the integration model of gamma activity (Herrmann et al., 2004b). Fig. 4 presents in a simplified manner the various states of integration of the input and the memory representations according to this model. Without a memory representation, there are only weak synaptic connections present between early and higher primary sensory areas (gray arrows in Fig. 4a), which leads to small gamma oscillations. If, however, memory representations are present (black arrows in Fig. 4b), then the feedback leads to stronger gamma oscillations, as they are observed in experiments (Herrmann et al., 2004a).

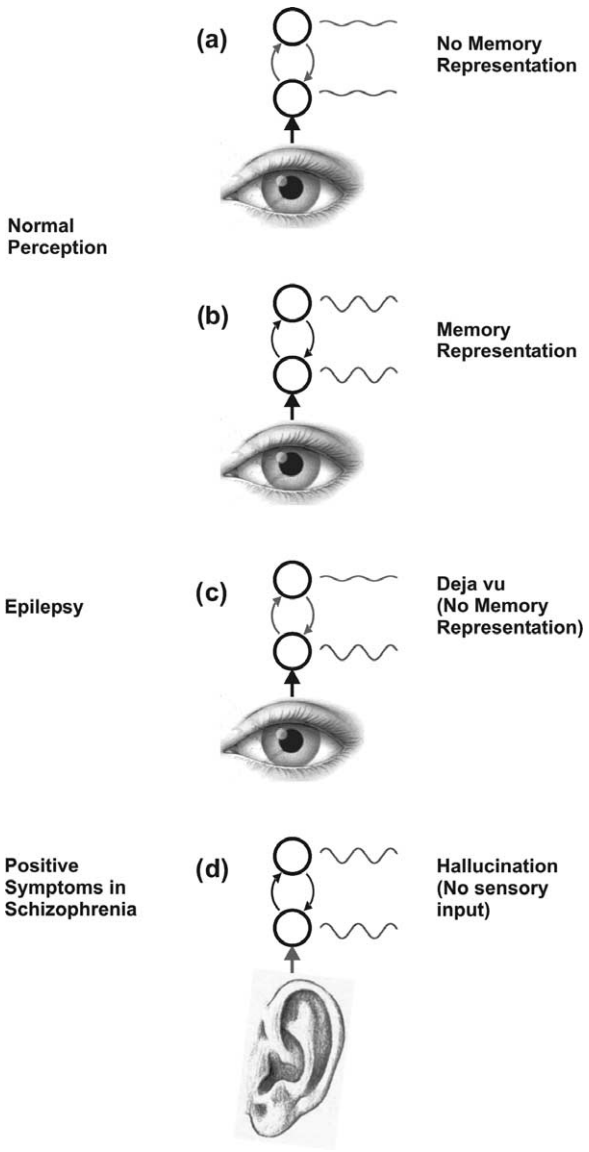

Fig. 4. Model for the occurrence of pathological states due to gamma activity. (a) If a memory representation is missing (gray arrows), then early and higher visual areas are only weakly coupled with each other, which leads to small gamma oscillations. (b) If a memory representation is present (black arrows), then the feedback through the synapses that represent the memory leads to increased gamma oscillations. (c) If high gamma oscillations occur in early visual areas due to an increased dopamine level, then this leads to the feeling that the perceived scene is already known (the déjà vu effect which often occurs in epileptic patients). (d) Hallucinations (positive schizophrenic symptoms) occur, when increased gamma activity occurs within the memory network despite the absence of an adequate stimulus. This may also be caused by excessive dopamine.

This model may also explain the déjà vu phenomena commonly observed in epileptic patients, and the hallucinations observed in schizophrenic patients. Déjà vu is the condition that a totally unknown scene induces the feeling of familiarity (Brown, 2003), which means that no memory representation exists for the perceived stimulus, but despite this a feeling of familiarity is present. There is no superordinate instance (homunculus) in the brain, which evaluates and interprets the brain activity, but the neuronal activity of certain brain areas is equivalent with our memories and perception (Crick, 1994). If an increase or reduction of gamma activity occurs due to a neurochemical disturbance in the brain (e.g. a dopamine imbalance), the brain cannot detect this dysfunction, and we perceive those phenomena, which are represented by increased or reduced gamma activity in a healthy brain. Normally, an increased gamma activity between early and higher sensory areas stands for a perceived scene being known (Herrmann et al., 2004a; b). If the pathologically increased gamma activity reaches a level that is normally present during the perception of known scenes, then this scene generates the feeling of familiarity (Fig. 4 c). Déjà vu is often observed as an accompanying phenomenon in epilepsy (Spatt, 2002). Déjà vu phenomena can, however, also be observed in healthy subjects, whose dopamine levels are increased by medications (Taiminen and Jääskeläinen, 2001), which strongly supports the presented hypothesis.

The occurrence of hallucinations could also be explained in a similar manner. If the gamma activity is increased in schizophrenics due to the increased dopamine release (Fig. 4d), then the patients get the feeling to perceive known sounds (tones, words), because such increased gamma activity is normally only then present, when the auditory input receives feedbacks through its correspondence to the memory content. Every perception is the product of sensory input and endogenous brain processes such as memory comparisons and attention. These mechanisms help us to perceive hidden objects and sounds in a noisy background. However, this mechanism may also lead to hallucinations by intrinsically increased gamma activity in the absence of an input (Behrendt, 2003).

Eventually, negative schizophrenic symptoms such as flat affect might also be explained by the gamma model. Emotionally significant stimuli evoke more gamma activity than neutral stimuli (Keil et al., 2001; Müller et al., 1999). It is probably the result of binding emotionally significant stimuli with memorized consequences in memory. The lack of this gamma increase due to a low dopamine level could result in an emotionally flattened perception of actually significant stimuli.

9. Concluding remarks

As a conclusion, it should be shortly discussed here what type of hypotheses the proposed gamma-axis of psychiatric disorders generates, how they could be verified, and what type of analyses could be carried out for their verification. On the one hand, a physiological e.g. neuronal model could explain the relationships between different disorders, which are already observed such as the increased risk for epileptic seizures in ADHD patients. On the other hand, we can line up further hypotheses. For example, according to our

gamma-hypothesis GABA agonists that are used as antiepileptics should also be helpful in the management of positive symptoms in schizophrenia, because they would suppress the gamma activity by their inhibitory effect. These medications were successfully applied for the management of schizophrenia in the past (Tamminga et al., 1978). However, it should be tested, whether this therapy really reveals a reduction in gamma activity as expected. Additionally, one would expect that during the inter-ictal time between epileptic seizures positive schizophreniform symptoms would occur. The appearance of such symptoms during the course of epilepsy has already been reported (Mace, 1993; Mendez et al., 1993; Sachdev, 1998), but it should be tested, whether increased gamma oscillations also occur during such states.

Naturally, the introduced gamma hypothesis for the described disorders is speculative and goes beyond the presented findings. Nevertheless, the significance of the high frequency oscillations for psychiatric and neurological diseases is well documented, and future experiments will show whether the hypothesis is valid. Additionally, in future studies more attention should be paid to the interindividual differences of gamma activity in healthy subjects as well as in patients.

Acknowledgements

Tamer Demiralp's stay in Magdeburg (Germany) during the preparation of this manuscript was supported by the Alexander von Humboldt Foundation. We want to thank Stefanie Junge and Daniel Lenz for preparing some of the figures.

Appendix A. Measuring and analyzing EEG gamma oscillations

A.1. Requirements

In order to record oscillations of frequencies up to 80 Hz the anti-aliasing filter of the recording hardware needs to be set to a value above that, i.e. to 100 Hz. This at the same time requires a sampling rate of at least 200 Hz. The amplitude resolution of the amplifier should be set to values less than the differences which are to be resolved, i.e. to below 0.1 μV if possible. A more detailed description of these aspects has been published by Herrmann (2003); Herrmann et al. (2005).

Some devices which are frequently found in EEG recording environments, like power outlets, monitors and ceiling lamps are operated on alternating current (AC), which oscillates at 50 Hz in Europe and at 60 Hz in the USA. An electrically shielded chamber (Faraday cage) will reduce the amount to which these fields are induced into the EEG leads. However, inside such cabins only battery-operated devices should be used. Even the EEG amplifier should be operated with rechargeable batteries rather than AC power adapters (they convert AC to DC with residual oscillations from the power line). Monitors can additionally introduce SSVEPs at the monitor refresh rate if operated at high brightness.

Appendix B. Analysis methods

B.1. Spontaneous gamma activity

The spontaneous EEG is usually separated into epochs of 1 sec, which are then transformed into the frequency domain by a Fourier transform. This typically yields a frequency resolution of 1 Hz. Multiple frequency spectra of such 1 s windows can be averaged after transformation.

B.2. Steady-state evoked gamma activity

In order to get a good steady-state response multiple epochs of one stimulation frequency are first averaged and then transformed into the frequency domain.

B.3. Stimulus-evoked and -induced gamma activity

Since stimulus-related gamma activity only peaks briefly after stimulation, it is not advantageous to transform 1 s epochs. Rather a time–frequency representation based on either continuous wavelet transform or a short-time Fourier transform should be used. Due to the small amplitude of the evoked and induced gamma responses, preferably more than 100 trials should be averaged. For evoked activity, single epochs are first averaged and the ERP is then transformed into the time–frequency plane. For induced activity, single epochs are first transformed into the time–frequency plane and then the magnitudes of the transform are averaged to cancel out the phase differences among the single trials.

Evoked activity is often limited to a specific region of the brain, e.g. primary sensory cortices, while induced activity is more widespread. Therefore, it is helpful to view evoked gamma activity in single sensors or averages over few sensors, while induced activity is often visible in averages over many sensors.

Software packages, which offer wavelet transform and have previously been used by the authors, are:

- EEGLAB by Scott Makeig (free: http://www.sccn.edu/eeglab)
- MATLAB - Wavelet Toolbox (commercial: http://www.mathworks.com)
- ASA by ANT Software (commercial: http://www.ant-software.nl)
- Brain Vision Analyser by BrainProducts (commercial: http://www.brainproducts.com)

Spontaneous gamma activity can be recorded during wakefulness with eyes opened or closed without a task for the subjects/patients. Steady-state gamma response can be obtained by applying repetitive stimuli like clicks, tone pips or tones that are amplitude modulated around 40 Hz without a specific task. When a stimulus-evoked or -induced gamma response shall be investigated, however, a task needs to be given for the patients. Since some of the patients are cognitively not challengeable (e.g. Alzheimer patients), a simple and robust task is preferable which yields good results under many circumstances. The oddball task has been used in healthy controls as well as in pathological conditions. It combines a frequent standard stimulus (80%) with an infrequent target stimulus (20%). Evoked gamma responses yield larger amplitudes to target stimuli in the visual (Herrmann and Mecklinger, 2001) as well as in the auditory domain (Debener et al., 2003; Yordanova et al., 1997a,b). The paradigm has successfully been applied to ADHD patients (Yordanova et al., 2001) and schizophrenics (Spencer et al., 2003; 2004).

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