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The role of gamma oscillatory activity in magnetoencephalogram for auditory memory processing

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Ich möchte mich an dieser Stelle ganz herzlich bei meinem Doktorvater Jochen Kaiser für seine Hilfe, sein Vertrauen und seine große Geduld mit mir bedanken.

Außerdem bedanke ich mich bei meiner Familie und meinen Freunden, die mir alle Freiheiten der Welt lassen, um meine Ziele zu verwirklichen.

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1. Introduction

The increasing interest in cortical oscillatory synchronization in the gamma frequency range (~30-100 Hz) in neuroscientific research can be attributed to its putative relevance for a variety of cognitive processes (Engel et al. 2001; Herrmann et al. 2004b; Kaiser and Lutzenberger 2005b; Jensen et al. 2007) as well as to its potential role for brain disorders (Herrmann and Demiralp 2005; Uhlhaas and Singer 2006). To test the notion of gamma-band activity (GBA) as a correlate of object representation, the present study examined stimulus-specific gamma-band components rather than differences between experimental conditions containing numerous stimuli. We used magnetoencephalography (MEG) to assess the maintenance of individual acoustic stimuli during an auditory spatial delayed matching-to-sample task.

The following chapter is subdivided into three subsections that describe the theoretical background to this thesis. Part one gives an overview of cortical oscillatory activity and its assumed relevance for higher cognitive processes. Subsection two includes an introduction to auditory processing and its functional correlates in the human cerebral cortex. The chapter is concluded by outlines of the technical basics of MEG. Chapter three describes the study population, experimental procedure, stimulus material and data analysis. In chapter four, the study results are described. We examined behavioral and MEG data. Concerning the MEG data, we analyzed cortical oscillatory activity and explored correlations between oscillatory activations and task performance. Chapter five consists of a discussion of the results. It is subdivided into three parts: part one on the topographical distribution of GBA in the spatial memory task, part two on gamma activation and task performance and part three on a brief outline of further research questions.

2. Background

2.1 Cortical oscillatory activity

Since the 1920s, electroencephalography (EEG) has been used to record electrical activity non-invasively from the human brain (Berger 1929). This activity is generated by graded postsynaptic potentials (PSPs) of vertically oriented pyramidal cells in the cortex (for more details, see ‘MEG’ section). Berger already recognized that this electrical activity contains a specific rhythmicity. Oscillatory activity can generally be described by two main parameters, frequency and amplitude. Synchronized cortical oscillations have been described as correlates of mental activity (Singer 1993; Klimesch 1996; Sauseng et al. 2008). They can be modulated by changes in psychological and physical conditions and depend on the brain’s degree of maturation (Uhlhaas et al. 2010). Cortical oscillations consist of wavelike patterns in different frequency ranges and are supposed to establish collective behavior of neurons (Buzsáki 2006). Spontaneous EEG/MEG signals consist of different rhythms reflecting the subjects’ activation state. Five major types of continuous rhythmic brain activity have been described: alpha, beta, gamma, delta and theta. The classification is based on the typical frequency range of each frequency band, see table 1. Signal amplitude generally decreases with increasing frequency.

Type	Frequency range	Signal amplitude
Delta	0–4 Hz	Variable
Theta	4–8 Hz	50–100 μV
Alpha	8–12 Hz	10–150 μV
Beta	12–29 Hz	< 25 μV
Gamma	30–100 Hz	1–10 μV

Table 1. Classification of EEG rhythms depending on characteristic frequency ranges and signal amplitudes. Oscillatory activity is mainly classified by the characteristic frequency bands ranging from delta- to gamma-band oscillations.

The following parts of this chapter give short overviews of the importance of well-known frequency ranges such as alpha, beta, delta and theta for particular mental activities. As we have investigated fast cortical oscillatory activity in the gamma band, a more detailed description of assumed functions of gamma activity follows below. Figure 1 gives an overview of typical EEG signals.

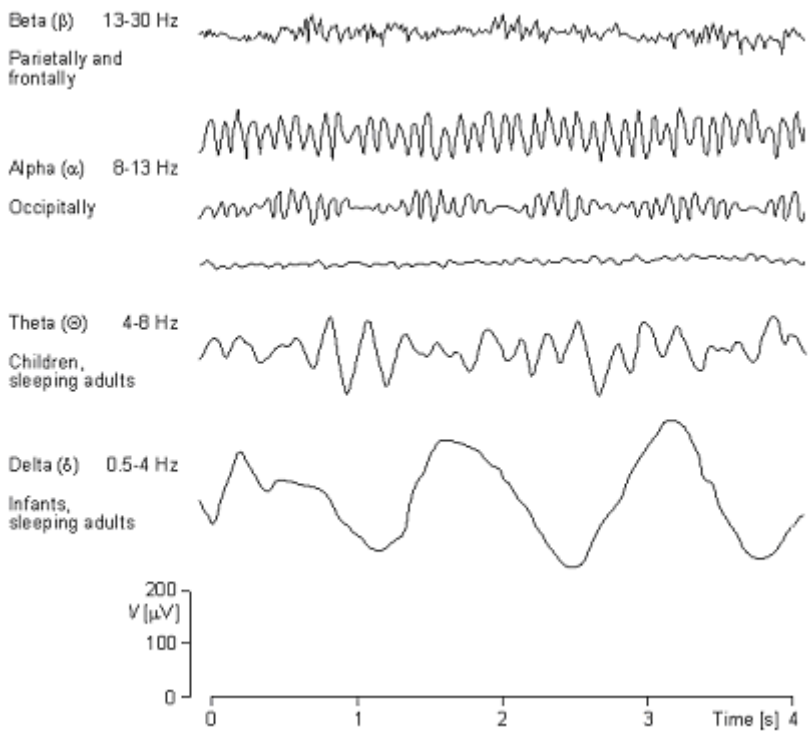

Figure 1. Typical EEG signals representing different brain functions and activation states. The beta range is shown in the first line. Beta can be typically located parietally and frontally. Three different states of alpha oscillations are shown in the second to forth line. The second line shows well accentuated alpha with strict rhythmicity. In the third line, intermittent occipital alpha is displayed. Line 4 shows a phenomenon known as alpha suppression (see text for explanations). The third frequency range displayed is theta. It is associated with sleep onset and can be found in children. Theta is followed by delta, which is associated with deep sleep and immature brain activity. See the following sections for more detailed information on the depicted frequency ranges. (Figure from http://members.arstechnica.com, modified)

2.1.1 Alpha oscillations

Alpha is the frequency range from 8 to 12 Hz and is characteristic for the awake but relaxed state. Consistent alpha rhythms are predominant in occipito-temporal regions and are best detected while subjects close their eyes. Alpha is blocked with increased concentration or attention. When the eyes are

opened, alpha is suppressed. Alpha oscillations are associated with several brain functions. Klimesch et al. (2007) have suggested a role of alpha activity for inhibitory control processes.

Oscillatory alpha activity also plays an important role for short-term memory processes. Leiberg et al. (2006b) have investigated memory load-dependent changes in cortical oscillatory activity during a modified auditory version of the Sternberg paradigm. In this study, memory trials triggered an increase of alpha activity at the end of the delay phase compared to a non-memory control task. Memory-related alpha-increases have also been found in visual tasks (Klimesch 1999; Schack and Klimesch 2002; Busch and Herrmann 2003) and in auditory tasks (Krause et al. 1996; Karrasch et al. 2004; Pesonen et al. 2006). Leiberg et al. suggested that alpha oscillations are relevant for the memorization of multiple stimuli (Leiberg et al. 2006b) as the amplitude of alpha activity was found to increase with working memory load in EEG (Jensen et al. 2002). Leiberg et al. interpreted their findings as a correlate of the top-down control of sensory processing areas.

Alpha-band activity is also supposed to contribute to an active inhibition of task-irrelevant functions. Kaiser et al. (2007c) used MEG to examine activity in the alpha band during an auditory spatial delayed matching-to-sample task. Subjects had to memorize the lateralization angle of a sample stimulus S1 and compare it with a test sound S2 after a delay phase of 800 ms. The authors found alpha synchronization at posterior parietal sensors during the delay phase of the memory condition, while this activity was not present in a non-memory control condition. They concluded that alpha activity during memory maintenance reflects active inhibition of interfering visual/spatial processes (Kaiser et al. 2007c). Haegens et al. (2010) used MEG to assess the temporal dynamics of areas involved in a somatosensory working memory task. They reported an increase of alpha activity over task-irrelevant regions during successful working memory performance. They assumed that alpha-band activity reflected the disengagement of task-irrelevant areas. This notion has been supported by other studies (Jensen et al. 2002; Cooper et al. 2003;

Klimesch et al. 2007). This assumed disengagement contributes to better working memory task performance: Haegens et al. (2010) reported that higher alpha activity correlated with better task performance. Prestimulus posterior alpha activity has been found to correlate positively with somatosensory detection performance (Linkenkaer-Hansen et al. 2004). Thus, Haegens et al. (2010) suggested that disengagement of task-irrelevant regions reflected by alpha-band activity is a necessity for optimal task performance. This notion was also examined by Hanslmayr et al. (2007) who used EEG to assess the electrophysiological correlates of perceiving shortly presented visual stimuli. The authors divided the subjects into two groups: ‘Perceivers’ were able to discriminate between the four different stimuli while ‘Non-Perceivers’ were not. Their results revealed significantly lower prestimulus alpha power for ‘Perceivers’ compared to ‘Non-Perceivers’. They suggested that synchronized alpha activity inhibits the perception of shortly presented stimuli.

Pfurtscheller et al. (1996) suggested EEG synchronization within the alpha band as a possible correlate of deactivated cortical areas. In this idling state, these areas do not process task-relevant information and thus are inhibited. This idea of alpha-band activity representing a resting or idling state was already suggested by Adrian and Matthews (1934). This notion is underlined by an increase of synchronized mu rhythms over the primary hand area during visual processing or foot movement as these tasks do not involve the primary hand area (Pfurtscheller et al. 1996). By analogy, occipital alpha oscillations are more pronounced during the state of closed eyes and decrease with opened eyes.

To summarize these findings, the occipital alpha rhythm can be regarded as a resting or idling rhythm of visual areas (Kuhlman 1978; Pfurtscheller 1992). By contrast, Klimesch et al. (1999) and Jensen et al. (2002) suggested that alpha activity rather reflects active inhibition of areas that could disturb performance in, e.g., memory tasks. Niedermeyer (1990) and Tiihonen et al. (1991) suggested that alpha activity in auditory areas reflects an idling state. The common feature of all these alpha rhythms is their blocking or decrease when

these areas are activated regardless of the cortical area in which they are located (Pfurtscheller et al. 1994).

2.1.2 Beta oscillations

The beta band is defined as the range between 12 and 29 Hz. It occurs in association with active thinking and concentration. General or frontal beta activity can be provoked by pharmaceutics such as barbiturates. Beta oscillations have also been associated with motor activity. Beta activity over primary motor areas drops shortly before and during movements and reoccurs when motor actions are stopped (Neuper and Pfurtscheller 2001). Thus, it is linked to movement preparation processes (Zhang et al. 2008). Kaiser et al. (2003b) studied the time courses and topographies of sensorimotor activations to behaviorally relevant, lateralized sounds. They used magnetoencephalographic event-related beta desynchronization (ERD) as a correlate of movement preparation processes. Their results suggest an important role of beta oscillations for an early activation of motor networks.

Furthermore, animal studies suggest an involvement of beta activity in attentional mechanisms (Bekisz and Wrobel 2003). Zhang et al. (2008) also reported an increase of beta activity during response inhibition in decision tasks examining macaque monkeys. These findings were supported by a recent study in humans examining decision making (Cohen et al. 2009).

2.1.3 Theta oscillations

Theta ranges from 4 Hz to 8 Hz and shows high amplitudes. It is associated with drowsiness and states such as trance, hypnosis, deep day dreams and light sleep. Theta is more pronounced in children than adults. Theta oscillations have been a topic of several studies in patients with schizophrenia. These patients showed reduced oscillatory activity in the theta range at rest and during

memory tasks (Doege et al. 2009; Haenschel et al. 2009). These findings underline possible functions of theta activity in cognitive tasks such as information processing.

Oscillations in the theta range have also been related to control processes in different memory systems (Klimesch et al. 2008; Klimesch et al. 2009). Human theta oscillations have been investigated in many different studies over the last decades (Klimesch et al. 1996; Klimesch et al. 1997; Klimesch 1999; Kahana et al. 2001; Raghavachari et al. 2001). Theta oscillations have been suggested to control access to episodic memories (Klimesch et al. 2009) and to play a vital role for the encoding of episodic information (Weiss et al. 2000; Fell et al. 2003b; Summerfield and Mangels 2005; Axmacher et al. 2006). Doppelmayr et al. (2000) have also shown a positive correlation between increased theta-band power and episodic memory performance in a recognition task. They suggested that an early time-locked theta response allows coordination of different encoding processes and contributes to successful performance in memory tasks. Sauseng et al. (2004) observed coupling between prefrontal and temporo-parietal brain areas within the theta band during a working memory task. They assumed that working memory functions depend on prefrontal-temporal networks and are mediated by theta frequency coupling.

2.1.4 Delta oscillations

Delta activity from 0 to 4 Hz occurs in deep sleep and is the predominant frequency in infants. During slow-wave sleep, delta oscillations are associated with synchronization processes facilitating neuronal interactions (Dang-Vu et al. 2008). Delta activity in awake adult subjects can be a sign of pathological brain processes. Recent studies have shown an importance of delta activity in schizophrenia. Ince et al. (2009) used MEG to assess oscillatory brain activity during a working memory task to discriminate between patients with schizophrenia and healthy control subjects. They found distinct activation patterns of brain oscillations during the maintenance period of the memory task

in the delta, alpha and beta range. In particular, patients showed ERD in the delta band over dorso-frontal areas, while controls showed event-related synchronization (ERS). These patterns served to classify patients and healthy controls.

Another study focused on EEG rhythms preceding spontaneous spike-wave discharges in epilepsy. Sitnikova and van Luijtelaar (2009) found a significant increase in delta and theta activity preceding spike-wave discharges in rats. These results implicate a correlation between delta activity and impaired brain activity in epilepsy. The authors suggested that spike-wave discharges in epilepsy might derive from a delta-theta EEG background. Mormann et al. (2008) observed independent delta and theta rhythms in subregions of the human medial temporal lobe in epilepsy patients with unilateral hippocampal sclerosis. They discussed a possible importance of interactions of delta and theta rhythms for memory processing which can be impaired in epilepsy patients (Fell et al. 2003b).

2.1.5 Gamma oscillations

Fast gamma oscillations in the range of 30–100 Hz have first been described by Jasper (1936), but their functional significance is not yet completely understood. The current understanding of fast cortical oscillations is that they reflect synchronous activity of large assemblies of rhythmically firing neurons which is associated with different cognitive processes (Engel et al. 2001; Kaiser and Lutzenberger 2003; Jensen et al. 2007). Buzsáki (2006) refers to synchronization in the gamma band to explain typical neuronal assembly behavior in the awake brain. As the present study focussed on this frequency band, research on gamma activity will be reviewed in detail in the following sections.

2.1.5.1 Perception

Regarding the huge stimulus variety all individuals constantly face, it is hard to imagine specialized neurons for the representation of every single stimulus. It has been proposed that the specific combination of stimulus properties corresponding to one object could be encoded by different neuronal assemblies located in specialized brain areas. These distributed cell assemblies could represent objects by communicating via synchronized gamma activity (Milner 1974; von der Malsburg and Schneider 1986; Singer and Gray 1995). In this context, it should be stressed that perception and object representation are more than just a passive reproduction of stimulus input in primary sensory areas but, in contrast, involve larger neuronal networks (Eckhorn et al. 2004).

GBA is thought of as a carrier of cortical information, communication and integration (Tallon-Baudry and Bertrand 1999; Kaiser and Lutzenberger 2003; Herrmann et al. 2004b; Fries 2005; Jensen et al. 2007). In earlier EEG and MEG studies, GBA was identified as a correlate of synchronized activity of cortical networks representing visual objects or object features. Over the last decades, an astonishing number of studies have examined the human or animal cortex. These studies have revealed small cortical subregions responsible for the representation of different input information. These specialized areas have distinct connections to other structures of the brain and could be shown for the somatosensory (Doetsch 2000), the motor (Kalaska and Crammond 1992), the visual (Zeki et al. 1993) and the auditory cortex (Kelly et al. 1991). All these differently specialized cortical areas respond to a defined subset of stimulus features. And even though they contribute to a complex perceptional process, they seem to respond very selectively. This evokes two crucial questions regarding perceptional processes: where and how are different object features of perceived input represented in the brain and how do these specialized cortical subregions communicate with other brain structures?

This process is referred to as the feature binding process and is triggered by external input. In visual search tasks, Tallon-Baudry et al. (1997) analyzed neuronal correlates of internal object representation. The non-phase-locked gamma activity discovered in the search tasks was suggested to serve two roles: binding of elementary features for a meaningful object and activation of neuronal assemblies coding an attended object.

In an early study on GBA, Gray et al. (1990) analyzed cortical activation in anesthetized cats that were presented with coherently moving bars. Synchronization in the gamma band could be shown for the coherently moving bars but not for independently moving patterns. These findings were supported by other studies investigating stimulus-dependent phase coupling in the gamma range in visual areas of cats (Eckhorn et al. 1988; Molotchnikoff and Shumikhina 2000). Later, similar findings were observed for intracranial recordings from awake monkeys (Eckhorn et al. 1993; Kreiter and Singer 1996) and in human EEG (Lutzenberger et al. 1995; Müller et al. 1997). These studies showed that synchronization in the gamma band was not induced by anesthesia but was even more pronounced in awake and attentive animals (Kreiter and Singer 1992, 1996; Fries et al. 1997; Friedman-Hill et al. 2000; Maldonado et al. 2000).

Singer and Gray (1995) have shown that specialized cell assemblies synchronize at distinct frequencies. Several authors working with unit recordings in animals have suggested an important role of oscillatory synchronization in the gamma band in neuronal assemblies representing the same object (Singer and Reed 1997). Tsunoda et al. (2001) studied object representation in macaque monkeys by visually presenting complex natural objects and simplified models thereof. After analyzing a combination of optical imaging and extracellular recordings, their results proposed a scheme in which an object is represented by different combinations of activated and inactive neuronal assemblies responsible for different object features. This activation could be detected in the gamma band and emerged from synchronized neuronal assembly firing.

Gamma-band oscillations do not only play an important role in object recognition, but are also involved in higher cognitive tasks such as auditory word perception. Pulvermüller et al. (1996) used MEG to assess gamma-band responses to the presentation of meaningful words and matched pseudowords. They found a depression of activity in the low gamma band at approximately 30 Hz after the presentation of pseudowords but not after the presentation of words. The authors concluded that the task-dependent patterns of GBA reflected different cognitive processes caused by words and pseudowords. Palva et al. (2002) examined the differences in perception of speech compared to non-speech sounds. They showed that stimulus-induced GBA after speech sounds peaked earlier in the left than in the right hemisphere. After the presentation of non-speech sounds, GBA peaked earlier in the right hemisphere. They suggested that evoked GBA could be sensitive to high-level stimulus properties and might reflect the neural representation of speech sounds.

Swettenham et al. (2009) examined the role of gamma oscillations for motion detection in a visual task. They used MEG to record gamma oscillations in human early visual cortex when subjects were presented with either stationary or moving stimuli. They could show motion-induced frequency increases in the gamma range. They concluded that early visual areas encode moving or stationary objects at distinct gamma frequencies.

By analogy to the visual system, several studies have examined the role of gamma-band oscillations for auditory perception both in animals and humans. In several MEG studies, Kaiser et al. (2002) investigated the notion of different specialized brain areas for the processing of either auditory pattern or spatial information. They presented sounds at different lateralization angles. Enhanced GBA to lateralization changes was found over temporo-parietal cortex at distinct frequencies between 63 and 83 Hz. These findings replicated the results of a previous study showing the involvement of posterior temporo-parietal areas in auditory spatial processing (Kaiser et al. 2000b).

Gurtubay et al. (2006) used an auditory search task to determine whether oscillatory GBA modulates afferent information. Subjects had to detect a randomly appearing silent period in a rhythmic auditory sequence. This task induced non-phase-locked gamma oscillations in temporo-parietal areas. The authors suggested that this induced activity is a neuronal correlate of stimulus detection and memory processes. Their results also revealed a positive correlation of GBA and task performance.

Several intracerebral electroencephalography (iEEG) studies in patients have found evidence for GBA in higher-order regions such as Broca's area and auditory and prefrontal cortices (Mainy et al. 2008). Jensen et al. (2007) interpreted these findings as an indicator for communication between sensory and higher-order cortical regions. This notion is supported by further findings by Mainy et al. (2008) who demonstrated simultaneous gamma-band responses to letter presentation in Broca's area and visual regions, respectively.

2.1.5.2 Attention

Brain activity in general is modulated by different states of activation and arousal. Performance in, e.g., memory tasks strongly depends on these modulations. This process of focusing is referred to as 'attention'. Attention is the cognitive process of selecting one aspect of the environment while ignoring others (Anderson 2004). Attention can target different sensory systems: it can be either concentrated on visual, auditory, tactile, any other input or a combination thereof. Human sensory systems have limited processing capacities. Attention prevents our consciousness from being exposed to excessive amounts of information and helps to detect attended stimuli or stimulus features which contain important information for behavior and decision-making. Thus, attention plays a vital role in effective cognitive processes.

At the physiological level, attention is thought to enhance the relative ability of neurons representing specific stimuli in sensory cortical areas to affect downstream cortical areas (Treue 2001). One possible model uses neuronal synchronization to explain this modulation of brain activity. Neurons receiving synchronized input at various synapses are more likely to fire (Salinas and Sejnowski 2001). Fries et al. (2001) have suggested that this synchronized neuronal activity is mediated by high gamma activity. As one of the neuronal correlates of attention is enhanced firing, different studies have examined neuronal activity during the unattended presentation of a specific stimulus. The experimental condition consisted of the presentation of the same stimulus, but the subjects had to focus their attention on the stimulus. Using this paradigm, differences in neuronal firing could be attributed to a change of mental state rather than to differences in the perceived information. Womelsdorf et al. (2006) examined receptive visual fields in rhesus macaque monkeys. They demonstrated that focussing voluntary perception effectively improves visual perceptive processes.

In another study, Womelsdorf et al. (2007) have shown that attention processes rely on a selective synchronization of rhythmic responses of neurons specifically tuned to features of attended stimuli. They have also shown a positive correlation between the strength of neuronal synchronization in the gamma range, perceptual accuracy and behavioral efficiency. These results support the model of neuronal synchrony in the gamma range being one of the cellular mechanisms underlying attention processes and relevant behavioral changes.

Similar conclusions were also drawn from several EEG and MEG studies in humans. GBA was higher for attended visual and somatosensory stimuli than for unattended stimuli (Howard et al. 2003; Tallon-Baudry et al. 2005; Bauer et al. 2006). Mainy et al. (2007) conducted an MEG study which showed increased GBA in cortical areas representing attended stimuli for both visual and auditory stimulation. An increase of gamma-band responses has also been found in intracranial recordings in the lateral occipital cortex and the fusiform gyrus in

subjects focusing their visual attention towards the position of an attended target (Tallon-Baudry et al. 2005).

These results strongly support the notion that neuronal synchrony in the gamma band mediates attention mechanisms (Fell et al. 2003a). Taking into account the results quoted above, attention thus involves synchronized activity in the gamma band to tune neuronal activity to specific sensory input. This information can then later be used for higher cognitive functions like memory or decision-making.

2.1.5.3 Memory

In order to cope with everyday tasks, basic memory functions are required: information has to be perceived, then memorized and, if needed, retrieved to be used again. There have been various studies on visual and auditory working memory tasks looking for the precise topographical and temporal underpinnings of these functions.

2.1.5.3.1 Short-term memory

Decision-making in daily life often depends on the comparison and assessment of stored information involving different types of memory. The ability to store information for a few seconds so that it can be used in the service of ongoing cognitive tasks is referred to as working or short-term memory. It is defined as the capacity to maintain and manipulate information that is no longer present in the environment (Baddeley 1992).

I have already described in the ‘Perception’ section that the representation of a specific stimulus is thought to rely on synchronously oscillating assemblies of neurons. A putative mechanism for maintenance of this stimulus information in

short-term memory is a memory trace established by sustained oscillations (Tallon-Baudry et al. 1998). This explanation is in line with Hebb's (1949) proposal that neuronal representations can be sustained by persistent firing of recurrently connected neurons.

Thus, synchronized oscillatory activity in the gamma band seems to play an important role in working-memory tasks. This hypothesis was supported by findings of Tallon-Baudry et al. (1998). They used EEG to assess induced GBA during the delay phase of a visual short-term memory task in humans. Enhanced GBA could be observed at both occipito-temporal and frontal electrodes during the maintenance of abstract visual shapes while it was absent in a control task which did not require memorization (Tallon-Baudry et al. 1998). Tallon-Baudry et al. hypothesized that GBA seems to be a specific functional correlate of sustained object maintenance in short-term memory. The results are depicted in Figure 2.

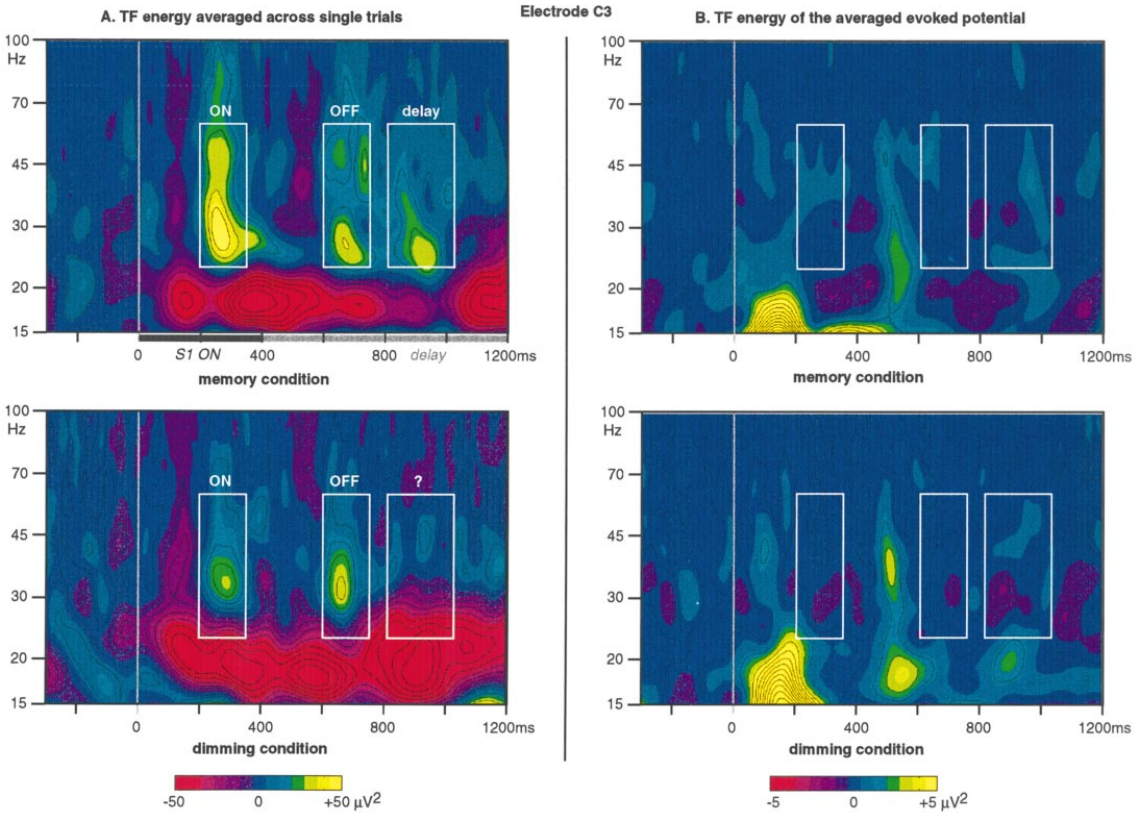

Figure 2. (A, left column): time-frequency (TF) plots of the energy at electrode C3, averaged across single trials for all subjects for the memory condition (upper graph) and the control (= dimming) condition (lower graph). Time is shown on the abscissa; frequency is displayed on the ordinate using a logarithmic scale. Energy differences are shown using a color scale: yellow codes for an increase of energy while red shows a decrease. Enhanced high-frequency activity could be identified at three time points: (1) 280 ms after stimulus onset (ON response), it was higher in the memory than in the control condition; (2) 680 ms after stimulus onset (OFF response), similar in both conditions; and (3) 700-1000 ms after stimulus onset during the retention phase, in the memory condition only. (B, right column): TF-plots of the energy of the averaged evoked potential at electrode C3, grand average across subjects for memory condition (upper line) and control (= dimming) condition (lower line). Only phase-locked activities that appear at a fixed latency from one trial to the next can be identified in these plots. These results suggest that the three areas of enhanced GBA in (A) correspond to induced activities. These activities appear with a latency jitter with respect to stimulus onset time from one trial to the next. (Figure from Tallon-Baudry et al. 1998)

To assess whether the memory-related GBA was temporally sustained, Tallon-Baudry et al. (1998) replicated their visual search task with variable delay durations. They found that active maintenance of abstract visual shapes in short-term memory was characterized by enhanced gamma-frequency power at occipital EEG electrode sites. The time course of this activity varied according to the duration of the retention interval (Tallon-Baudry et al. 1999). These results underlined the importance of oscillating synchronized cell assemblies for the formation of short-term memory.

An MEG study identified sustained GBA in a spatial, delayed match-to-sample task (Jokisch and Jensen 2007). Subjects had to memorize the orientation of faces during a 3-s retention period. Jokisch and Jensen found sustained gamma activity during the retention period occurring over occipital areas. The information presented so far suggests that synchronized oscillatory activity in visual cortex, e. g. over occipital areas, is involved in the maintenance of visual information in short-term memory. However, higher-order areas are probably also involved in memory processes (Jokisch and Jensen 2007).

While the studies quoted above have investigated the role of gamma oscillations during visual short-term memory, several studies have examined auditory short-term memory. In precursor studies to the present one, increased GBA was detected during auditory short-term memory tasks. MEG revealed oscillatory GBA over left parietal cortex during the retention period. Additionally, gamma-band coherence was enhanced between left parietal and right frontal sensors (Lutzenberger et al. 2002). These findings supported the notion of memory being established by synchronized oscillatory activity in a distributed auditory working memory system. Kaiser et al. (2003a) used MEG to examine GBA during an auditory pattern memory task. They found memory-related increases in gamma-frequency power over left inferior frontal and anterior temporal cortex during the retention period.

Two other studies showed evidence for memory-related sustained GBA outside early sensory cortices. Howard et al. (2003) and Mainy et al. (2007) asked patients to memorize visually presented letters. They both reported an increase of GBA with memory load in nonvisual cortical areas. Mainy et al. (2007) found sustained gamma oscillations in regions associated with phonological processing including Broca's area and both auditory and prefrontal cortices.

These findings suggest that synchronized oscillatory activity in the gamma band in sensory and association areas contributes to the maintenance of stimulus information in short-term memory. Another important finding is that the localization of this activity depends on the type of information that has to be retained. GBA during short-term memory tasks may thus reflect a higher-level representation of relevant information (Jensen et al. 2007).

2.1.5.3.2 Long-term memory

While short-term or working memory is needed to store information for short periods of a few seconds so that it can be used in ongoing cognitive tasks, long-term memory serves as a permanent storage of memories. This information is handled by large distributed networks of cortical areas (Martin et al. 1996). These networks contribute to different kinds of information processing, including the comparison of known objects with newly perceived stimulus information.

There is evidence to suggest that synchronized oscillatory activity in the gamma band plays a role in encoding long-term memory by modifying synaptic connections. This was first described as a mechanism for learning and memory on the basis of a theoretical analysis by Hebb (1949) who proposed that if a neuron influences the activity of other neurons, their synaptic connection will be potentiated. By contrast, synaptic depression can occur if two neurons are not sufficiently coactive (Stent 1973; Sejnowski 1977). These two theoretically

proposed forms of synaptic plasticity have their experimental correlates in long-term potentiation (LTP) and long-term depression (LTD). In a previous study, it has been shown that synaptic plasticity is modulated by the timing of synaptic discharges with respect to the phase (e. g. peak or trough) of oscillatory gamma activity (Wespatat et al. 2004).

Human EEG and MEG studies concerning GBA and effective formation of long-term memory have been performed by Gruber et al. (2004), Osipova et al. (2006) and Sederberg et al. (2003; 2007). They have demonstrated that the presence of oscillatory GBA at encoding positively correlated with successful retrieval from long-term memory. They hypothesized that synaptic changes in downstream areas could be induced by synchronized gamma activity in early visual areas. Similar results have been found using intracranial recordings in epileptic patients. Fell et al. (2001) found that successful formation of long-term memory corresponded with gamma-band synchronization in the hippocampus. The studies presented above have examined the role of oscillatory activity in the gamma band for the encoding into long-term memory. On the other hand, gamma-band oscillations have also been shown to play an important role for retrieval from long-term memory (Gruber et al. 2004; Osipova et al. 2006). The subjects were shown different stimuli they had to memorize. Correctly remembered stimuli caused an increase of GBA compared with unknown items. Hermann et al. (2004a) and Osipova et al. (2006) have suggested that gamma oscillations in the occipital cortex reflect visual representations of recalled objects.

All the studies quoted above have provided evidence for the role of gamma-band oscillations for effective encoding into and retrieval from long-term memory. Oscillatory activity in the gamma band may represent a means of creating and accessing memory traces in the human brain.

2.2 Auditory processing

Audition is besides vision one of our most powerful sensory systems and it contributes to various everyday tasks. Auditory information is not just supplementary to visual input - even when objects are not visible, we can most often distinguish their origin and properties. These two different qualities, spatial localization and auditory patterns, both have to be perceived and processed to form one coherent perception of a sound source. Exploring the auditory system with functional brain imaging methods as EEG, MEG or functional magnetic resonance imaging (fMRI) requires general knowledge about functional brain structure. Therefore, a short overview of the assumed localization of brain areas involved in auditory perception is given in this section.

Auditory perception and processing begins at the outer ear where sound waves are reflected and attenuated by the folds of cartilage. This adds information about the localization of sound sources. The signal then enters the ear canal toward the tympanic membrane which marks the beginning of the air-filled middle ear. The sound waves are transmitted by three small bones – the malleus, incus and stapes – on another membrane called the oval window. This is the beginning of the inner ear containing the cochlea. The organ of Corti in the cochlea transforms the mechanical sound wave information into electrical signals. This is mediated by hair cells which are afferently connected to primary auditory neurons. These form the vestibulocochlear nerve. The following auditory pathway includes several intermediate stages where sound information is further processed. First, the information is processed at the level of the brainstem in the cochlear nucleus and in the superior olivary complex. Sound information travels to the inferior colliculi and is then transmitted to the medical geniculate nucleus which is part of the thalamic relay system. Auditory information is relayed to the primary auditory cortex which is located in the temporal lobe. The perception and processing of auditory signals takes place in the range of the superior temporal gyrus (STG). This region is split in primary (Brodmann area 41) and secondary (Brodmann area 42, 22) auditory cortex.

The primary cortex has a frequency-dependent (tonotopic) structure. The secondary auditory cortex or association area plays an important role for the processing of more complex acoustic signals (Hudspeth 2000; Trepel 2008).

2.2.1 Animal studies

The structures presented above form the auditory system responsible for perception and first processing steps of auditory information. By contrast, higher-order processing of stimulus information takes place in specialized brain regions that are located outside of the primary cortex. These regions process distinct stimulus features and interact with each other in order to form coherent perception. A similar specialization has been shown for the visual system. ‘What’ and ‘where’ streams for visual perception have been first described in nonhuman primates. This notion was based on different behavioral effects of brain lesions in monkeys (Ungerleider et al. 1982). These findings have led to the identification of a ventrolateral object and a dorsolateral spatial processing stream (Ungerleider et al. 1982; Wilson et al. 1993; Webster et al. 1994).

Rauschecker (1998b) proposed the presence of similar pathways for auditory processing in the macaque monkey. He hypothesized two separate streams for the processing of spatial information and patterns, respectively. Romanski et al. (1999) identified such pathways in macaque monkeys. They combined microelectrode recordings with anatomical tract tracing to assess the existence of two separate auditory streams. They found evidence for the presence of two different streams originating in separate auditory fields of the superior temporal region and projecting to distinct regions of the frontal lobes. The dorsal stream projects from the caudolateral field to caudal dorsolateral prefrontal cortex, while the ventral stream targets rostral and ventral prefrontal areas from the anterolateral field. As these target regions have been described as either spatial (dorsal prefrontal region) or non-spatial (ventral prefrontal region) functional domains (Goldman-Rakic 1987; Wilson et al. 1993; Goldman-Rakic 1996), Romanski et al. (1999) hypothesized that the two separate streams have

different functions. The dorsal stream could serve as a ‘where’ stream, while the frontal pathway processes ‘what’ information. A simplified model of the two separate auditory streams is depicted in Figure 3.

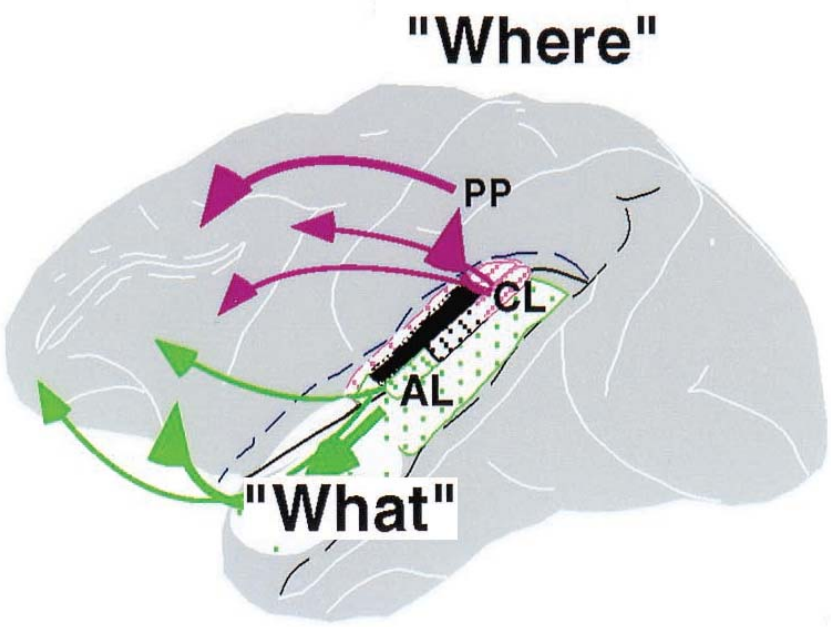

Figure 3. Schematic model of ‘where’ and ‘what’ streams in the auditory cortical system of primates. The dorsal ‘where’ stream is illustrated by the purple arrows, the ventral ‘what’ stream is shown in green. PP, posterior parietal cortex; CL, caudolateral area; AL, anterolateral area. (Figure from Rauschecker and Tian 2000, modified)

These findings were also examined using single-cell recordings in monkeys. A study by Tian et al. (2001) investigated the existence of a specialized ‘where’ region in the auditory cortex by identifying regions in which neurons show greater specificity for auditory spatial information than others. Using response profiles of single neurons to differently located sound sources, they found a clear dissociation of auditory spatial tuning between anterior and caudal belt in the auditory cortex. Specificity for auditory spatial properties was found to be most pronounced in the caudolateral field, while it was lowest in the anterolateral field. This has also been shown in other studies (Rauschecker et al. 1997; Recanzone et al. 2000). These results have supported a functional

specialization within the cortex of monkeys, as the caudolateral field could be regarded as the source of a dorsally oriented ‘where’ stream (Tian et al. 2001). On the other hand, the anterolateral field seems to be part of a rostrally oriented pathway that is supposed to be specialized in the processing of ‘what’ properties of auditory information (Belin et al. 2000; Binder et al. 2000) rather than spatial information (Tian et al. 2001). This supports the notion of specialized higher-order processing streams for auditory perception in non-human primates (Romanski et al. 1999; Rauschecker and Tian 2000). These studies have supported the notion that auditory processing is functionally separated in the primate cortex. This separation has also been investigated in several studies in humans.

2.2.2 Human studies

By analogy to the findings in non-human primates, a model of two parallel auditory processing streams has been proposed in recent human brain research: a ventral pathway located in the temporal lobe and responsible for auditory pattern processing and a dorsal pathway in the parietal lobe which processes auditory spatial information (Rauschecker 1998b).

Arnott et al. (2004) have reviewed this hypothesis in a meta-analysis of 36 auditory studies in humans using fMRI and positron emission tomography (PET). The studies were divided into either spatial studies involving different sound locations or non-spatial studies involving different sound patterns in identical position. The results of this meta-analysis were consistent with the auditory dual-pathway model (Rauschecker and Tian 2000). The authors concluded that auditory spatial information is processed in the lateral inferior parietal lobe (IPL), superior frontal sulcus (SFS) and posterior areas of the temporal cortex. Even though not all of the areas mentioned above were activated in every spatial study, Arnott et al. (2004) suggested them to be part of a neuronal network processing auditory spatial information. Conversely, the anterior temporal lobe seemed to play an important role for non-spatial auditory

tasks, as this area was almost exclusively involved in non-spatial processing. These findings were in line with the results from previous animal studies (Romanski et al. 1999; Rauschecker and Tian 2000; Romanski and Goldman-Rakic 2002). Arnott et al. (2004) concluded that the reviewed results strongly support the notion of specialized spatial and non-spatial processing networks in the human brain.

Altmann et al. (2007) tested this proposed segregation of human auditory processing with EEG and fMRI in the same subjects. They listened to sequences of repetitive spatial animal vocalizations. The stimuli consisted of two different animal vocalizations and were spatially localized either 90° to the left or to the right. Both vocalization types were presented at both lateralization angles, so the subjects were stimulated with four different stimuli. The authors used a roving-stimulus mismatch paradigm to contrast the different conditions. Possible changes consisted of a simple location or pattern change or a combined location and pattern change. FMRI revealed significantly increased responses in the bilateral anterior superior temporal gyrus and superior temporal sulcus, the planum polare, lateral Heschl's gyrus and anterior planum temporale for pattern changes. Changes in sound source location resulted in significantly increased fMRI responses in bilateral posterior superior temporal gyrus and planum temporale. In the EEG analysis, Altmann et al. (2007) found that location changes were processed faster than pattern changes (see also Kaiser et al. 2000a). They suggested that the human brain is segregated in different auditory processing streams. Apparently, anterior parts of the superior temporal lobe play an important role for sound pattern processing while more posterior parts of the superior temporal lobe are involved in spatial processing of auditory information.

Previous MEG studies have also found reproducible evidence for this structure of auditory processing areas. This segregation in different processing streams could be shown in passive change detection tasks. Kaiser et al. (2000b) used an auditory oddball paradigm. They presented a monosyllabic word which was either right- or left-lateralized and compared it to the same word presented at

the midline plane. Higher amplitudes of evoked mismatch fields were found contralaterally to the side of the deviant stimulus. In the left supratemporal plane, the response was faster for contralateral than ipsilateral deviants, while there was no difference for the right-hemisphere response. Kaiser et al. (2000b) reported induced GBA over right posterior parietal and posterior temporal regions for both deviants. In homologous left-hemisphere regions, increased GBA was only shown for rightward sound-source shifts. The authors concluded that their findings might support the notion of posterior parietal networks playing an important role for the coding of auditory space.

In a subsequent study, Kaiser et al. (2002) used MEG to examine gamma-band responses to changes in auditory patterns. They presented consonant-vowel syllables, animal vocalizations and artificial noise stimuli which differed in their spectral composition. They found increased GBA over the left anterior temporal/ventrolateral prefrontal cortex for all types of stimuli. The authors concluded that these activations supported the role of anterior temporal/prefrontal regions in the processing of auditory pattern changes.

Auditory short-term memory tasks also supported the existence of different auditory processing streams. Lutzenberger et al. (2002) used pairs of filtered noise stimuli in a delayed matching-to-sample task. They presented two stimuli S1 and S2 with an interstimulus interval of 800 ms. Both stimuli had different possible lateralization angles. Subjects had to judge whether the lateralization angle of the second stimulus differed from the first one. In a control condition, they had to detect a possible sound volume change. The authors observed increased GBA in MEG sensors over the parietal cortex and enhanced gamma-band coherence between left parietal and right frontal sensors in the delay phase of the memory task. They assumed that this parietal activation contributes to the processing of audiospatial information in the auditory dorsal stream. Lutzenberger et al. suggested that the enhanced gamma-band coherence between parietal and frontal regions might reflect increased coupling between areas forming a working memory network. Furthermore, they concluded that GBA over inferior frontotemporal regions during the volume

change task might represent auditory pattern encoding in auditory ventral stream areas.

Kaiser et al. (2003a) used an auditory pattern memory task to assess GBA with MEG while subjects performed a working memory task requiring same-different judgments about pairs of syllables. The syllables differed either in voice onset time or formant structure and were presented using an interstimulus interval of 800 ms. In a control task, subjects had to detect possible spatial changes of the background noise. In the memory condition, Kaiser et al. (2003a) found an increase in GBA over left inferior frontal/anterior temporal regions during the delay phase and in response to the second stimulus. GBA was also enhanced over prefrontal cortex at the end of the delay period of the memory condition. The results are depicted in Figure 4. Furthermore, gamma-band coherence between left fronto-temporal and prefrontal sensors was enhanced during the delay phase. The authors concluded that oscillating networks in fronto-temporal cortex contribute to a putative auditory ventral pattern processing stream.

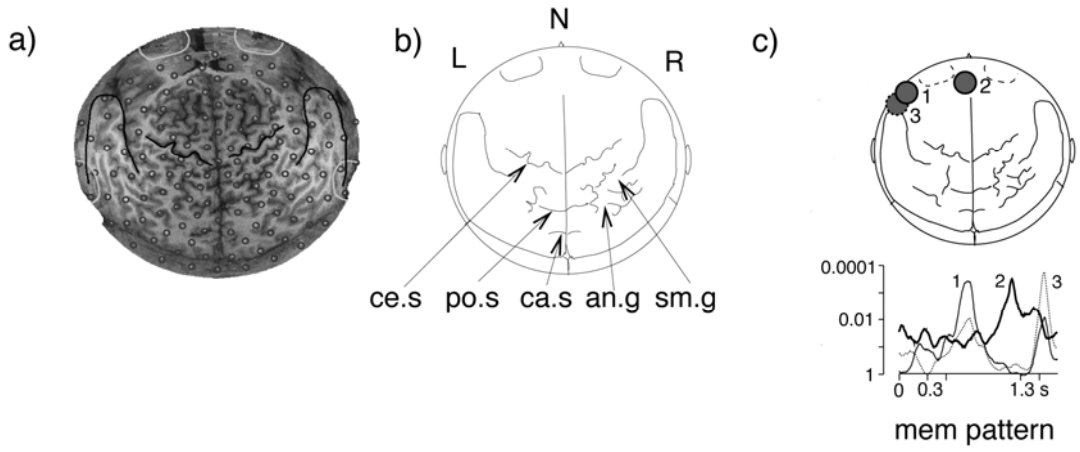

Figure 4. Topography and time course of magnetoencephalographic GBA during an auditory pattern short-term memory task. (a) Projection of MEG sensor positions (small circles) onto a two-dimensional magnetic resonance image of the brain surface (seen from above, nose up). (b) Map with anatomical landmarks derived from the magnetic resonance image (ce.s, central sulcus, po.s, parieto-occipital sulcus, ca.s, calcarine sulcus, an.g, angular gyrus, sm.g, supramarginal gyrus). (c) The map shows the locations

of MEG sensors projected onto the map from part (b) of the figure to depict the topography of significant GBA increases. The graph below shows the time course of statistical differences (*p*-values) between experimental and control condition for each of the sensors (see numbers to assign *p*-value curves to sensor positions). Midline frontal GBA was increased during the auditory pattern short-term memory task (mem pattern) at 67 ± 2.5 Hz in addition to left inferior frontal, putative ventral stream areas. (Figure from Kaiser and Lutzenberger 2005a, modified)

Bidet-Caulet and Bertrand (2005) used EEG to examine the notion of putative 'what' and 'where' pathways. Subjects were presented with pitch-varying acoustic streams alternating with spatially varying streams. In the attention task, subjects had to follow the sound variations and report the changes. In the control task, subjects had to focus on a noise-burst at the end of the streams. The authors reported an activation of a temporo-parieto-frontal network during all conditions, whereas the left superior temporal cortex was the only region which showed different activations for spatial versus pitch variations. They concluded that parietal and frontal regions were involved in attention processes and motor preparation. By contrast, they suggested that the differential processing of spatial versus non-spatial auditory features takes place at the level of the temporal cortex which is in accordance with the results quoted above.

The presence of two specialized auditory processing streams could also be shown for auditory decision making by Kaiser et al. (2007a). They investigated the temporal dynamics of decision making during an auditory task with MEG. They presented two stimuli S1 and S2 with an interstimulus interval of 200 ms. The stimuli consisted of syllables which could differ either in their spatial or pattern characteristics. The level of difficulty was adjusted to form easy or difficult trials by varying the similarity of S1 and S2. The analyses showed enhanced GBA over posterior parietal cortex for spatial and over left inferior frontal cortex for pattern changes at 120 to 200 ms after S2 onset. These responses were more pronounced for easy compared to difficult trials. A later gamma-band component was found at approximately 280 to 430 ms after S2 onset over dorsolateral prefrontal cortex, which was stronger for easy than

difficult trials. These results underline the notion of two specialized auditory processing streams and illustrate the temporal dynamics of perceptual decision making.

Even though the studies quoted above have provided evidence for a system of separate auditory processing streams, it is still argued if the dorsal pathway is clearly specialized for the processing of spatial information. Zatorre et al. (2002) used PET to examine the functional characteristics of auditory cortical areas that are sensitive to spatial cues. Subjects were presented with differently lateralized environmental sounds or white noise bursts. The authors found activations over the posterior auditory cortex for stimuli which varied in spatial characteristics only if multiple complex stimuli were presented simultaneously. They concluded that both spatial and pattern characteristics might interact within in the dorsal pathway.

In summary, most of the studies quoted above support the notion of two specialized auditory processing streams in humans. While spatial information seems to be mainly processed in posterior areas of the temporal cortex, anterior temporal regions play an important role in the processing of non-spatial auditory information.

2.3 Magnetoencephalography

Human brain function can be studied non-invasively based on analysis of data acquired using various brain imaging techniques like EEG, MEG and fMRI. FMRI measures increases in hemodynamic activity using the blood oxygen level dependency (BOLD)-effect. FMRI signals are generated by changes of blood oxygenation associated with brain activity and peak in the range of seconds after neuronal activity. Therefore, the temporal resolution of fMRI is low. By contrast, its spatial resolution lies within the range of millimeters. This makes fMRI the appropriate technique for localizing the sources of neuronal activity.

EEG is the most established brain imaging method which has been known for almost a century (Berger 1929). It records voltages from electrodes placed on the scalp and has a high temporal resolution in the range of approximately 1 ms. However, the spatial resolution of high-density electrode arrays lies within the order of centimeters. MEG, by contrast, records magnetic fields generated by cortical neurons. This is performed by using superconductive quantum interference devices (SQUIDs) placed above the head. Its temporal resolution is similar to the EEG but it is more sensitive to signals with smaller amplitudes. Its spatial resolution is superior compared to EEG as the magnetic signals are less distorted by the skull and scalp (Cuffin and Cohen 1979). As both EEG and MEG offer the best temporal resolution in noninvasive brain imaging methods, they serve to examine the timing of complex cognitive processes (Gevins 2002).

Both EEG and MEG reflect electric activity in cortical neurons. MEG data acquisition is based on measurements of magnetic fields which derive from the net effect of ionic currents flowing in neurons and dendrites during synchronized synaptic transmission (Hämäläinen and Hari 2002). These postsynaptic currents derive from parallelly arranged cortical pyramidal cells. A simplified illustration of the cortical origin of surface signals is depicted in Figure 5.

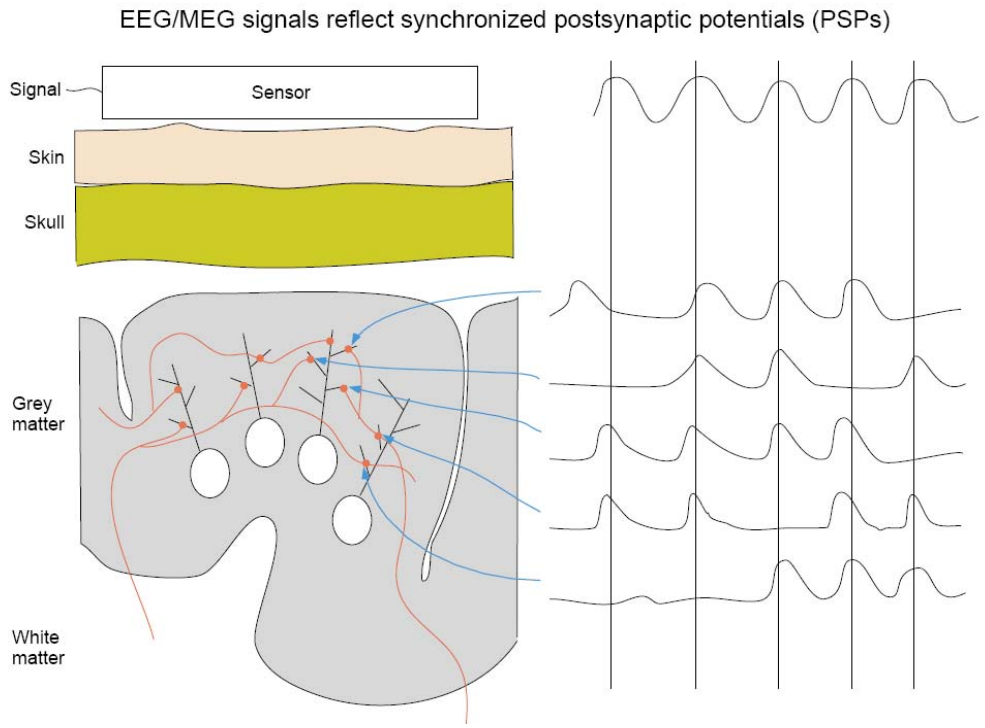

Figure 5. Postsynaptic potentials of aligned cortical pyramidal cells sum up and form synchronized potentials. These can be measured over the scalp using either EEG or MEG. (Figure P. Fries, FC Donders TOOLKIT Course, Nijmegen, Netherlands, 2006)

According to the principles of Maxwell's equations, electric currents induce an orthogonally oriented magnetic field. A current dipole model is used as an equivalent source for a primary electrical current causing the magnetic fields measured with MEG. The magnetic field generated by a current dipole is rotating around the axis of the electric vector component. This dipole is formed by aligned cortical pyramidal cell patches of at least 10^4 to 10^5 cells. Fewer neurons do not produce sufficiently strong currents to be seen on the surface. The orientation of these activated cortical cells is important because MEG is limited to the measurement of magnetic flux exiting and entering the skull. This is only caused by sources that are situated tangentially to the head; radial sources do not produce net magnetic fields outside the skull. Figure 6 illustrates a model of electric currents and the resulting magnetic field over the human skull.

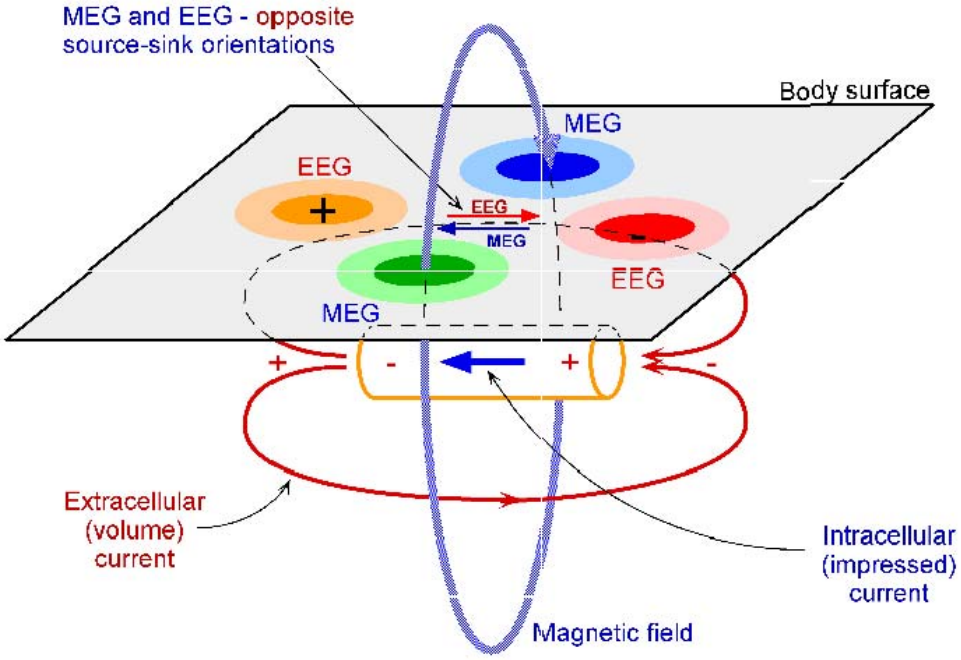

Figure 6. Generation of EEG/MEG signals. Simplified model of the generation of magnetic fields measured by MEG. Postsynaptic potentials of aligned cortical cells sum up to form a current dipole. The current in the dipole generates an orthogonally oriented magnetic field. This field exits and enters the skull if the dipole source is located tangentially to the skull. (Figure from VSM MedTech Ltd., Port Coquitlam, Canada)

The neuromagnetic signals generated by the brain are extremely weak compared to the earth's magnetic field. They can only be recorded with SQUIDs which are extraordinarily sensitive magnetic field-to-voltage transducers, see Figure 7. They are placed in a helmet-shaped liquid helium cryogenic vessel (Dewar) at a temperature near 4.2 K (-268.95 °C) to obtain superconductivity. The magnetic fields from the brain generate minuscule currents within the flux transformer circuit. The low-level voltage output from the SQUIDs is later amplified before being processed (VSM MedTech Ltd. 2005).

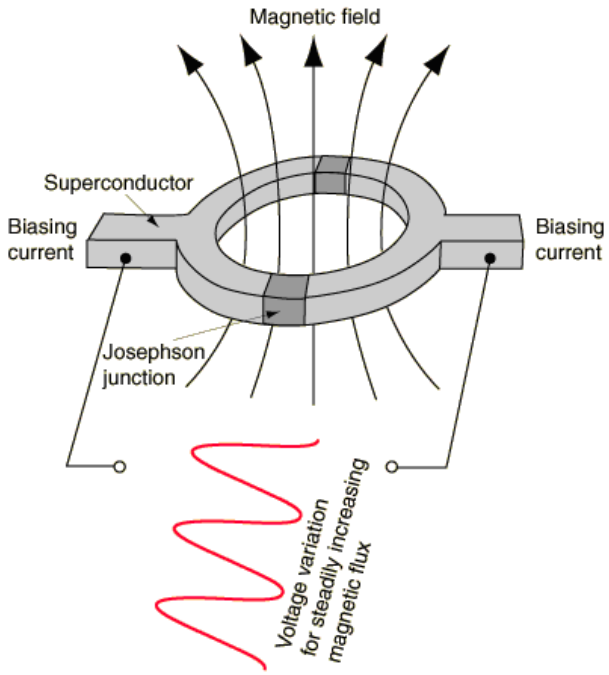

Figure 7. Superconductive quantum interference device. The device consists of a superconducting ring (light grey) which is separated by two thin insulating layers (dark grey). These gaps are called Josephson junctions. Both parts of the superconducting ring are connected to a direct current. Changes of the magnetic field passing through the SQUID result in voltage changes. This voltage variation is detected. (Figure from http://hyperphysics.phy-astr.gsu.edu/Hbase/solids/squid.html, modified)

The present study was conducted with a whole-head magnetoencephalography system (VSM MedTech Ltd., Port Coquitlam, Canada) at the Brain Imaging Center (BIC), Frankfurt/Main, Germany. The system is located in a magnetically shielded room (VAC, Hanau, Germany), see Figure 8. Neuromagnetic signals are typically 50-500 fT (Hämäläinen et al. 1993) while the earth's geomagnetic field is about 10^8-10^9 times bigger. Therefore, magnetic shielding is necessary to reduce external magnetic signals emanating from moving magnetized objects such as, e.g., trains or other sources like radio fields. Additional noise cancellation is performed by the gradiometer technology and additional channels inside the Dewar mounted above the main sensors to deliver a reference signal of background noise. This signal is subtracted from the normal channel output to reduce external noise (Vrba and Robinson 2001).

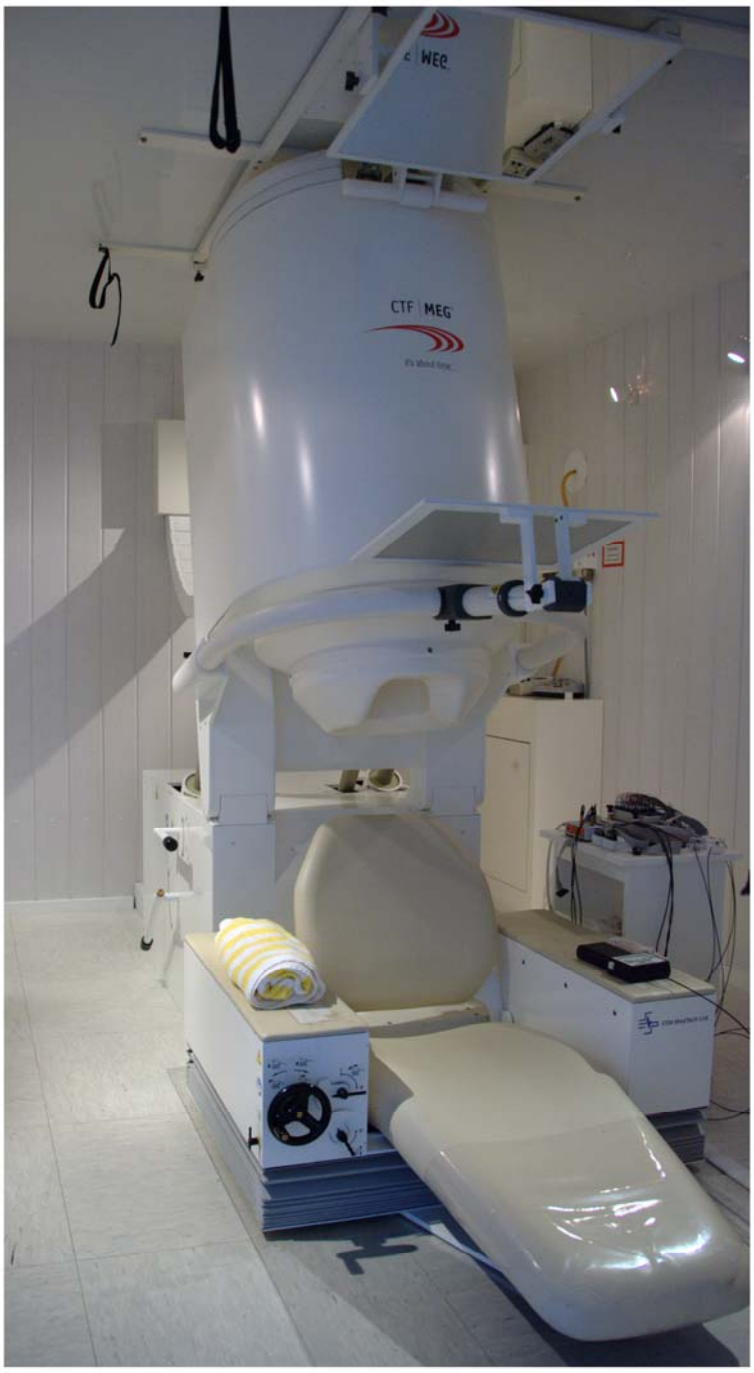

Figure 8. MEG system Frankfurt/Main, Germany. The VSM whole-head magnetoencephalography system in the magnetically shielded room. Subjects are placed in a reclining chair and the chair's position is adjusted to fit the subject's head into the MEG helmet. The sensors are placed inside the Dewar filled with liquid helium. (Photo U. Wibral)

Unlike EEG, subjects are not fixed to the MEG helmet, so excessive head movements have to be avoided in order to guarantee correct signal-source assignment. Therefore, head movements are monitored. Head localization is performed using specially designed coils fixated at the preauricular points and the nasion. The coils are simultaneously energized at different frequencies through a head localization unit while their positions are determined by special tracking software before and after every measurement.

2.4 Aims and hypotheses

The role of oscillatory activity in the gamma band has been examined for various higher cognitive processes. Previous studies applied different experimental conditions to assess possible functions of GBA. They could show task-specific GBA increases. However, there is little evidence in support of the notion that GBA reflects the representation of individual stimuli or even of specific task-relevant stimulus features. If GBA underlies the activation of object representations, it should be possible to identify stimulus-specific components of GBA during information maintenance in short-term memory. These components might be characterized by distinct spectral and topographical properties.

In this study, I aimed at identifying gamma-band components that represent local synchronized networks tuned to specific auditory stimulus features. I used MEG to assess GBA during the maintenance of auditory stimuli in short-term memory. To examine stimulus-specific GBA, I focused on the spectral and topographical characteristics of GBA for each stimulus. The stimuli used in the present study differed in their perceived lateralization angles, as I aimed at the identification of gamma-band components reflecting neuronal networks tuned to auditory spatial characteristics. By analogy to previous studies quoted in the ‘Auditory processing’ section, increased GBA was expected over areas of the putative dorsal auditory stream responsible for the processing of auditory spatial information.

The second aim of the study was to identify possible correlations between the activation strength of the GBA and memory performance. If GBA reflected the perception and maintenance of task-relevant stimulus characteristics in short-term memory, an activation of the regions involved should contribute to task performance. Thus, I expected a positive correlation between the magnitude of oscillatory components and task performance.

3. Material and methods

3.1 Subjects

28 adults gave their informed and written consent to participate in the study. The study population consisted of 18 male (64.3 %) and 10 female (35.7 %) subjects. Age ranged from 21 to 30 years with an average of 25.4 years (SD = 2.3 years). Subjects were paid € 10 per hour for participation. The study was approved by the ethics committee of the University of Frankfurt Medical Faculty.

Subjects were randomly assigned to either group R or group L. Both groups were equally balanced and consisted of 9 male and 5 female subjects and did not differ in age (R: 24.8 years [SD = 2.1 years], L: 26.0 years [SD = 2.5 years], t_{26} = 1.40). Group L received lateralized stimuli left from the midsagittal plane, group R right from the midsagittal plane. Lateralization angles and stimulus characteristics are described in more detail in the following section ‘Experimental procedure and stimulus materials’.

All 28 subjects were healthy adults. Before being included in the study population, subjects were interviewed about the following exclusion criteria:

- Claustrophobia
- Hearing deficits
- Ferromagnetic implants

Each participant was given a written and oral introduction to the experiment. For the consent form (12.1), the information sheet (12.2) and the written instructions (12.3), please refer to section 12 ‘Appendix’.

3.2 Experimental procedure and stimulus materials

Subjects had to change into metal-free clothing and were seated upright on a hydraulic chair of the whole-head MEG system in the magnetically shielded room (VAC, Hanau, Germany). They had to place their heads in the MEG helmet and then were fixated with an air-filled head stabilizer in order to minimize head movements during the recordings. Participants were instructed to sit still and keep their eyes open, looking at a fixation cross in the center of their visual field about 2 m in front of them. The room was lit during data collection. Auditory stimuli were presented binaurally via air-conducting tubes with ear inserts (E-A-R-Tone 3 A, Aero Corporation, Indianapolis, USA).

The trial structure is depicted in Figure 9. The trial onset was characterized by soft low-pass filtered midline noise (at 6 kHz: -24 dB/octave) presented for 300 ms. Then the first lateralized stimulus S1 (sample stimulus) was presented for 200 ms. The intensity of the background sound and the sample stimuli measured with a Reed 120-0014 sound level meter (TechniCal Systems Inc., Hamilton, Canada) amounted to 85 dB(A) and 98 dB(A), respectively. The intensity of the sample sounds was thus in the range that has been shown to elicit pronounced evoked gamma responses to sinusoidal tones in EEG (Schadow et al. 2007). Lateralized sounds were generated by convolution with head-related transfer functions (HRTF) (Gardner and Martin 1995), creating the impression of lateralized sounds in extrapersonal space (http://sound.media.mit.edu/KEMAR.html). This is achieved by introducing both intrapersonal amplitude and time differences and by simulating the localization-dependent filtering properties of head and outer ears.

During the following 800-ms delay phase the midline noise was presented again. This was followed by the second lateralized stimulus S2 (probe stimulus) which had to be compared to the first one regarding the lateralization angle. After that, subjects had to give feedback by raising both index fingers using an infrared light barrier. Half of the subjects within each group were instructed to

signalize a match when lateralization angles were identical, while the other half was to respond when lateralization angles differed between S1 and S2. Reponses could be given up to the beginning of the baseline of the subsequent trial.

Group R received S1 from the right with a deviation of either 15° or 45° from the midsagittal plane. For group L, S1 was presented on the left at the same lateralization angles. S2 was always presented on the same side as S1. If S1 was presented at 15°, S2 could appear at either 15° (same lateralization) or at 0° or 60° (different lateralization). If S1 was presented at 45°, S2 appeared at either 45° (same lateralization) or at 5° or 90° (different lateralization). For an overview of these combinations of stimulus lateralization angles, see table 2.

	S2 lateralization angles		
S1 lateralization angles	equal	different medial	different lateral
15°	15°	0°	60°
45°	45°	5°	90°

Table 2. Stimulus lateralization angles. The first stimulus S1 (first column) could either be presented at 15° or 45° from the midsagittal plane. The possible lateralization angles of the second stimulus S2 (second column) depended on S1. There were three possible combinations for each of the two S1 stimuli.

These combinations included two possible match trials, 15°-15° and 45°-45°, and four possible mismatch trails. The lateralization angles of S1 were presented in randomized order with equal probabilities for angles of 15° or 45°. The lateralization angle of S2 was equal to S1 in half of the trials and different in the other half. The two possible deviant angles were presented with equal probability. The duration of the intertrial interval was randomized between 1700 and 2700 ms to avoid adaptation effects.

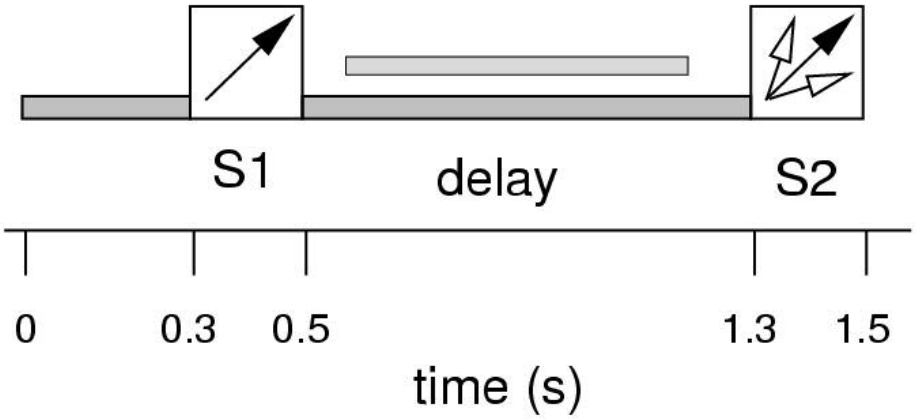

Figure 9. Trial structure of the task. Low-pass filtered noise (pre-S1) and the 200 ms presentation of the sample stimulus (S1) were followed by a delay phase of 800 ms midline noise. Then a probe stimulus (S2) appeared for 200 ms. Subjects had to compare the sound lateralization angle of S1 and S2. Arrows symbolize the lateralization angles of S1 and S2. The light gray horizontal bar above the symbol for the delay phase shows the latency window for spectral analysis (600–1200 ms after trial onset).

Two consecutive blocks of 120 trials were presented, i.e., there were 120 trials with sample sound S1 lateralized at 15° and 120 trials with S1 lateralized at 45°. Prior to recordings, participants performed up to 60 trials for practice reasons. In the first half of the practice session they received a periodic sequence of example trials with identical versus different S2 lateralization angles. In the second half of the practice phase subjects had to respond to randomly presented stimuli and were given feedback about their performance by the experimenter.

The 120 trials per run resulted in a mean duration of 480 s of data collection. Combined with head localization time, a total of approximately 10 min per run was needed. Overall measurement time including preparation and test runs was about one hour.

3.3 Data recording

MEG was recorded using a whole-head system (VSM MedTech, Port Coquitlam, Canada) comprising 275 first-order magnetic gradiometers with an average distance between sensors of about 2.2 cm. Signals from one defunct channel were discarded.

The signals were recorded continuously at a sampling rate of 600 Hz with an anti-aliasing filter at 150 Hz. The final signal was computed using a synthetic third-order order gradiometer configuration to suppress environmental noise and downsampled at 300 Hz.

The subject's head position was determined at the beginning and the end of each recording to ensure that head movements did not exceed 0.5 cm. To reduce eye movement and blink artifacts we rejected trials containing signals exceeding 1.5 pT in fronto-temporal sensors. This left an average of ~95 % of trials for analysis.

All stimuli were delivered using Presentation® 9.9 software. MEG and behavioral data were simultaneously recorded. Additionally, the subjects were observed by a camera to make sure they kept their eyes open.

3.4 Data analysis

The algorithms needed for data analysis were developed by Prof. W. Lutzenberger, Tübingen, Germany. Spectral analysis was designed to identify GBA components that distinguished between sample stimuli lateralized at 15° and 45° in each of the two groups. The analyses focused on stimulus maintenance-related activity during the middle 600 ms of the delay phase. All

artifact-free trials were included in the analyses. No baseline correction was performed.

We followed a procedure that has been applied in a series of previous studies on MEG oscillatory responses (Lutzenberger et al. 2002; Kaiser et al. 2003a; Kaiser et al. 2005a). First, spectral analysis was performed to identify the frequency ranges with the most robust differences between both stimuli. Significance of the observed spectral power values for each frequency bin and MEG sensor was tested with a statistical probability mapping including corrections for multiple comparisons. Second, topography (sensors) and time courses of activations were assessed after filtering in the frequency ranges with the most pronounced differences between conditions.

Spectral analysis was conducted for frequencies between 55 and 80 Hz for the time window of 0.6-1.2 s after trial onset, i.e. the middle 600 ms of the delay phase starting 100 ms after the offset of S1 and lasting until 100 ms prior to the onset of S2. To reduce the frequency leakage for the different frequency bins, the records were multiplied by Welch windows. The nominal frequency resolution was 1.17 Hz; however, the true frequency resolution was somewhat lower because Welch windowing led to a certain smearing of frequencies across bins. Fast Fourier Transforms were carried out on single-trial basis and square roots of the power values in each frequency bin were computed to obtain more normally distributed spectral amplitude values.

These values were averaged across trials to obtain measures of the total spectral activity in response to each of the two sample sounds. Spectral activity contrasts were evaluated with a statistical probability mapping procedure which has been used in numerous previous studies (e.g., Kaiser et al. 2005a). It included corrections both for multiple comparisons and for possible correlations between data either from neighboring frequency bins (for spectral analysis) or time points (for time course analysis).

Significance criteria (corrected *t*-values t_{corr}) were determined on the basis of permutation tests (Blair and Karniski 1993). Permutation tests allow to identify the probability of observing a difference of a certain size between two experimental conditions on the basis of the distribution obtained by randomly assigning the recorded data to the conditions. In general, the significance criteria obtained from the present procedure correspond to approximately $p = 0.003$ for two neighboring frequency bins.

Starting point was the comparison of group average spectral amplitude values for each of the two sample stimuli at each sensor and each frequency bin. This yielded the observed distributions of the *t*-values for all frequency bins $I \times$ sensors j. To avoid spurious findings in individual frequency bins, we introduced the requirement that two neighboring frequency bins had to differ significantly between conditions. To ensure that tests for two consecutive frequency bins were significant, a new distribution of the minimal *t*-values t_m was computed for all pairs of neighboring frequency bins (time points) i and i+1 at all sensors j:

$$t_{mij} = \min (t_{i,j}, t_{i+1,j}).$$

The next analysis step was designed to take into account possible correlations between neighboring frequency bins. The *t*-value t_m and its corresponding *p*-value $p_{0.05}$ were determined for which 5 % of the observed t_{mij} were larger. In the case of highly correlated data, $p_{0.05}$ would be close to or smaller than 0.05, whereas for highly independent data, $p_{0.05}$ would be greater than 0.05. The next step was to assess the random distribution of maximal *t*-values in the present data set by exchanging the values for each trial type (or: the signs of the differences between the two sample stimuli) at a time for all sensors j and frequency bins (time points) i on a subject-by-subject basis. This was done for 2^{14} permutations of the 14 subjects in each group. Each of these permutations now yielded a new maximum *t*-value. The distribution of these maximal *t*-values t_{max} for each of the $n_{rand} = 2^{14}$ permutations was computed as follows:

$$t_{max} = \max_{ij} (t_{mij})$$

The corrected *t*-value t_{corr} was now defined as the value where $p_{0.05} \times n_{rand}$ of the obtained t_{max} were greater. This corrected *t*-value t_{corr} was then applied as significance criterion to the observed data.

To explore the time course and the topographical localization of the observed spectral amplitude differences between conditions, the signals across the recording interval were multiplied with cosine windows at their beginnings and ends and filtered in the frequency ranges in which the statistical probability mapping had yielded significant effects. Noncausal, Gaussian curve-shaped Gabor filters in the frequency domain (width: ± 1.5 Hz around center frequency, length in the time domain: 100 ms) were applied to the signals on a single-epoch basis for each of the two S1 stimuli. The filtered data were amplitude demodulated by means of a Hilbert transformation (Clochon et al. 1996) and then averaged across epochs for each stimulus. Differences in amplitude between stimuli in the filtered frequency band were assessed with the statistical probability mapping procedure described above.

To depict the topographical localization of the observed differential spectral amplitude enhancements, we assigned the sensor positions with significant spectral amplitude effects of each subject to common spatial coordinates (’common coil system’). Sensor positions with respect to the underlying cortical areas were determined using a volumetric magnetic resonance image of one subject. The error which is introduced by not using individual sensor locations was estimated in previous studies by using a single dipole for somatosensory evoked fields and two dipoles for the localization of the first auditory evoked component (N1m) (Kaiser et al. 2000b). The comparison of individual sensor locations and the ‘common coil system’ revealed differences ranging below the spatial resolution determined by the sensor spacing.

In addition, we calculated an index of strength of representation of the two S1 stimuli across groups. First, for each subject the spectral amplitude differences in response to the 15° minus the 45° sample stimulus were calculated at the more medial and the more lateral parieto-occipital sensors, respectively. Second, the difference was computed between these amplitude difference values at the medial minus the lateral sensor. The resulting score thus reflected the degree to which oscillatory signals differentiated between the two stimuli. Positive values indicated a 'consistent' differentiation with larger amplitudes to the preferred stimulus (in the sense of the initial statistical parametric mapping), whereas negative values stood for an 'inconsistent' differentiation with larger amplitudes to the nonpreferred sound.

4. Results

4.1 Behavioral data

For group R (stimulus presentation in the right hemifield) 86.5 % (SD = 8.8 %) of trials with sample sounds at 15° lateralization were performed correctly. The mean reaction time for correct responses amounted to 675 ms (SD = 157 ms). For S1 at 45°, the correct response rate amounted to 87.6 % (SD = 8.7 %) with a mean reaction time of 646 ms (SD = 183 ms).

Group L who had received all stimulation in the left hemifield showed a performance of 86.4 % (SD = 7.7 %) correct answers to sample stimuli at 15°. The mean reaction time in correct trials amounted to 687 ms (SD = 123 ms). S1 stimuli lateralized at 45° gave rise to 91.1 % (SD 6.4 %) correct responses with a mean response time of 651 ms (SD = 143 ms).

Separate ANOVAs were conducted for correct response rate and reaction time with group (left versus right stimulation) as between-subjects factor and stimulus (15° versus 45°) as within-subject factor. Both analyses yielded main effects for stimulus (correct response rate: $F_{1,26} = 4.3$, $p = 0.048$; reaction time: $F_{1,26} = 8.3$, $p = 0.008$). As there were no significant group main effects or group × stimulus interactions, dependent-samples *t*-tests were calculated for both dependent variables across groups (Figure 10). Correct response rates tended to be lower for sounds lateralized at 15° than 45° (15°: 86.4 % [SD = 8.2 %], 45°: 89.4 % [7.8 %], $t_{27} = 2.05$, $p = 0.051$) and reaction time was longer for 15° than 45° stimuli (15°: 680 ms [SD = 139 ms] after the onset of S2, 45°: 648 ms [SD = 161 ms], $t_{27} = 2.92$, $p = 0.007$). Across all subjects, correct response rate and reaction time were negatively correlated ($r = -0.54$, $p = 0.003$).

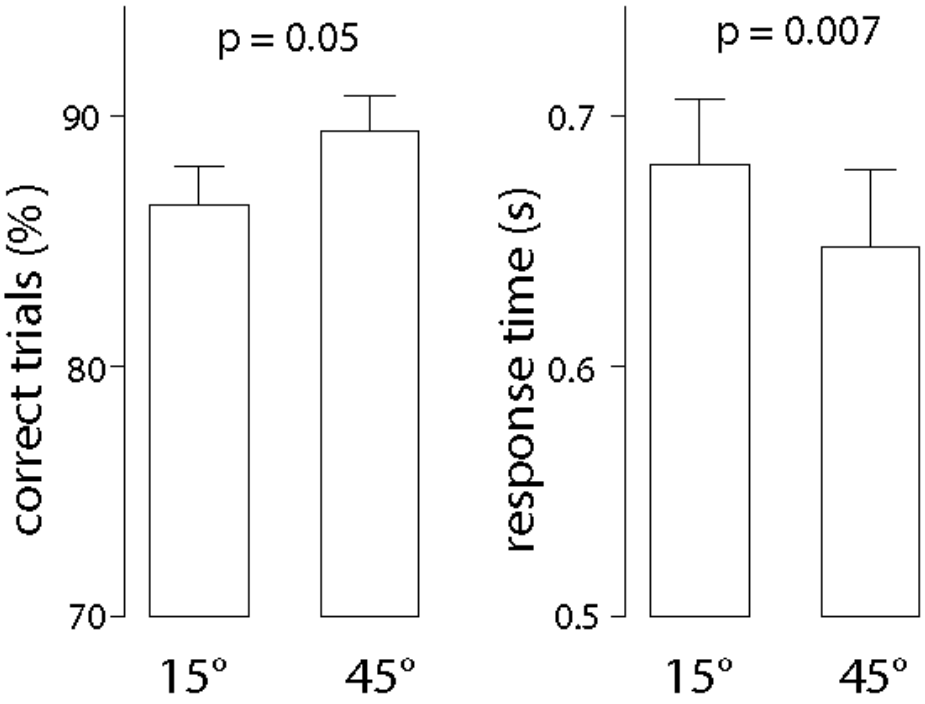

Figure 10. Correct response rates and reaction times (means and standard errors) for S1 stimuli presented at 15° and 45° deviation from the midsagittal plane calculated across the entire group of subjects.

4.2 Oscillatory activity

The results of frequency analysis for the comparison of the two S1 stimuli during the time window of 0.6-1.2 s after trial onset in each group are depicted in Figure 11.

In group R, right-lateralized sample stimuli at 15° deviation from the midsagittal plane were associated with a relative enhancement of GBA at ~68 Hz at a left parieto-occipital sensor (MLP52). For right-lateralized sample sounds at 45°, higher spectral amplitude was observed at ~72 Hz at a slightly more lateral

parieto-occipital sensor (MLP53). These effects met the criterion of t_{corr} = 3.41 for two consecutive frequency bins in the frequency range of 55-80 Hz.

In group L, left-lateralized S1 stimuli at 15° were accompanied by a relative enhancement of GBA at ~59 Hz at a right parieto-occipital sensor (MRP53). Left-lateralized sample sounds at 45° gave rise to higher spectral amplitude at ~62 Hz at a more lateral parieto-occipital sensor (MRO13). These effects met the criterion of t_{corr} = 3.0 for two consecutive frequency bins in the frequency range of 58-65 Hz.

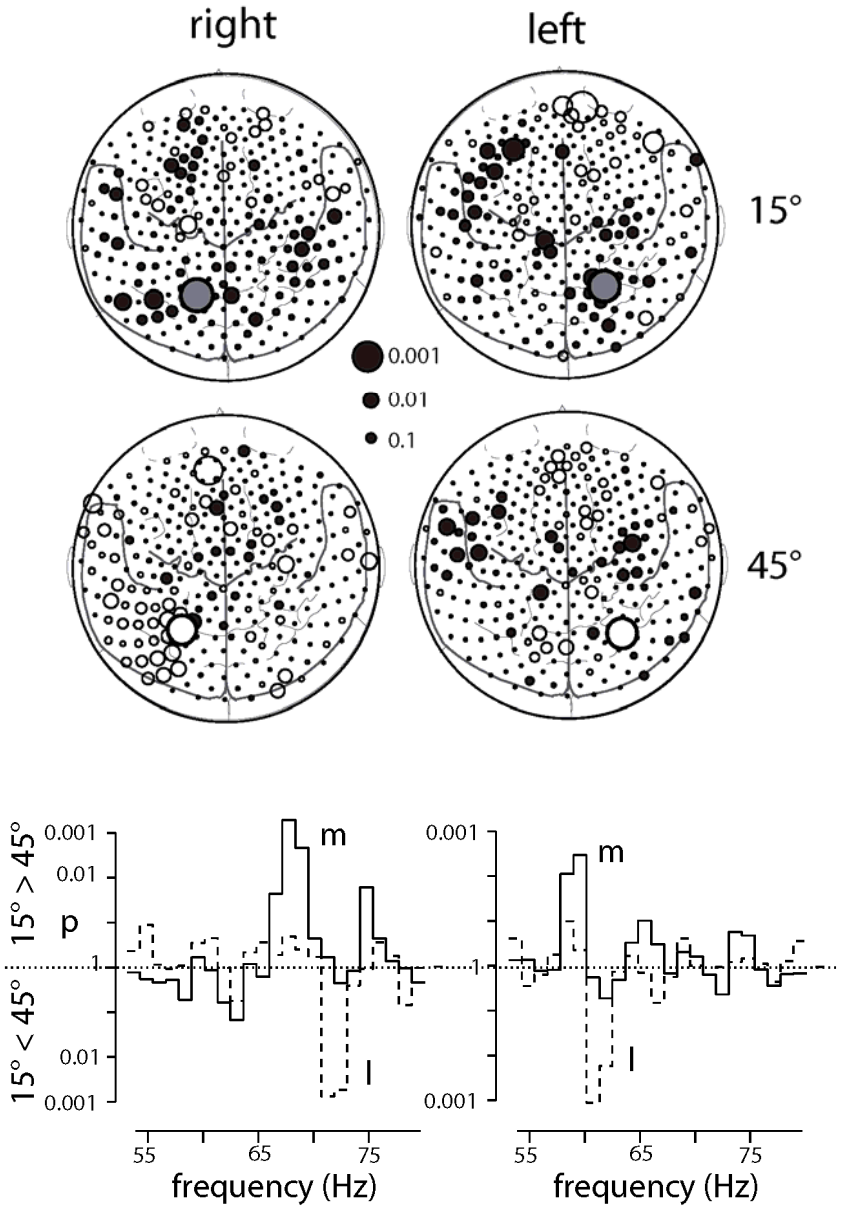

Figure 11 (previous page)**.** Comparison of oscillatory responses to S1 stimuli at 15° versus 45° for both groups (left column: group R with stimulus presentation in the right hemifield and right column: group L with stimulus presentation in the left hemifield). The maps depict the topography of GBA differences between both S1 stimuli in the frequency ranges, where the statistical probability mapping had revealed significant effects (top left: 68 ± 1.5 Hz, bottom left: 72 ± 1.5 Hz, top right: 59 ± 1.5 Hz and bottom right: 62 ± 1.5 Hz). Each circle represents one of the 275 MEG sensors projected onto a 2-dimensional cortical surface map with some major anatomical landmarks (dorsal view, nose up). The size of each circle reflects the statistical strength of the GBA difference between both S1 stimuli. Filled circles symbolize relative spectral amplitude increases in response to 15° stimuli, whereas open circles stand for relative spectral amplitude enhancements for 45° stimuli. The circles with the bold borders represent the sensors with the most robust GBA differences between stimuli, i.e. where the statistical criterion was fulfilled for two neighboring frequency bands. The more medially located sensors showed a preference for 15°, the more lateral sensors for 45° stimuli.

The graphs at the bottom show the results (*p*-values) of *t*-tests comparing spectral amplitudes between both S1 stimuli at the two sensors showing the most pronounced effects. The solid line gives *p*-values for the comparison of S1 at 15° versus 45° at the more medial sensor (m) responding more strongly to S1 at 15°, whereas the dotted line represents *p*-values for the opposite contrast (plotted downwards) at the more lateral sensor (l) responding more strongly to S1 at 45°.

In group R, right-lateralized sample stimuli at 15° deviation from the midsagittal plane gave rise to a spectral amplitude enhancement at 68 ± 1.5 Hz at a left parieto-occipital sensor (Figure 11, top left map) which was maximal at 0.8-1.0 s after trial onset. The difference amplitude for this sensor during this time window amounted to 0.55 fT (SD = 0.11 fT), $t_{13} = 4.82$, $p < 0.001$. Right-lateralized sample sounds at 45° were accompanied by a relative GBA enhancement at 72 ± 1.5 Hz at a more lateral left parieto-occipital sensor (Figure 11, bottom left map). Here, the mean difference amplitude during the same time window of 0.8-1.0 s after trial onset amounted to 0.51 fT (SD = 0.09 fT), $t_{13} = 5.90$, $p < 0.001$.

In group L, left-lateralized sample stimuli at 15° deviation from the midsagittal plane were associated with a spectral amplitude enhancement at 59 ± 1.5 Hz at a right parieto-occipital sensor (Figure 11, top right map) which was maximal at

0.7-0.9 s after trial onset. The difference amplitude for this sensor during this time window amounted to 0.58 fT (SD = 0.12 fT), t_{13} = 4.99, p < 0.001. Left-lateralized sample sounds at 45° induced a relative GBA enhancement at 62 ± 1.5 Hz at a slightly more lateral right parieto-occipital sensor (Figure 11, bottom right map). Here, the mean difference amplitude during the same time window of 0.7-0.9 s after trial onset amounted to 0.52 fT (SD = 0.11 fT), t_{13} = 4.85, p < 0.001.

To explore the time course and topography of these spectral amplitude differences, the data records were Gabor filtered (filter width: ± 1.5 Hz around center frequency) in frequency ranges with center frequencies of 68 and 72 Hz for group R, and 59 and 62 Hz for group L, respectively. The time courses of the GBA differences between sample sounds at 15° and 45° in these frequency ranges are depicted as statistical time-frequency plots in Figure 12 and as spectral amplitude and statistical time curves for the filtered signals in Figure 13.

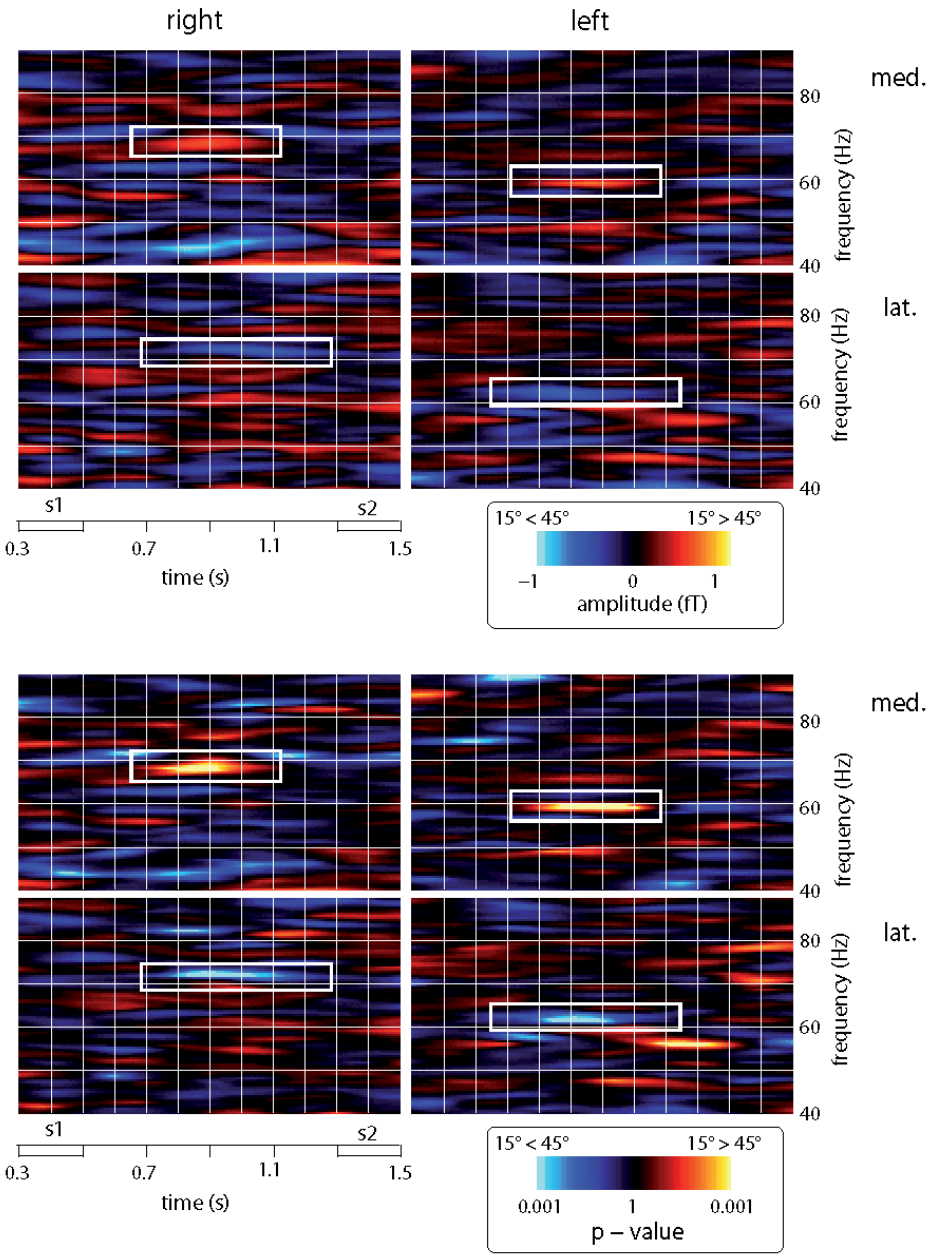

Figure 12. Time-frequency plots depicting the spectral values and statistical strength (top and bottom panels, respectively) of differences between 15° and 45° sample stimuli (warm colors: relative increases for S1 at 15°, cold colors: relative increases for S1 at 45°) for both groups. Data are shown for the interval from the onset of S1 to the offset of S2 and for frequencies between 40 and 90 Hz. The top left graphs in each panel depict activity differences at the more medial posterior sensor for group R (med., symbolized by the largest circle in the top left map of Figure 11), the bottom left graphs show activity differences for the more lateral parieto-occipital sensor for group R (lat., symbolized by the largest circle in the bottom left map of Figure 11). The plots in the left half of the figure show the corresponding sensors for group L. Effects that met the statistical significance criteria described in the 'Data analysis' section, are marked with white rectangles.

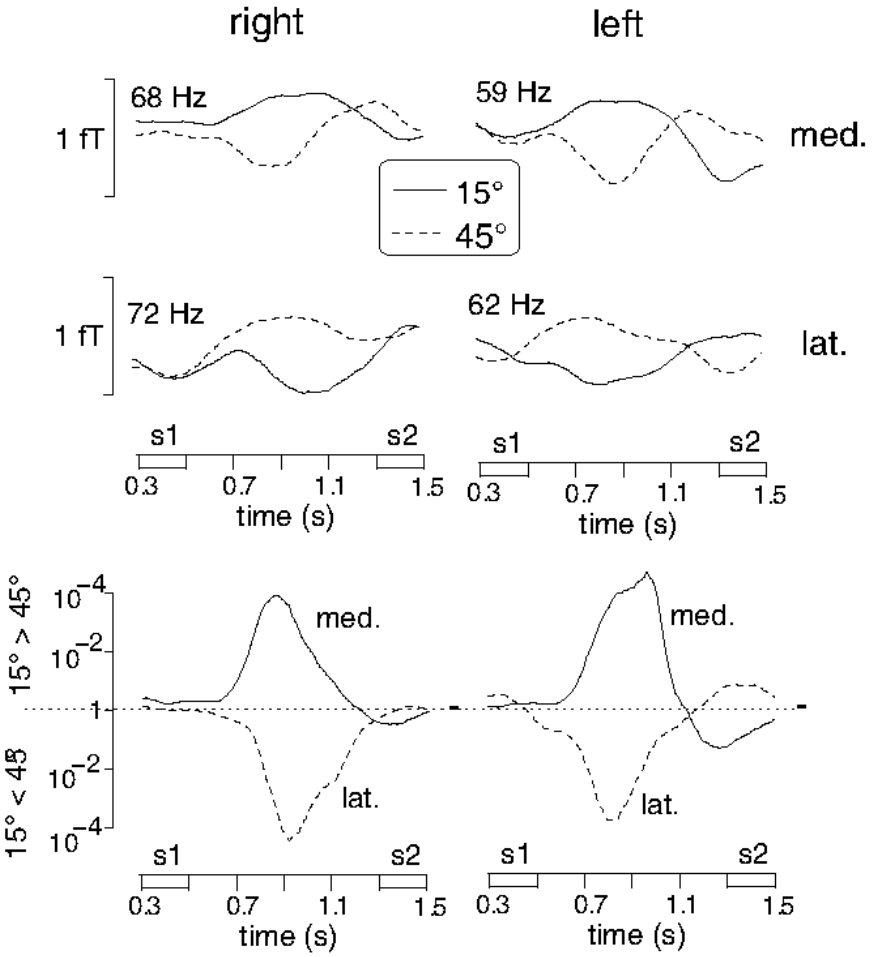

Figure 13. Time courses between the onset of S1 and the offset of S2 of filtered signals for the frequency ranges with the most pronounced differences between sample stimuli at 15° and 45° for group R and L (left and right columns, respectively). The graphs in the top two rows show spectral amplitude time courses, the graphs in the bottom row depict the time course of the statistical difference between 15° and 45° S1 stimuli. The top left graph depicts spectral amplitude (68 ± 1.5 Hz) time courses at the more medial posterior sensor (med., symbolized by the largest circle in the top left map of Figure 11) for sample sounds at 15° and 45° (symbolized by the solid and dotted lines, respectively). The middle left graph depicts spectral amplitude (72 ± 1.5 Hz) time courses at the more lateral posterior sensor (lat., symbolized by the largest circle in the bottom left map of Figure 11) for both sample sounds. The top and middle graphs on the right depict amplitude time courses at 59 and 62 ± 1.5 Hz at the more medial and lateral sensors shown in the right maps of Figure 11, respectively. Time courses of *p*-values for the statistical difference between 15° and 45° stimuli at each sensor (solid lines: medial sensors, hatched lines: lateral sensors) are depicted in the bottom part of the figure.

Based on previous findings (Lutzenberger et al. 2002; Leiberg et al. 2006a; Kaiser et al. 2007a), the present analyses focused on activity in the higher gamma range. In addition, we also explored differences in oscillatory activity between the two sample sounds in the lower frequency ranges including theta, alpha, beta and the lower gamma range up to 55 Hz. Here, no significant effects were found.

4.3 Correlations between oscillatory activity and task performance

To explore a possible relationship between the stimulus-specific GBA components and task performance, we calculated an index of strength of representation of the two S1 stimuli across groups (for calculation details, see 'Data analysis' section).

This score was then correlated with correct response rate, i.e. the combined proportion of hits and correct rejections. As subjects had to respond to one type of S1-S2 comparison only (either to matches or nonmatches), a distinction between both types of responses was not possible. Across groups, a significant positive correlation of $r = 0.47$ ($p = 0.012$) was observed between correct response rate and the averaged differentiation score for the final 100 ms of the delay phase only (Figure 14), i.e. a more pronounced differentiation was associated with better performance. In contrast, there was no significant correlation between GBA amplitude and reaction time during this time window ($r = 0.07$).

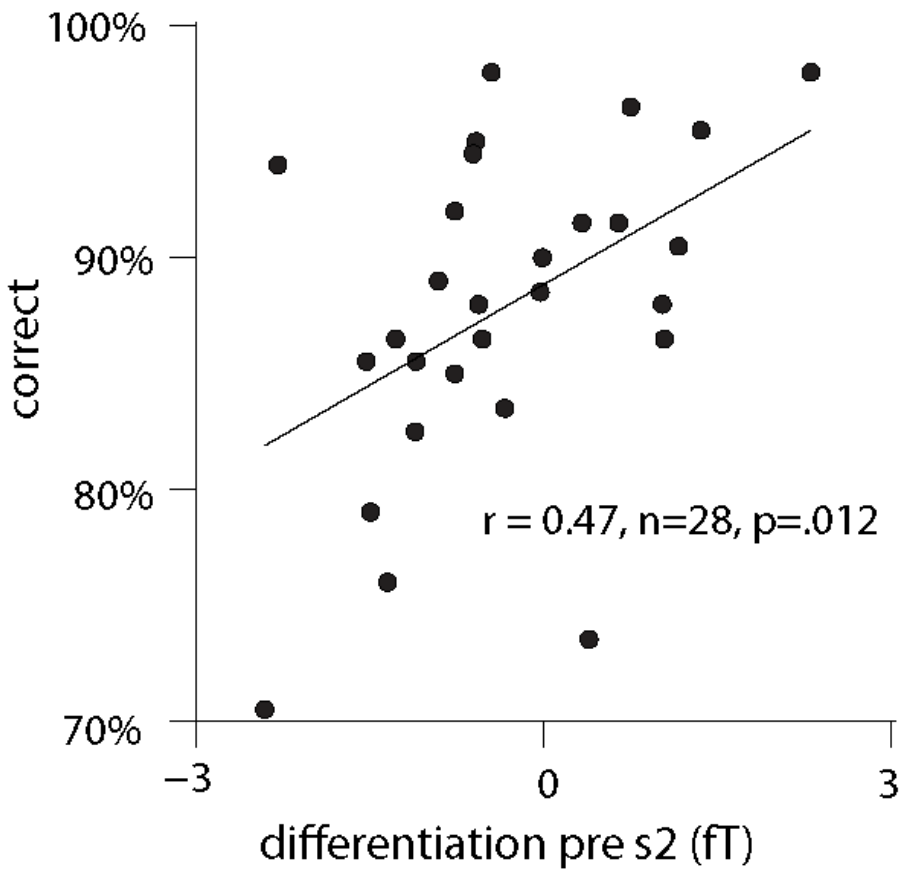

Figure 14. Correlations between correct response rate (ordinate) and a spectral amplitude measure reflecting the strength of differentiation between the two sample stimuli (abscissa) for the entire subject sample across both groups (*N* = 28). The differentiation measure was computed as the difference between the stimulus-specific GBA spectral amplitude changes at the two sensors where these effects were localized during the final 100 ms of the delay phase.

As the correlation between performance and differentiation score was observed for a time window when in the group average there was no differentiation between the two sample stimuli, for exploratory purposes we split the subject group into three groups of 10 good, 8 medium and 10 poor performers. The mean amplitudes and standard errors of the differentiation index in these three groups are plotted in Figure 15 for ten 100-ms time windows between 0.3 s after trial onset (onset of S1) and 1.2 s (end of the delay phase). Good performers

upheld the consistent differentiation for longer than average or poor performers whose differentiation score decreased or even changed its sign prior to the onset of S2. The figure further suggests that there were no substantial differences in amplitude variability between groups.

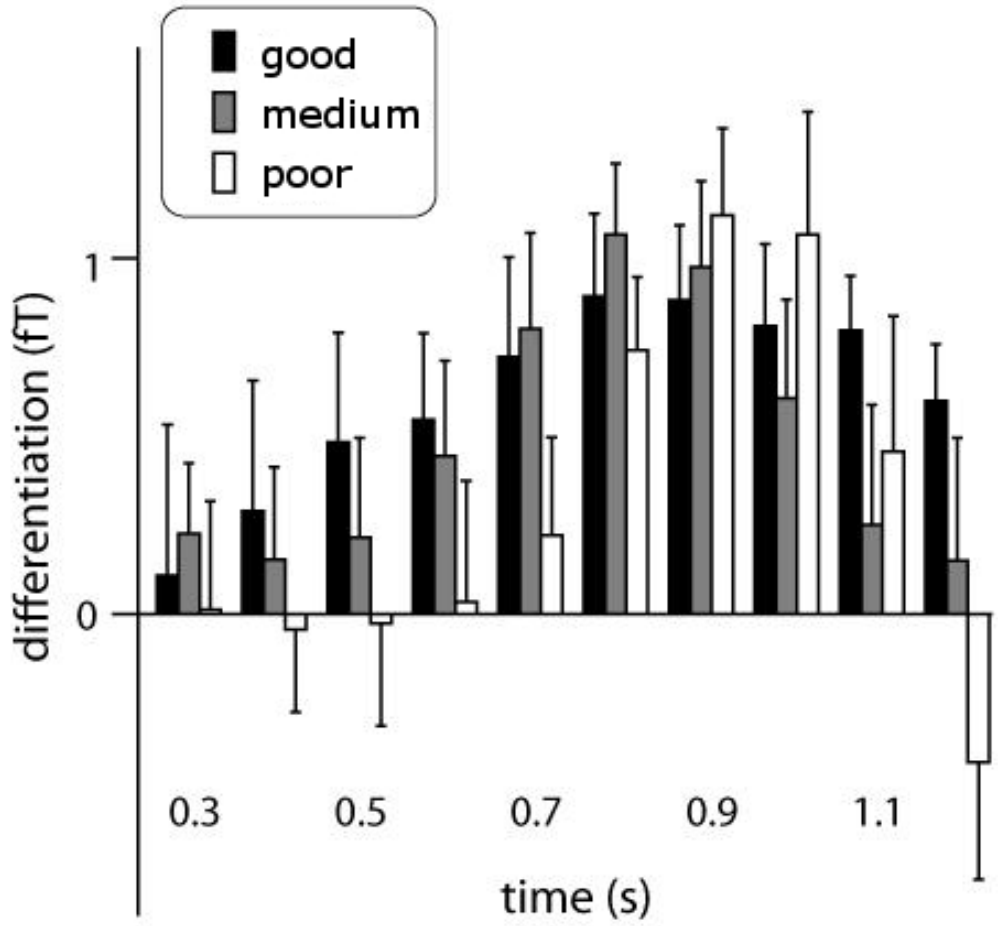

Figure 15. Amplitudes and standard errors of the differentiation index for ten 100-ms time windows between 0.3 s and 1.2 s after trial onset for groups of 10 good, 8 medium and 10 poor task performers.

5. Discussion

The present study investigated induced GBA during the delay phase of an auditory spatial delayed matching-to-sample task requiring the maintenance of the lateralization angle of a sample noise sound in short-term memory and to compare it with a subsequent probe stimulus.

5.1 Topographical distribution of gamma-band activity

In contrast to previous work using a similar paradigm (Lutzenberger et al. 2002; Leiberg et al. 2006a), here we did not contrast this task with a nonmemory control condition, but we compared oscillatory responses between two different sample sounds lateralized at 15° and 45° deviation from the midsagittal plane, respectively. Oscillatory responses to these stimuli were investigated in two nonoverlapping groups of subjects who were either presented with stimuli lateralized in the left or right hemifield only. Statistical probability mapping revealed distinct GBA components for each of the sample sounds. These components had an intermediate amplitude during the presentation of S1 and showed subsequently either an amplitude increase in response to their 'preferred' stimulus or a decrease to the 'nonpreferred' stimulus (Figure 13). The maximum differentiation between 'preferred' and 'nonpreferred' stimuli was reached during the middle of the delay phase approximately 0.2-0.5 s after the offset of S1. The average differentiation returned to zero immediately prior to the onset of S2. GBA components distinguishing between the two lateralization angles were observed at parieto-occipital sensors contralateral to the side of stimulation (Figure 11). These sensors were localized over homologous areas for the two groups. The present study thus demonstrates that distinct GBA components for each stimulus lateralization angle can be identified in MEG. Effects were replicated in a similar frequency range and with a highly

comparable topography for two independent groups, arguing for the robustness of the findings.

Increased GBA in EEG in response to attentively perceived familiar sounds compared with unfamiliar acoustic stimuli has been interpreted as reflecting matches with representations in long-term memory (Lenz et al. 2007). In contrast, the present findings were obtained with meaningless noise stimuli, suggesting that GBA represents the activation of networks processing task-relevant information also for abstract stimuli that do not have a meaningful long-term memory representation (Basar 2005). The finding of distinct oscillatory components in response to each sample stimulus is in keeping with my hypothesis that GBA reflects the cortical representations of individual stimuli. These components could only be identified by directly contrasting two stimuli. As they showed amplitude increases for their 'preferred' stimulus but decreases for the 'nonpreferred' one, they would not be visible if data were averaged across stimuli. In earlier studies that compared oscillatory activity during a memory task with a control condition (Lutzenberger et al. 2002; Kaiser and Lutzenberger 2003; Leiberg et al. 2006a), GBA during the delay phase reflected memory-specific activations that were common to the different sample stimuli maintained during this phase. The present results show that direct contrasts between two stimuli reveal spectrally narrow and topographically local GBA components in MEG, possibly reflecting networks tuned to a task-relevant stimulus feature like sound lateralization angle. In both groups, the 15° sample stimuli elicited GBA components at lower central frequencies than the sounds lateralized at 45°. As lower frequencies have been related to increased cortical activation (Herculano-Houzel et al. 1999), this finding could be attributed tentatively to the fact that the 15° stimuli were more difficult to process in short-term memory as indicated by lower correct response rates and longer reaction times.

The topography of stimulus-specific components seems to depend on the particular feature that is to be attended or maintained in short-term memory. During a previous sound duration matching-to-sample task, stimulus-specific

GBA components were found over prefrontal cortex (Kaiser et al. 2007b), whereas here the maintenance of spatial sounds elicited GBA over posterior cortical regions. The topography of the present GBA components is consistent with the notion of a putative auditory dorsal stream involved in the processing of auditory spatial information (Rauschecker 1998a). Previous studies of spatial sound processing have found activations in or over posterior parietal areas with functional magnetic resonance imaging (Alain et al. 2001; Arnott et al. 2004) and MEG (Kaiser et al. 2000b; Lutzenberger et al. 2002; Kaiser et al. 2005a; Kaiser et al. 2007a).

However, the existence of an auditory dorsal spatial processing stream is debated (Belin and Zatorre 2000); activations in posterior parietal areas could also reflect supramodal spatial attention or visual imagery (Bidet-Caulet and Bertrand 2005). The oscillatory activations in the present study were localized in slightly more posterior sensors than in previous MEG studies. Their topography is akin to the one reported by Siegel et al. (2007) for magnetoencephalographic high-frequency gamma activity in relation to visual motion strength where sources were localized in occipito-parietal and lateral occipito-temporal regions attributed to human visual area MT+/V5. GBA peaks at similar sensor positions over motion-relevant areas possibly including the visual area V3A, the kinetic occipital region and the dorsal intraparietal sulcus have also been found in a previous unpublished visual motion processing study from our laboratory. Recently, it has been suggested that human area V5 may be involved in auditory motion processing (Poirier et al. 2005). However, it is quite likely that in the present study representations of the sound lateralization angles were coded by visual or supramodal space processing networks in posterior parietal/occipito-parietal areas (Macaluso and Driver 2005) and that visuo-spatial imagery processes might have been involved in stimulus maintenance during the delay phase. This interpretation is supported by a post-experimental interview in which 14 out of 19 available participants indicated having used a visual (12) or an audiovisual (2) strategy. The fact that the present stimulus-specific GBA components were localized in sensors contralateral to the side of stimulation and that stimuli lateralized at 15° were

consistently accompanied by more medial GBA than stimuli lateralized at 45° could reflect the existence of spatial maps in posterior parietal cortex (Sereno et al. 2001).

The present study has revealed stimulus-specific gamma-band activations over parieto-occipital sensors during auditory spatial processing, supporting the notion of an auditory dorsal space processing stream. In contrast, the putative auditory ventral pattern processing stream was not assessed. Dorsal and ventral stream activations were investigated in a subsequent study using sample sounds with a variable interaural time delay and a variable central frequency. Kaiser at al. (2009a) assessed the question whether the topography of stimulus-specific GBA depended on task demands. Subjects were asked to memorize either the lateralization or the frequency of the presented stimuli in separate blocks. The authors used a similar statistical approach to map differences in oscillatory activity responses to the memorization of sample sounds as in the present study. They could replicate the present findings by showing GBA components over occipital/occipito-temporal sensors contralateral to the stimulation side distinguishing between medial and lateral sounds in the spatial memory task. The frequency task, however, resulted in frontal gamma-band activations. Oscillatory responses over occipital/occipito-temporal sensors were enhanced when subjects were instructed to memorize the lateralization angle while frontal GBA was increased when subjects had to memorize frequency patterns. The authors attributed this enhancement to the modulation of gamma-band components by task demands. Kaiser et al. (2009a) also examined the correlation of task performance and the amplitude of gamma-band activation. They found a negative correlation between the proportion of incorrect ‘non-match’ responses and delay-phase GBA to the task-relevant feature. Furthermore, a positive correlation was found between the frequency of incorrect ‘match’ responses and GBA to the irrelevant feature. The authors concluded that their results supported the notion of GBA reflecting stimulus-specific representations of task-relevant features. They suggested that these activations might reflect representations of stimulus features in memory that are used in subsequent recognition.

Similar to previous studies from our lab, we have chosen a conservative statistical procedure to identify the most robust differences between the two acoustic stimuli. This procedure included the determination of a statistical threshold on the basis of nonparametric permutation tests and required that *t*-tests comparing conditions reach a certain critical *t*-value in two neighboring frequency bins. In previous investigations where e.g. memory tasks were compared with control tasks (Lutzenberger et al. 2002; Kaiser et al. 2003a), this analysis procedure has typically yielded effects for small numbers of sensors only.

While this approach may include a certain risk to overlook more transient effects, previously reported effects could usually be replicated in independent studies (Kaiser and Lutzenberger 2003, 2005b), arguing in favor of such a conservative approach. In the present study where we assessed the differential representation of sound lateralization angles, effects at single sensors were expected because it seemed plausible that such a subtle difference would be processed by highly local networks.

In general, the topography of the current effects has to be interpreted with caution because the relationship between surface data and the underlying generators is not straight forward. The present surface GBA patterns do not suggest simple dipolar sources which would produce two patches with strong magnetic fields. In contrast, the single patches typically found both in the present study and in previous work from our lab could possibly be attributed to a more complex structure of local sources that might generate a relatively weak field which is maximal over the area between the dipoles (see Kaiser et al. 2000b, for a detailed discussion of the possible source structure). According to this model, the cortical generators would thus have to be localized in the vicinity of the sensors showing the strongest activations. Moreover, differential effects were found in sensors separated only by short distances. This topography may reflect the activities of partly overlapping sources.

5.2 Oscillatory activity and task performance

The relative strength of the present stimulus-specific GBA components correlated moderately with task performance. The more pronounced the relative GBA increase to the 'preferred' and the relative decrease to the 'nonpreferred' stimulus was, the higher the correct response rate (Figure 14). This supports the notion that the stimulus-specific oscillatory activity reflected processes relevant to the short-term memory maintenance of acoustic information. Interestingly, the correlation was only found for relative GBA differences during the final 100 ms of the delay phase, when the mean differentiation between the two sample stimuli had already returned to zero. In contrast, there was no correlation between the peak amplitude of S1-related gamma components and correct response rate or reaction time.

Apparently, good performance relied more on the maintenance of the consistent representation at the end of the delay phase than on the strength of the differentiation earlier during the delay period. Good performers seemed to be able to maintain a representation of S1 until the end of the delay period even if it may have been a weak one. Their differentiation score showed a broader temporal distribution than in average or poor performers who both showed a clearer differentiation peak and a more pronounced subsequent decrease (Figure 15). At the end of the delay phase, poor performers even showed an inverse differentiation with higher spectral amplitudes to the incorrect stimuli. However, good and poor performers did not differ in the variability of their differentiation amplitudes. The larger variance between subjects during the final part of the delay phase may have helped to find a significant correlation.

Towards the end of the delay phase the time course of the average stimulus-related oscillatory activity returned to the intermediate level found during S1 presentation (Figure 13). This is a phenomenon already observed in earlier studies on visual short-term memory. For example Tallon-Baudry et al. (1998) argued that with a fixed 800-ms delay phase (as the one used in the

present study) it was difficult to distinguish whether the gamma response during the delay was transient or sustained. They also speculated that GBA decreased because S2 could be anticipated and it may not have been necessary to maintain the full strength of this activity until the end of the delay period. In a subsequent study using variable delay durations, sustained posterior gamma components were described which, however, also showed a constant power decrease over time (Tallon-Baudry et al. 1999). A recent study from our laboratory aimed at elucidating the effects of delay duration on the temporal dynamics of stimulus-specific GBA components in auditory short-term memory tasks. Kaiser et al (2009b) used MEG to asses GBA during a similar auditory spatial short-term memory task as in the present study. The study design was kept exactly the same but two possible delay phases of 800 or 1200 ms were used. Kaiser et al. (2009b) applied statistical probability mapping to identify oscillatory activations in the gamma band differentiating between the two sample sounds. In both delay conditions, GBA over posterior cortex peaked about 400 ms prior to the onset of the test stimuli, i.e. its timing varied with the delay duration. In accordance to the present results, the magnitude of these gamma-band activations correlated with performance in the short-term memory task. The authors concluded that these GBA components might reflect the preparatory activation of memory representations. An alternative interpretation by Kaiser et al. (2009b) attributed the activations to the shifting of attention to specific expected locations of the test stimuli.

It has also been hypothesized that GBA amplitude increases do not represent the only relevant mechanism underlying stimulus maintenance in short-term memory. Previous studies have suggested that cortico-cortical gamma-band synchronization between higher sensory areas and frontal regions may play an important role in short-term memory maintenance (Kaiser et al. 2005b). Alternatively, a temporal modulation of GBA would be in keeping with the proposed correlation of this activity with the cycle of power in the theta band (Canolty et al. 2006).

5.3 Outlook

The results quoted above all derive from studies examining healthy subjects. Another interesting research field concerns neuropsychiatric disorders and the putative role of abnormal neuronal oscillations and their synchronization in patients. Abnormal neuronal oscillatory activity has been attributed to various neuropsychiatric disorders, such as autism, Alzheimer's disease and epilepsy (Uhlhaas and Singer 2006) and may thus represent important changes in cognitive functions. In neuropsychiatric research, schizophrenia has been the subject of various studies examining the putative role of abnormal oscillatory activity in its pathophysiology. These studies found abnormal activity in all frequency bands (for review, see Uhlhaas et al. 2008). Abnormal GBA was found not only in patients who suffered from chronic schizophrenia but also in first-degree relatives (Hong et al. 2004) and first-episode patients with schizophrenia (Spencer et al. 2008). This suggests the possible use of oscillation monitoring as a biomarker for abnormal neuronal activity in schizophrenia. Furthermore, this could lead to the development of new pharmacological interventions targeting abnormal neuronal oscillations and synchrony in schizophrenia or other neuropsychiatric disorders (Uhlhaas et al. 2008).

In summary, spectrally and topographically distinct oscillatory components in the higher gamma range were associated with the maintenance of different sound lateralization angles during the delay phase of a short-term memory task. These components were localized at MEG sensors over parieto-occipital cortex contralateral to the side of stimulation, suggesting an involvement of this region in the representation of sound lateralization angles. The present findings add to the growing number of studies demonstrating that GBA not only plays a role in sensory feature binding but may reflect representations of task-relevant stimulus attributes that are modulated by attention or memory processes (Jensen et al. 2007). Moreover, GBA may index the specific contents of short-term memory, i.e. the stimulus representation itself. Finally, the monitoring of neuronal oscillatory activity might possibly be used as a biomarker for

neuropsychiatric diseases and could help to discover new therapeutic approaches.

6. Summary

Recent studies have suggested an important role of cortical gamma oscillatory activity (30-100 Hz) as a correlate of encoding, maintaining and retrieving auditory, visual or tactile information in and from memory. It was shown that these cortical stimulus representations were modulated by attention processes. Gamma-band activity (GBA) occurred as an induced response peaking at approximately 200-300 ms after stimulus presentation. Induced cortical responses appear as non-phase-locked activity and are assumed to reflect active cortical processing rather than passive perception.

Induced GBA peaking 200-300 ms after stimulus presentation has been assumed to reflect differences between experimental conditions containing various stimuli. By contrast, the relationship between specific oscillatory signals and the representation of individual stimuli has remained unclear. The present study aimed at the identification of such stimulus-specific gamma-band components. We used magnetoencephalography (MEG) to assess gamma activity during an auditory spatial delayed matching-to-sample task. 28 healthy adults were assigned to one of two groups R and L who were presented with only right- or left-lateralized sounds, respectively.

Two sample stimuli S1 with lateralization angles of either 15° or 45° deviation from the midsagittal plane were used in each group. Participants had to memorize the lateralization angle of S1 and compare it to a second lateralized sound S2 presented after an 800-ms delay phase. S2 either had the same or a different lateralization angle as S1. After the presentation of S2, subjects had to indicate whether S1 and S2 matched or not. Statistical probability mapping was applied to the signals at sensor level to identify spectral amplitude differences between 15° and 45° stimuli.

We found distinct gamma-band components reflecting each sample stimulus with center frequencies ranging between 59 and 72 Hz in different sensors over parieto-occipital cortex contralateral to the side of stimulation. These oscillations showed maximal spectral amplitudes during the middle 200-300 ms of the delay phase and decreased again towards its end.

Additionally, we investigated correlations between the activation strength of the gamma-band components and memory task performance. The magnitude of differentiation between oscillatory components representing 'preferred' and 'nonpreferred' stimuli during the final 100 ms of the delay phase correlated positively with task performance.

These findings suggest that the observed gamma-band components reflect the activity of neuronal networks tuned to specific auditory spatial stimulus features. The activation of these networks seems to contribute to the maintenance of task-relevant information in short-term memory.

7. Zusammenfassung

Ergebnisse aus aktuellen Studien legen nahe, dass kortikale oszillatorische Aktivität im Gamma-Bereich (30-100 Hz) eine wichtige Rolle für verschiedene kognitive Prozesse spielt. Dazu zählen das Kodieren, die Aufrechterhaltung und der Abruf auditorischer, visueller oder taktiler Informationen in das bzw. aus dem Gedächtnis. Es konnte gezeigt werden, dass diese kortikale Aktivität durch Aufmerksamkeitsprozesse beeinflusst wird. Gamma-Aktivität trat bei vorangegangenen Untersuchungen als induzierte Antwort ca. 200-300 ms nach Stimuluspräsentation auf. Es wird angenommen, dass diese nicht phasengebundenen kortikalen Reizantworten aktive kortikale Verarbeitungs-prozesse widerspiegeln. In früheren Studien wurde induzierte Gamma-Aktivität während der Aufrechterhaltung von Stimulusinformationen über Regionen gefunden, die an der Verarbeitung aufgabenrelevanter Reizmerkmale beteiligt sind.

Diese Antworten im Gamma-Bereich spiegelten Unterschiede zwischen verschieden experimentellen Bedingungen wider, jedoch ist wenig über die Repräsentation spezifischer Stimuluseigenschaften durch Gamma-Aktivität bekannt. Mit der vorliegenden Studie haben wir versucht, solche stimulus-spezifischen Gamma-Komponenten zu untersuchen. Dafür verwendeten wir Magnetenzephalographie (MEG) und eine auditorische räumliche “delayed matching-to-sample“ Aufgabe. 28 gesunde Erwachsene wurden dabei zwei verschiedenen Gruppen zugeordnet. Gruppe R bekam rechtslateralisierte Stimuli präsentiert, während diese in Gruppe L linkslateralisiert waren. Dabei unterschieden sich die Reize nur in ihrer räumlichen Charakteristik, die Klangmuster blieben unverändert.

In beiden Gruppen wurden zwei Beispielstimuli S1 mit Lateralisierungswinkeln von 15° bzw. 45° verwendet. Die Probanden mussten sich den

Lateralisierungswinkel von S1 merken und anschließend mit einem zweiten Stimulus S2, der nach einer Verzögerungsphase von 800 ms präsentiert wurde, vergleichen. S2 hatte dabei entweder den gleichen Lateralisierungswinkel wie S1, oder unterschied sich darin von dem ersten Stimulus. Nach der Präsentation von S2 mussten die Probanden signalisieren, ob die Lateralisierungswinkel der beiden Stimuli übereinstimmten oder nicht. Die Signale der einzelnen Sensoren wurden mit einem statistischen Wahrscheinlichkeitsmapping untersucht. Dabei wollten wir Unterschiede in der spektralen Amplitude für Stimuli mit 15° bzw. 45° Lateralisierungswinkel identifizieren.

Wir konnten spezifische Gamma-Aktivität für alle Beispielstimuli nachweisen. Die Signale wurden im Bereich von 59-72 Hz gefunden und waren über dem parieto-okzipitalen Kortex jeweils kontralateral zur stimulierten Seite lokalisiert. Die maximalen Spektralamplituden dieser Oszillationen traten während der mittleren 200-300 ms der Verzögerungsphase auf und nahmen zu ihrem Ende hin ab.

Zusätzlich haben wir Korrelationen zwischen der Aktivierungsstärke der Gamma-Komponenten und dem Abschneiden bei der Gedächtnisaufgabe untersucht. Dabei zeigte sich, dass der Unterschied der oszillatorischen Antworten auf bevorzugte und nicht-bevorzugte Stimuli während der letzten 100 ms der Verzögerungsphase positiv mit der Leistung in der Gedächtnisaufgabe korrelierte.

Diese Ergebnisse sprechen dafür, dass die beobachteten Gamma-Komponenten die Aktivität neuronaler Netzwerke, die auf die Verarbeitung räumlicher auditorischer Information spezialisiert sind, widerspiegeln. Die Aktivierung dieser Netzwerke scheint zur Aufrechterhaltung aufgabenbezogener Information im Kurzzeitgedächtnis beizutragen.

8. Abbreviations

AL	Anterolateral area
AN.G	Angular gyrus
BOLD	Blood oxygen level dependency
CA.S	Calcarine sulcus
CE.S	Central sulcus
CL	Caudolateral area
EEG	Electroencephalography
ERD	Event-related desynchronization
ERS	Event-related synchronization
fMRI	Functional magnetic resonance imaging
GBA	Gamma-band activity
HRTF	Head-related transfer functions
iEEG	Intracerebral electroencephalography
IPL	Inferior parietal lobe
LTD	Long-term depression
LTP	Long-term potentiation
MEG	Magnetoencephalography
MRI	Magnetic resonance imaging
PET	Positron emission tomography
PO.S	Parieto-occipital sulcus
PP	Posterior parietal cortex
PSP	Postsynaptic potential
SFS	Superior frontal sulcus

SM.G	Supramarginal gyrus
SQUID	Super conductive interference device
STG	Superior temporal gyrus
TF	Time-frequency

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10. Erklärung

Ich erkläre ehrenwörtlich, dass ich die dem Fachbereich Medizin der Goethe-Universität Frankfurt am Main zur Promotionsprüfung eingereichte Dissertation mit dem Titel

The role of gamma oscillatory activity in magnetoencephalogram for auditory memory processing

im Institut für medizinische Psychologie der Goethe-Universität Frankfurt am Main unter Betreuung und Anleitung von Prof. Dr. Jochen Kaiser ohne sonstige Hilfe selbst durchgeführt und bei der Abfassung der Arbeit keine anderen als die in der Dissertation angeführten Hilfsmittel benutzt habe. Darüber hinaus versichere ich, nicht die Hilfe einer kommerziellen Promotionsvermittlung in Anspruch genommen zu haben. Ich habe bisher an keiner in- oder ausländischen Universität ein Gesuch um Zulassung zur Promotion eingereicht. Die vorliegende Arbeit wurde bisher nicht als Dissertation eingereicht. Daten aus der vorliegenden Arbeit bildeten die Grundlage der folgenden Publikationen:

- Kaiser, J., Heidegger, T., Wibral, M., Altmann, C. F. and Lutzenberger, W. Distinct gamma-band components reflect the short-term memory maintenance of different sound lateralization angles. *Cereb Cortex* 18, 2286-95 (2008)

- Kaiser, J., Heidegger, T. and Lutzenberger, W. Behavioral relevance of gamma-band activity fort short-term memory-based auditory decision-making. *Eur J Neurosci* 27, 3322-8 (2008)

- Kaiser, J., Heidegger, T., Wibral, M., Altmann, C. F. and Lutzenberger, W. Alpha synchronization during auditory spatial short-term memory. *Neuroreport* 18, 1129-32 (2007)

Frankfurt/Main, 01.12.2010

11. Curriculum vitae

Persönliche Daten

Name	Tonio Felix Heidegger
Geburtsdatum	20. Mai 1982
Geburtsort	Nußloch
Familienstand	Ledig

Ausbildung

2006 – heute	Promotion am Institut für Medizinische Psychologie der Goethe-Universität Frankfurt/Main
20.11.2008	Approbation als Arzt
2002 – 2008	Studium der Medizin an der Goethe-Universität Frankfurt/Main und an der Claude-Bernard-Universität Lyon, Frankreich
1988 – 2001	Grundschule und Gymnasium Mühldorf/Inn

Arbeitserfahrung

2009 – heute	Assistenzarzt an der Klinik für Neurologie der Goethe-Universität Frankfurt/Main
2001 – 2002	Zivildienst beim Sozialpsychiatrischen Dienst Mühldorf/Inn

Wissenschaftliche Erfahrung

2009	ICH-GCP Basiskurs
2009	Prüfarzt in einer klinischen Phase 1-Studie A randomized clinical trial to assess the effects of single doses of MK-2637 and Riluzole on cerebral cortex excitability in healthy subjects
2009	Prüfarzt in einer klinischen Phase 1-Studie A randomized clinical trial to assess the effects of single doses of Dextromethorphan and Riluzole on cerebral cortex excitability in healthy subjects

Veröffentlichungen

- Alle, H. Heidegger, T., Krivanekova, L. and Ziemann, U. Interactions between short-interval intracortical inhibition and short-latency afferent inhibition in human motor cortex. *J Physiol* 587, 5163-76 (2009)

- Kaiser, J., Heidegger, T., Wibral, M., Altmann, C. F. and Lutzenberger, W. Distinct gamma-band components reflect the short-term memory maintenance of different sound lateralization angles. *Cereb Cortex* 18, 2286-95 (2008)

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- Kaiser, J., Heidegger, T., Wibral, M., Altmann, C. F. and Lutzenberger, W. Alpha synchronization during auditory spatial short-term memory. *Neuroreport* 18, 1129-32 (2007)

Sprachen

Deutsch	Muttersprache
Englisch	Fließend
Französisch	Fließend

Frankfurt/Main, 01.12.2010

12. Appendix

12.1 Informed consent

Studie zur "Gedächtnisverarbeitung von räumlichen Geräuschen mittels Magnetenzephalographie (MEG) bei gesunden Probanden"

EINVERSTÄNDNISERKLÄRUNG

Hiermit erkläre ich mich zur Teilnahme an dieser wissenschaftlichen Studie einverstanden. Ich wurde sowohl schriftlich als auch mündlich umfassend über den Zweck der Studie und die Vorgehensweise informiert. Ich habe darüber hinaus den Text der Probandeninformation und dieser Einverständniserklärung gelesen und verstanden. Ich hatte ausreichend Gelegenheit Fragen zu stellen.

Ich bin darüber informiert, dass meine Teilnahme an der Studie freiwillig ist. Ich kann jederzeit, auch ohne Angabe von Gründen, meine Teilnahme widerrufen, ohne dass mir hieraus Nachteile entstehen.

Datenschutz: Die Untersuchungsergebnisse werden statistisch ausgewertet und in anonymer Form veröffentlicht. Bei allen Untersuchungen werden die erhobenen Daten mit einem Code, der aus den letzten beiden Buchstaben des Nachnamens, den letzten beiden Buchstaben des Vornamens und dem Geburtsdatum besteht, versehen und in digitaler Form auf der Festplatte eines Rechners gemäß den Vorschriften des Datenschutzes gespeichert. Die Schlüsselliste wird vom Studienleiter bei der Untersuchung angelegt und getrennt von den erhobenen Daten unter Verschluss aufbewahrt. Die gewonnenen Daten werden pseudonymisiert und zu rein wissenschaftlichen Zwecken verwendet. Die Daten werden strikt vertraulich behandelt, und es erfolgt keine Weitergabe an Dritte. Ich bin mit der Aufzeichnung der im Rahmen der Studie an mir erhobenen Daten und ihrer anonymisierten Verwendung, z.B. für Veröffentlichungen, einverstanden.

Eine Kopie der Probandeninformation/Einverständniserklärung mit der Information zum Datenschutz habe ich erhalten.

12.2 Subject information

INFORMATIONSBLATT

Sehr geehrte Probandin, sehr geehrter Proband,

Wir möchten Sie bitten, an unserer wissenschaftlichen Untersuchung teilzunehmen, die sich mit der Verarbeitung von Geräuschen im Gehirn beschäftigt. Nach einer Übungsphase werden Sie beurteilen müssen, ob zwei mit einem kurzen Abstand von 0.8 Sekunden aufeinander folgende Geräusche (Rauschen) die gleiche räumliche Position hatten. Die auditorischen Reize werden Ihnen über Kopfhörer mit einer Lautstärke von maximal 70 dB (A) dargeboten, die nicht als unangenehm empfunden wird. Von der Studie erwarten wir uns ein besseres Verständnis derjenigen kortikalen Mechanismen, die an der Gedächtnisrepräsentation von Geräuschpositionen beteiligt sind, sowie der zeitlichen Dynamik der auftretenden Aktivierungsmuster.

Praktische Durchführung:

Das Experiment wird insgesamt etwa 1,5 Stunden dauern. Zur Aufzeichnung der Gehirnaktivität wird ein Magnetenzephalograph (MEG) verwendet. Hierbei handelt es sich um ein Ganzkopfsystem, welches über 275 Messeinheiten in der Lage ist, die Magnetfelder des Gehirns zu registrieren. Diese entstehen aufgrund der elektrischen Ströme, welche bei Verarbeitungsprozessen jeglicher Art im Gehirn auftreten. Die Messeinheiten befinden sich in einer Haube, die bei der Messung den ganzen Kopf und die Ohren bedeckt. Die ideale Position wird über einen verstellbaren Sitz eingestellt.

Da es sich bei den zu messenden Magnetfeldern um Feldstärken von nur 10^{-15} bis 10^{-12} Tesla handelt (im Vergleich: das Magnetfeld der Erde beträgt 10^{-4} Tesla), ist dieses System sehr empfindlich. Aus diesem Grund befindet sich die Messeinheit in einer Abschirmkammer, die während der einzelnen Messungen geschlossen sein muss. Zudem sollten alle Metallgegenstände am Körper entfernt werden (Schmuck, Schlüssel, Gürtel, Reißverschlüsse, BHs mit Metallverschlüssen usw.). Als Bekleidung stehen OP-Kittel und -Hosen zur Verfügung. Es sind keine gesundheitlichen Risiken bekannt, die aus dem Experiment entstehen könnten.

Zu Beginn der Untersuchung werden Sie auf dem Sitz in der Abschirmkammer Platz nehmen. Um brauchbare Daten zu gewährleisten, ist es unbedingt notwendig, dass Sie sich während der Messung sehr ruhig verhalten. Das bedeutet, dass Sie sich auf dem Sitz eine möglichst bequeme Position suchen sollten, in der Sie mit dem Kopf in der Messhaube hinten Kontakt haben. Vor der Messung werden an der Nase und an den Schläfen Messspulen befestigt, die Ihre Position in der Messhaube vor und nach der Messung kontrollieren.

Die Teilnahme an der Untersuchung ist freiwillig. Sie können jederzeit, ohne Angabe von Gründen und ohne Nachteile davon zurücktreten, auch wenn Sie die unten stehende Einverständniserklärung schon unterschrieben haben. Der Sie untersuchende Studienleiter behält sich vor, Ihre Teilnahme aus bestimmten Gründen vorzeitig beenden zu können.

Wir wollen Sie auch darüber informieren, dass die Ethikkommission diese wissenschaftliche Untersuchung zustimmend bewertete. Die Verantwortung für die Untersuchung liegt aber beim Leiter, Prof. Dr. Jochen Kaiser.

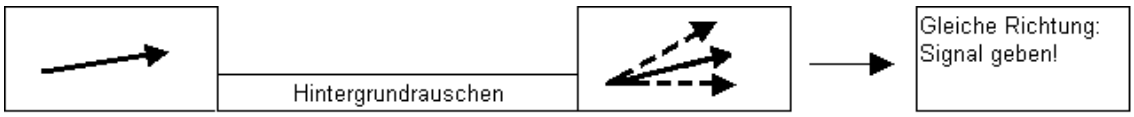
12.3 Subject instructions

VERSUCHSANLEITUNG MATCH

Sie nehmen heute an einem Versuch teil, in dem es um die Unterscheidung von akustischen Reizen geht. Dieser Versuch gliedert sich in zwei Teile.

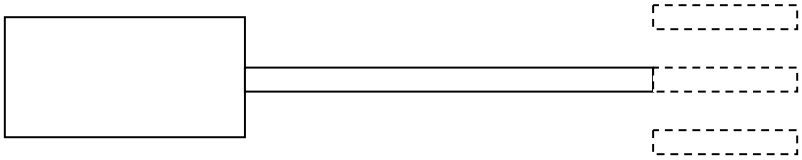
I. Memory-Bedingung

In einem Teil sollen zwei aufeinander folgende akustische Reize danach beurteilt werden, ob sie aus der gleichen Richtung erklingen. Zunächst wird Ihnen ein Rauschen aus einer bestimmten Richtung (es gibt drei Richtungen) dargeboten. Merken Sie sich die Richtung. Nach einer kurzen Pause folgt ein zweites Rauschen. **Wenn dieses Rauschen aus der gleichen Richtung ertönt wie das Erste, so heben Sie bitte Ihre Finger in der Lichtschranke an.** Geben Sie das Signal bitte zügig, machen Sie aber auch so wenig Fehler wie möglich. Vor, zwischen und nach dem Rauschen hören Sie ein leises Hintergrundrauschen, welches Sie nicht zu beachten haben.



II. Control-Bedingung

Im zweiten Teil des Experiments geht es um das Wahrnehmen von Lautstärkeveränderungen im Hintergrundrauschen. Anfänglich hören Sie wieder ein Rauschen, danach das Hintergrundrauschen, welches nach einer Weile entweder gleich bleibt, lauter oder leiser wird. **Heben Sie bitte Ihre Finger in der Lichtschranke an, wenn Sie keine Veränderung wahrnehmen.** Geben Sie das Signal bitte zügig, machen Sie aber auch so wenig Fehler wie möglich.



Bevor die eigentliche Studie beginnt, werden Sie die Möglichkeit haben, einige Übungsdurchgänge zu absolvieren, um sich so an das Experiment und an die an Sie gestellten Anforderungen zu gewöhnen. Dazu werden Ihnen anfangs regelmäßige und im zweiten Teil der Übung zufällig kombinierte Sequenzen dargeboten. Zu diesem Teil erhalten Sie Feedback, d. h. Sie können das Schwierigkeitsniveau der Aufgabenstellung in etwa einschätzen.

Beide Versuchsteile der eigentlichen Studie mit je 120 Einzelmessungen werden dann jeweils zweimal wiederholt, d. h. Sie werden an zwei Durchgängen der Memory- und zwei der Control-Bedingung teilnehmen. Zwischen den Versuchsblöcken können Sie zu Ihrer Entspannung eine Pause machen.

Für die MEG-Messung ist es wichtig, dass Sie ruhig und entspannt sitzen und sich möglichst wenig bewegen. Sie sollten außerdem darauf achten, wenig zu blinzeln und wenig Augenbewegungen zu machen. Zu diesem Zweck befindet sich in Ihrem Blickfeld ein Fokussierungskreuz, bitte richten Sie Ihren Blick darauf.

Vielen Dank für Ihre Mitarbeit!