Basic components of cortical processing are shared in visual and auditory modality

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1 Introduction

> It is late in the afternoon. The traffic in the city is chaotic and everywhere the cars are anxious for a green traffic signal. Probably, everyone in the city have left off work at the same time. Tom and his wife are on the way home. He drives the car, while talking to his wife about his day, and further tapping his finger in the rhythm of the radio music.

It is fascinating, how we are able to process all these simultaneously occurring sensations in just a few milliseconds. Mostly, we reason very little about our perception of the world around us. When we think about the aforementioned situation more intensely, this requires multiple processing systems regarding perception and cognition in parallel, in this example the visual, auditory, motor, and speech system. To understand the complex interplay of several perceptual systems, the first step is to study how these systems work on their own at different processing stages. Within the current thesis, I will focus on the visual and auditory system to investigate the following three issues: At first, I will consider low-level processes during the auditory and visual modality. Second, I will study how cognitive functions influence the processing of auditory information. Third, I will compare which processing mechanisms in the visual and auditory system are shared and which are different.

For an introduction in perceptual processes, let us consider the visual modality more precisely. This system is required to build a representation of the world surrounding us and accomplishes a variety of complex tasks, including the identification and categorization of visual objects, assessing distances to and between objects, and guiding body movements towards visual objects. Two examples of object perception in different contexts are displayed in Figure 1.1 and your task is it to identify the face in both pictures. To identify the 'object' (face), a multiplicity of object features such as color, form, texture, distance, spatial orientation, or movement direction can be of relevance and all of them are processed at the same time. Afterwards, all of these different information about the same object have to be integrated into a whole percept. This process is known as binding. A determining step to identify the object is the decision, which features belong to the same object. The binding-by-synchronization hypothesis for neuronal object coding proposes that those neurons which participate in the representation of the same visual object are characterized by synchronous activity, while those

Figure 1.1: Where is the face? Two pictures, in which a face is hidden, are displayed. Although the face is not obviously seen in both pictures, you will most probably find the face faster in the right picture, since it is a natural scene as we perceive it every day. We would rather expect a face in this context than among coffee beans. It is further helpful for detection that there is not only a face but a whole moving person. If you need a hint to find the face on the left, concentrate your attention to the bottom.

neurons which code information of different objects show a different temporal pattern (Eckhorn et al., 1988; Gray et al., 1989; Singer, 1993; von der Malsburg, 1995). The process of segmentation of objects that belong together is a prerequisite for figure-ground segregation that will be elucidated in more detail in the next paragraph.

In the early 20th century, theorists such as Kurt Koffka, Max Wertheimer, and Wolfgang Köhler emphasized that the perception of objects was not achieved by an assembly of parts of objects but rather that perception was based on holistic and well-organized patterns. Gestalt theorists believed that the context, in which we notice an object, is very important in perception, so that perception of the object is 'more than only the sum of its parts'. The very success of everyday vision implies mechanisms that discount irrelevant information and organize local image features into objects and surfaces (Kersten et al., 2004; Yuille and Kersten, 2006). The main point of this research is the idea of 'grouping' or how we tend to interpret things as belonging together. This was summarized in a multitude of Gestalt laws, while the most common are for example grouping by proximity, similarity, simplicity, closure, or continuity. If one could observe the situation displayed in Figure 1.1 (right), not only as a picture but as a real scene, the principle of common fate might play a role in detection of the face: The person behind the grass and branches seems to walk and regarding the principle of common fate, elements with the same moving direction are perceived as a unit. However, our perception also depends on attention, expectation, and prior knowlegde about different situations and contexts. Since a natural scene is displayed, namely a person walking through a forest, it is very simple to identify the face, although it is only a picture in which movements cannot be seen. In such a context, one would rather expect to find a face than among the coffee beans (see left part of 1.1).

If we consider the auditory system and I ask you to imagine several people simultaneously speaking, singing, or argueing at a party with loud music, there are some possibilities what you can perceive: (i) It might be that you hear a mix of sounds, maybe some music and different voices, however, you are not able to understand about what people are discussing. (ii) Further, it might be that you are concentrated on the singing person and notice that this person is trying to sing along with the currently played song and the result is very out of tune. Of course, there are much more possibilities of another acoustic perception. However, both mentioned cases (i) and (ii) are enough to explain some of the previously described grouping mechanisms. In audition, the way sensory inputs are grouped by our nervous system is very similar to grouping in visual perception (Bregman, 1994). The first depicted example (i) implies that one is able to differentiate simultaneously occurring sounds by a mechanism termed as auditory stream segregation. The second example (ii) emphasizes the influence by high-level functions, namely attention and shows further that attention facilitates a more detailed and elaborated perception. According to that, there are some general processing mechanisms that are comparable between both sensory systems. However, the auditory system is not a quarter as good studied than the visual system. Therefore, the thesis aims to investigate auditory perception more precisely in comparison with visual perception.

This dissertation presents experiments investigating low-level as well as higher level perceptual processes in both, the visual and auditory modality, using the electroencephalography (EEG). The EEG is a method for recording electrical activity from the human brain. Although its spatial resolution is very imprecise (in the range of several centimeters), the EEG provides an excellent temporal resolution in the range of milliseconds which appears to be relevant for addressing the subsequently defined issues. I will mainly focus on the analysis of oscillatory brain activity in the gamma-band (30-80 Hz) and how and at which latency it is modulated by different perceptual processes.

1.1 Oscillatory activity in the human brain

Information processing in the human brain is characterized by parallel information streams as well as by a hierarchical organization of different cortical areas based on complex neuronal networks (Felleman and Van Essen, 1991). The exchange of information can occur simultaneously in terms of activation patterns via connections between neurons. The processing of incoming information in the cerebral cortex is characterized by distributed representations in different neuronal assemblies. Distributed representations enable the mapping of the complexity and variability of the natural environment by a large number of possible combinations of neurons that can encode the representation of a certain stimulus or something else. However, this raises the question, how it is possible to identify and distinguish a single activated representation from other related activity at the same time?

A good candidate for a mechanism that delineates and structures neuronal assemblies is the synchronization among neurons. This synchrony can form a sort of tag to mark cells that belong together (Singer and Gray, 1995). Neurons can exhibit a wide range of oscillations and these oscillations can enter into precise synchrony over a limited period of time. The frequency of such oscillatory activity can be ordered from slow oscillations in the delta (1.5-3 Hz), theta (4-7 Hz), and alpha (8-12 Hz) ranges to faster oscillations in the beta (12-30 Hz) and gamma (30-80 Hz) ranges (Buzsáki and Draguhn, 2004). Within this spectrum, gamma-band oscillations have received particular interest, since their relationship to higher brain functions is frequently reported (Engel et al., 2001; Karakaş et al., 2001). Evidence from electrophysiological experiments of animals and humans showed that gamma-band responses (GBRs) can be found in the visual, auditory, and somatosensory modality (Başar et al., 2000).

In general, most studies distinguish between two types of GBRs based on the temporal occurrence and phase-locking across different trials. The early **evoked GBR** is phase-locked to stimulus onset, whereas the later **induced GBR** jitters in latency from trial to trial and is, therefore, not phase-locked (Başar-Eroglu et al., 1996). In the visual modality, early evoked GBRs occur with a peak latency around 90 ms and with a posterior scalp distribution (Böttger et al., 2002; Senkowski and Herrmann, 2002; Busch et al., 2006; Schadow et al., 2007b), suggesting the generators of the GBR in visual cortices. The auditory evoked GBR peaks much earlier at 60 ms after stimulus onset and is often observed with an amplitude maximum at fronto-central electrodes (Haenschel et al., 2000; Schadow et al., 2007a). Because of the temporal proximity to the auditory middle latency response (MLR) and long latency response (e.g. N1), a number of studies argued about whether the auditory evoked GBR represents a functionally distinct brain response (Başar et al., 1987; Bertrand and Pantev, 1994; Pantev, 1995; Jacobson et al., 1998; Müller et al., 2001). Dipole localizations suggested that generators underlying the gamma-band field are spatially distinct from those underlying the MLR as well as the N1 (Pantev et al., 1993).

The early phase-locked GBR was initially associated with sensory coding processes, while the non-phase-locked activity between 200 and 400 ms represents perceptual and cognitive functions (Karakaş and Başar, 1998). Later, it was shown that early gamma-band activity might also reflect cognitive processes (Karakaş et al., 2001). In this regard, recent reports describe modulations of these early gamma-band oscillations by memory matching (Herrmann et al., 2004b) and attention (Tiitinen et al., 1993; Senkowski and Herrmann, 2002; Fell et al., 2003; Busch et al., 2006). Non-phase-locked GBRs on the other hand have been related to cognitive processes including memory encoding and retrieval (Sederberg et al., 2003; Gruber et al., 2004), working memory (Tallon-Baudry et al., 1998), and learning (Gruber et al., 2001; Keil et al., 2001b; Axmacher et al., 2006). In the 'match-and-utilization model', memory was discussed as a global underlying mechanism for both early and late GBRs (Herrmann et al., 2004c).
Some of the earliest studies on this topic investigated the role of synchronous neuronal firing in binding different features of the same perceptual object (Eckhorn et al., 1988; Singer, 1993), suggesting that object perception is associated with enhanced gamma-band activity. Tallon et al. (1995) and Tallon-Baudry et al. (1996) studied oscillatory gamma-band activity during the perception of coherent (Kanizsa triangles) and non-coherent (non-Kanizsa triangles) stimuli (see Fig. 1.2).

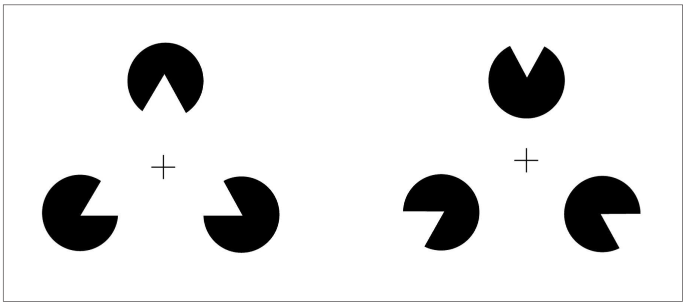

Figure 1.2: Example stimuli applied in the studies of Tallon et al. (1995) and Tallon-Baudry et al. (1996): virtual Kanizsa triangle (left) and non-Kanizsa triangle stimulus (right). The authors reported a larger induced GBR at 280 ms to the Kanizsa triangle than to non-Kanizsa triangle.

In the left part of this figure you will probably see the edges (illusory contours) of an entire triangle, even though the figure is defined only by the notches in the inducers. The researchers reported a larger induced GBR at 280 ms in response to Kanizsa figures compared with non-Kanizsa figures in which the inducers were rotated and therefore no figure was perceived. They concluded that the late induced gamma-band activity is functionally relevant for feature integration or for matching with an internal representation of the object.

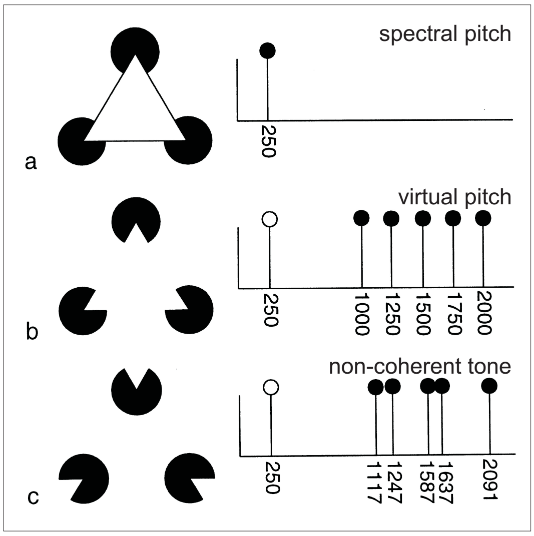

Figure 1.3: Kanizsa stimuli (left side) vs. equivalent sound stimuli (right side). (a) Spectral pitch of 250 Hz corresponding to the real triangle. (b) Virtual pitch consisting of the 4th to 8th harmonics of the missing fundamental frequency of 250 Hz. (c) Non-harmonic complex tone with components corresponding to prime numbers within the frequency range 1117-2091 Hz (Parts of the figure are redrawn from Knief et al., 2000.).

An auditory experiment was performed by Knief et al. (2000) as an analog to this Kanizsa experiment. They investigated gamma-band activity in response to different coherent and non-coherent complex tones (see Fig. 1.3). The participants were ask to detect a target tone (not contained in Fig. 1.3) and reporting it by pressing a button as quickly as possible. The authors did not find any differences in the induced gamma-band activity between the stimulus categories. However, the cortical sources of the evoked GBR for spectral and virtual pitches (comparable with the real and illusory triangle in the visual modality) were found to be closer together. The cortical source for the non-coherent tones were located more anterior to those of the coherent tones, suggesting that different cortical areas were active in processing spectral/virtual pitches and non-coherent tones.

The processing of perceptual information further underlies the distinction whether it appears in a bottom-up or top-down fashion. The classical view of information processing is that of a bottom-up process in a feedforward hierarchy from lower to higher cortical areas. The perceptual process starts at sensory receptors and continues with the integration of sensory information. Therefore, it

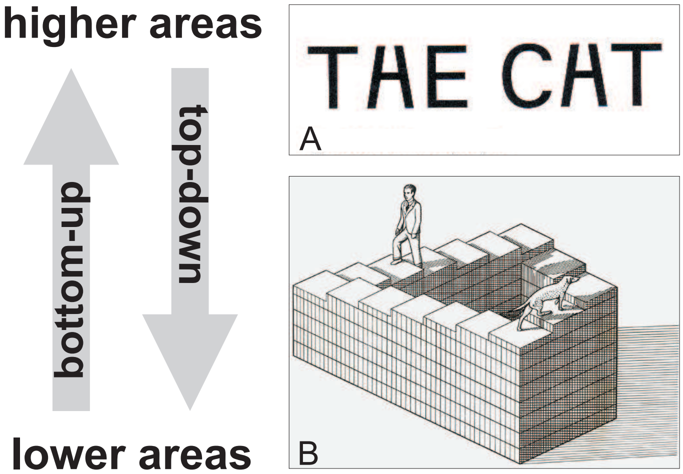

Figure 1.4: Bottom-up and top-down processing: Left: Bottom-up processing occurs from lower to higher cortical areas, whereas higher associative areas influence lower cortices by feedback connections during top-down processing. Right: The influence of top-down processing by knowledge and the context (A) and by knowledge about geometrical rules (B) is exemplified.

is termed data- or stimulus-driven. In many situations, however, our perception is subjective and influenced by past experiences, knowledge, attention, or expectations. As an example, in Figure 1.4A you probably read "THE CAT", although the middle letter in each word is identical in form. The context, given through the knowledge of the English words, causes us to perceive the same object differently. This is labeled as top-down processing or schema-driven because higher brain functions exert a dominant influence over stimulus processing involving feedback connections from higher associative to lower primary cortices. In reading, as the example shows, we do not only register the letters and words (bottom-up), but also perceive the letters depending on our expectations and the particular context (top-down). As a further example of a top-down process, Figure 1.4B[1] shows a picture of an endless staircase that was painted by the English biologist Lionel Penrose in 1962. By the knowledge about geometrical objects and rules, this staircase emerges as an impossible object and we are not able to group features into a meaningful object.
In the end, both bottom-up and top-down processes are important during our perception and frequently work together to ensure accurate and rapid processing of information.

In the following both Sections 1.2 and 1.3, I give a more precise overview about the psychophysiological evidence suggesting that both bottom-up and top-down effects play a crucial role during processing of input stimuli in the auditory as

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[1] The image was found at http://www.ucl.ac.uk/Library/special-coll/knowledge.shtml

well as visual modality.

1.2 Bottom-up modulation in the auditory and visual system

Information processing typically starts with basic sensory aspects concerning for example the perception of brightness, color, or loudness. The investigation of how sensory experiences are related to physical stimulation and physiological functioning is a basic prerequisite for studying and understanding cognitive processing. This is exemplified in Figure 1.5, showing two natural scences with an animal that you can meet in everyday life. Although the pictures widely contained the same colors, there is one meaningful difference: it might be much easier to detect the dog in the right than the paddock in the left picture. This is caused by a different contrast ratio between the animal and background in both pictures. The contrast between the dog and background is much larger and lead therefore to more defined contours. Stimulus contrast is a fundamental variable encoded by the early visual system and has been shown to influence behavioral responses. Reaction times were shortened as the contrast level of visual stimuli increased (Felipe et al., 1993; Vassilev et al., 2002; Chakor et al., 2005). Thus, a higher contrast results in a faster behavioral reaction and might also influence higher stages of information processing. According to this, it is of high relevance to be aware of stimulus related modulations on early processing.

Figure 1.5: Natural scenes and visual contrast: The paddock (left) on the ground appears to be more difficult to detect than the dog (right). This is caused by a different contrast ratio between the animal and background (Both pictures were taken by E. Schadow.).

In this section, I will concentrate on early visual and auditory processing mechanisms. Since the current dissertation exclusively presents EEG experiments, I will mainly report results of EEG studies concerning event-related potentials (ERPs) and GBRs. ERPs reflect phasic modulations of brain activity, which are time-locked to the onset of an event, and have been linked to many perceptual and cognitive processes.

Bottom-up modulations in the ERPs are reflected in the early components during the first 100 milliseconds after stimulus onset. The influence of visual stimulus properties, for instance size, luminance, contrast, or spatial frequency is well examined in the ERP literature. These so called exogenous effects on visually evoked potentials (VEPs) have been investigated predominantly using checkerboard stimuli or sinusoidal gratings in steady-state paradigms (Celesia, 1993). Changes of the aforementioned stimulus parameters lead to changes in the latency and amplitude of the early VEP, in particular of the P100. For instance across a wide range of luminance or contrast levels, the P100 amplitude increased and the latency decreased with increasing luminance (Pastrnáková and Peregrin, 1977) or contrast (Campbell and Kulikowski, 1972; Spekreijse et al., 1973). The size of the stimlus area modulates the VEP amplitude as well: Bartl et al. (1978) reported an amplitude enhancement with increasing size of the stimulus area and further a maximal amplitude at 7.5 - 10 degrees of visual angle.
A number of studies in animals and humans reported that oscillatory responses in the gamma-frequency range change depending on a change in different stimulus features. In recordings from cat retinal ganglion cells, large, but not small, stimuli elicited high-frequency oscillatory potentials (Neuenschwander et al., 1999). The same size dependency was observed in frogs (Ishikane et al., 1999) and rabbits (Ariel et al., 1983). Similar results in humans have been reported. Busch et al. (2004) demonstrated that stimulus features such as size and eccentricity significantly influence the evoked gamma-band activity. The largest and most centrally presented stimulus yielded the strongest GBR. Other studies in humans reported that gamma-band activity varies with the spatial frequency as a further stimulus characteristic (Tzelepi et al., 2000; Bodis-Wollner et al., 2001; Fründ et al., 2007a). Thus, the occurrence of evoked gamma-band activity was shown to be most sensitive to stimulus properties.

Exogenous auditory evoked potentials (AEPs, e.g. N1 at 100 ms) also primarily depend on characteristics of the external stimulus. Many studies consistently reported a strong intensity dependency of the early AEP (Rapin et al., 1966; Beagley and Knight, 1967; Polich et al., 1996; Carrillo-de-la-Peña, 1999; Neukirch et al., 2002). With increasing stimulus intensity the N1 response increases in amplitude and decreases in latency. At constant levels of intensity, the N1 amplitude varies with the tonal frequency of the stimulus (Picton et al., 1978). The N1 decreases with increasing tonal frequency particularly at frequencies greater than 2000 Hz. For the auditory GBR, a similiar effect was demonstrated by Lenz et al. (2008). However, in that study the gamma-band amplitude increased from 250 Hz to frequencies around 1000 Hz and decreased at higher frequencies. This finding suggests that the auditory GBR is also modulated by physical stimulus parameters, but compared to the visual domain, bottom-up modulation of the auditory GBR are sparsely investigated. To my knowledge, further effects of auditory stimulus features on gamma-band activity such as sound intensity, pitch, timbre, or the combination of multiple frequencies have not yet been reported. Knowing and controlling such effects is necessary for investigations of auditory cognition in order to yield optimal GBRs and not to confound task (cognitive) effects with stimulus effects (see Busch et al., 2004, for a similar discussion in the visual modality).

1.3 Top-down modulation in the auditory and visual system

Our visual and acoustic environment appears to be very complex and different visual impressions or sounds occur simultaneously. This requires a fast perceptual analysis and organization of incoming information which is often influenced and facilitated by top-down processes. The auditory system has to segregate and integrate different sounds into meaningful auditory units or objects, which is also known as auditory scene analysis (Bregman, 1994). Mechanisms for this perceptual organization in the visual system are summarized in the Gestalt laws (Koffka, 1935). During this perceptual analysis attentional processes, memory content, and expectations play a decisive role and are related to oscillatory activity in the gamma-band in several studies (for a review, see Engel et al., 2001).

Most notably, the influence of **attention** has been studied both in animal and in human experiments showing that GBR is enhanced during attentional selection of sensory information. Visual neurons in monkeys responding to a presented stimulus fire in synchrony if the target stimulus is attended (Fries et al., 2001; Bichot et al., 2005). In humans, several visual and auditory experiments have demonstrated similar effects. Target stimuli, capturing a higher amount of attention, trigger a stronger early GBR than non-target stimuli (Yordanova et al., 1997; Herrmann et al., 1999; Debener et al., 2003; Busch et al., 2006). The effect of top-down processes specifically on the auditory evoked GBR was examined in a study reporting a modulation of the evoked GBR by selective attention, whereas the activity in other frequency bands was not influenced (Tiitinen et al., 1993). Similar attentional effects on the induced GBR in a later time interval (200 - 400 ms) were found during a visual spatial attention task where participants had to shift their attention to the left or right half of the screen to detect target stimuli (Gruber et al., 1999).

Further, gamma-band activity has been associated with maintenance of working and short-term **memory** as well as long-term memory (Herrmann et al., 2004c). It has been proposed that the representation of a specific stimulus relies on a synchronously oscillating assembly of neurons and a memory trace could be established when the synchronous oscillatory firing is maintained in the absence of the stimulus (for a review, see Jensen et al., 2007). This hypothesis was supported by an experiment by Tallon-Baudry et al. (1998), who observed enhanced gamma-frequency power during active maintenance of visual shapes in short-term memory. Recent studies also pointed out that gamma-band activity is involved in matching sensory input to long-term memory representations in the visual and auditory system. The match of a presented stimulus with a memorized template resulted in an enhanced GBR compared to new stimuli (Gruber et al., 2004; Herrmann et al., 2004d; Lenz et al., 2007; Busch et al., 2008). These results were summarized in the 'match-and-utilization model' (MUM), proposed by Herrmann et al. (2004c). The model suggested that such matching processes between bottom-up (sensory signals) and top-down (memory content) information result in increased evoked gamma-band oscillations due to stronger feedback from higher cortical areas. Obviously, it appears that the early evoked GBR reflects an interaction of bottom-up and top-down processes in such a way that early perceptual processes were controlled by higher cognitive mechanisms such as attention or memory (Busch et al., 2006). While during a visual experiment, the match with long-term memory content could already be observed for the early evoked GBR peaking at 90 ms, this effect occurred in the later induced GBR in the auditory domain. Lenz et al. (2007) reasoned that effects of matching processes with auditory long-term memory on the evoked GBR are very improbably, since the perception of complex sounds becomes available in a serial order. Changes in frequency and amplitude have to be analyzed over time and therefore it takes more time to identify a complex sound than a picture which appears at once. For the visual modality it was shown, that sources of the induced gamma-band activity are located in the occipital cortex (Osipova et al., 2006). Therefore, the authors have assumed that retrieval from long-term memory involves a top-down drive, reactivating the visual representation of the familiar stimulus. In contrast to these rather late top-down effects on the induced GBR, Widmann et al. (2007) reported a very early modulation of auditory stimulus processing by top-down guided expectation in an audio-visual integration study.

As another factor that can facilitate efficient processing of information, **expectations** about our environment or incoming signals are discussed (Engel et al., 2001). Most events in everyday life occur predictably for us, which is for instance very important in competitive sports. During the preparation of the next return in a tennis match, the tennis player will be more accurate if the trajectory of the ball fits his expectation. This anticipatory state is presumably represented

as a pattern of neural activity in specific areas of the brain, which might also modulate the brain activity of successive cognitive or motor processes. Thus, at the one hand expectation guided processes can be studied during the preparation of a task (e.g. cueing paradigms) and on the other hand during the task itself if a preparation phase is ensured.
The status of anticipation or expectation and its influence on the processing of forthcoming stimuli was previously investigated with respect to oscillatory activity (Gonzalez Andino et al., 2005; Snyder and Large, 2005; Gómez et al., 2004; Widmann et al., 2007). GBRs were reported to precede the perceptual processing of a visual stimulus and correlated significantly with reaction times (Gonzalez Andino et al., 2005). This activity, occurring before stimulus onset, might facilitate the amplification of neural activity in sensory areas in response to the stimulus. Furthermore, effects of expectation were already found in cueing paradigms, in which a previously presented cue can give some information about the forthcoming stimulus (valid cue vs. invalid cue). In such an experiment, Fründ et al. (2008b) investigated evoked electroencephalographic responses from human participants. On some trials, the participants were cued about the category of the stimulus before it appeared on the screen, on other trials this was not the case. Stimulus anticipation effects were observed for the phase-locking of oscillatory activity in the β-band indicating larger amplitudes for stimuli that were preceded by a valid cue. In the same frequency band, Liang et al. (2002) reported pre-stimulus oscillatory power and coherence in prefontal cortex of a macaque monkey during visual stimulus anticipation, that were highly correlated with the amplitude and latency of early evoked potential components and with response time. This is not only observed in the visual modality: Snyder and Large (2005) studied the relationship between GBRs and the processing of rhythmic tone sequences. Here, induced GBRs appeared to predict tone onsets and persisted even for expected tones that were omitted. In contrast, evoked GBRs occurred in response to tones, but not to tone omissions. The authors concluded that induced gamma-band oscillations might play a role in developing a mental representation of a temporally structured tone pattern, whereas the evoked activity would reflect more stimulus driven aspects. In contrast, Widmann et al. (2007) observed a much earlier modulation of auditory stimulus processing by top-down guided expectation in an audio-visual integration study. Here, visual symbolic information served as a cue and preceded the auditory stimulus, while visual and auditory stimuli could be either congruent or incongruent. In particular, the authors used a symbol-to-sound-matching paradigm in which simple score-like patterns (e.g. ¯- -¯ ¯- -) predict corresponding sound patterns. Only in the case of congruent stimulus presentations, where the prediction about the forthcoming sound matched the sensory input, an enhanced evoked GBR at 42 ms was observed.

In conclusion, top-down related effects on the GBR were demonstrated during early and late processing of auditory as well as visual information. In the case of anticipatory processing, the given literature suggests on the one hand a strong relationship between pre-stimulus oscillatory activity during stimulus anticipation and behavioral responses. Otherwise, there exist diverse results, whether top-down guided expectation is reflected in early or late GBR. Thus, it remains unexplained, if expectation to an event can influence subsequent processing at such an early stage as was already reported for memory- and attention-related influences on stimulus processing.

2 Hypotheses and objectives

The preceding part of the Introduction emphasized that oscillatory brain activity in the gamma-band is involved in bottom-up as well as top-down processes in the visual and auditory modality. Based on this theoretical framework, the current section will give an outline about the conducted experiments including the respective aims and hypotheses.

2.1 Bottom-up modulation in the auditory and visual system

To investigate top-down influences of gamma-band activity it necessitates research about how bottom-up factors modulate the GBR. Thus, two of the current experiments focus on the influence of stimulus features on the GBRs. Since size, eccentricity, and spatial frequency of a stimulus strongly affect the visual gamma-band activity (Tzelepi et al., 2000; Bodis-Wollner et al., 2001; Busch et al., 2004; Fründ et al., 2007a), the first experiment (Chapter 4) investigates the effects of different stimulus contrasts in a discrimination paradigm. As already illustrated in the Introduction, modulations of auditory stimulus characteristics on the GBR have been studied sparsely. Therefore, a second experiment was conducted similar to the first visual experiment, examining the auditory gamma-band activity in response to different sound intensities of sinusoidal tones (Chapter 5). Since most research groups found bottom-up effects in a very early time window, I also expected amplitude differences within the range of evoked GBR.

In conclusion, two hypotheses for the first studies are derived:

> **The early evoked GBR is modulated by the contrast of visual stimuli.**
>
> **The early evoked GBR is likewise influenced by the sound intensity of sinusoidal tones.**

2.2 Top-down modulation in the auditory system

To date the number of studies investigating the functional role of auditory gamma-band activity in higher level perceptual tasks is sparse compared to the visual domain. A substantial difference between perceptual processing of visual and auditory information, for example in binding single features to a coherent percept, is due to the temporal processing. While visual information (e.g. pictures) appears at once, auditory information (e.g. melody, speech) becomes available in a serial order which takes more time to perceive an auditory object. It has been widely accepted that the processing of stimuli is controlled by top-down information, and that gamma-band oscillations are particularly important during this process. Top-down processes can be active also before stimulus appearance, when one has a specific expectancy or anticipation about what will happen in context of a specific task. During such states of expectancy, researchers observed a precise synchrony between local field potentials recorded from different areas in the cat even before the behaviorally relevant stimulus appeared (Engel et al., 2001). In humans, influences of expectation were often investigated in cueing paradigms, mainly constrained to the visual domain. In a third experiment, I have therefore studied the impact of stimulus anticipation on auditory stimulus processing and how early potential effects can be observed (Chapter 6). Since anticipatory-related activity, occurring before stimulus onset, might facilitate the amplification of brain activity in sensory areas in response to the stimulus, it is most likely that an effect of anticipation is reflected in the early evoked GBR. In the visual modality, this process was discussed as matching between the incoming stimulus and a previously activated template (i.e. by anticipation) which results in enhanced evoked GBR in the case of a successful match (Herrmann et al., 2004c).

Therefore, the third hypothesis reads as follows:

> **The influence of anticipation on the auditory stimulus processing is reflected in an increased early evoked GBR.**

3 General Method

While the specific methods of each study are reported in the corresponding sections, I will describe the more general methodology in this chapter. At first, I will introduce the electroencephalogram (EEG), which was recorded in all reported experiments.

3.1 Electroencephalogram

The EEG is a measure of electrical brain activity from the scalp. The first recordings were made by the German psychiatrist Hans Berger in 1929 in Jena (Berger, 1929). The waveforms recorded are thought to reflect the activity of the surface of the brain, the cortex. This activity is influenced by the electrical activity from the brain structures underneath the cortex as well. The amplitude of the EEG is about 100 μV when measured on the scalp, and about 1-2 mV when measured on the surface of the brain (electrocorticogram, ECoG). The EEG represents temporally and spatially summed postsynaptic potentials of cortical pyramidal cells (Zschocke, 2002, Chap.1). When neurons are activated, local current flows are produced. The currents that flow during synaptic excitations of the dendrites of many pyramidal neurons in the cerebral cortex constitute the main part of the EEG. Differences of electrical potentials are caused by summed postsynaptic graded potentials from pyramidal cells that create electrical dipoles between soma (body of neuron) and apical dendrites (neural branches). Only large populations of active neurons can generate electrical activity recordable on the head surface.

A prerequisite in order to functionally and anatomically interpret EEG data is a standardized positioning of the electrodes on the scalp relatively to the cerebral structure beneath. Therefore, the internationally standardized 10-20 system is employed to record the EEG (Jasper, 1958). In this system, electrodes are located in special positions on the surface of the scalp. The head is divided into proportional distances in steps of 10% and 20%, respectively, starting at prominent skull landmarks (nasion, preauricular points, inion). This provides adequate coverage of all regions of the brain and allows between subjects comparisons.

The EEG is often contaminated by signals without cerebral origin. These are termed artifacts and can be divided into physiological and non-physiological origin. While physiological artifacts are generated by the participant, non-physiological artifacts arise from the immediate participant surroundings (i.e. equipment, environment). The most common types of physiological artifacts are cardiac, glossokinetic, muscle, eye and body movements, respiratory, pulse, and skin artifacts. Non-physiological artifacts are generated e.g. by impedance fluctuations, cable movements, or broken wire contacts. Artifacts should be removed or corrected by specific algorithms within the EEG traces. For a better discrimination of different physiological artifacts, additional electrodes for monitoring eye movement activity are important. In all of the current studies, EEG epochs containing artifacts were removed by an automatic algorithm and further by visual inspection.

In the following sections, two different measures for analyzing EEG data will be introduced and explained: the event-related potential and event-related oscillatory activity in the frequency range between 30-80 Hz. Both measures provide the basis of the data analysis in the presented experiments.

3.2 Event-related potentials

Hans Berger reported variations within the ongoing EEG signal in response to changes of psychological variables (which may be an auditory or visual stimulus). Differences between such experimental variables are not directly seen in the raw signal since the amplitude change is too small in comparison to the amplitude of the 'background' EEG (noise). To extract the specific brain activity in response to an event or stimulus, a larger number of trial repetitions (typically between 20 and 50) of the same stimulus category is necessary. All trials belonging to the same stimulus category are averaged in a specified time window to improve the signal-to-noise ratio. The result of this averaging is termed the event-related potential (ERP). Thus, ERPs are a trial-based measure showing a high temporal resolution that allow an extensive application for studying perceptual and cognitive functions (Picton et al., 2000). By means of ERP analysis, the onset (latency), duration, and the level of engagement (amplitude) of a perceptual or cognitive process can be assessed and, thus, represented in real time. The fact of the high temporal resolution is advantageously, since cognitive processes can be analyzed in temporal correlation with behavioral responses such as reaction times.

However, this method reveals some limitations, which are important to mention as well. The ERPs reflect only a partial record of neural activity engaged in the respective experimental condition, because the activity from subcortical structures is less detectable. The EEG represents only superficial sources of neural activity, while the strength of the signal declines with the distance from its source. Further, the EEG provides a small spatial resolution compared to the functional magnetic resonance imaging (fMRI). The signal which is measured on the scalp results from the summation of electrical activity that may by generated by several different sources in the brain. Therefore, it is very difficult to localize potential sources of the measured neural activity in a specific condition. However, there has been a continuous development of techniques that allow ERP source localization directly based on the scalp fields themselves. The larger the number of electrodes the more improved are source localizations or topographic analyses (Liu et al., 2002).

3.3 Oscillatory brain activity

Until the beginning of the nineties, perceptual and cognitive processes were exclusively studied by employing ERP analyses. Rhythmic brain activity was usually considered as something indicating activation or vigilance (cf. Niedermeyer, 1997).
In the traditional view, it is assumed that ERP components reflect transient bursts of neuronal activity that are time-locked to an external event. Here, ERPs are superimposed on and impedded in ongoing background EEG that is completely unrelated to processing of the task events. This view has been changed, since it was shown that EEG oscillations at a specific frequency changed their magnitude and phase in response to an external event (Engel et al., 2001; Makeig et al., 2004; Yeung et al., 2004). This was revealed by time-frequency analysis of single trial EEG epochs, supporting the role of oscillatory activity in information processing. Such an analysis method can tell us which frequencies have the most power at specific time points and electrode positions. Before explaining time-frequency analysis, I will present a general overview about characteristics and classification of oscillatory brain activity.

3.3.1 Classification of brain oscillations

An EEG signal generally consists of a series of sine waves of different frequencies overlapping in time and with different phase angles with regard to a stimulus presentation. A sine wave is characterized by several parameters: amplitude, frequency, and phase. The amplitude corresponds to the maximum height of the sine waves's peaks (or valley) and is in terms of an EEG signal typically between 0 and 10 μV. The frequency describes the number of complete cycles or oscillations within a 1-second time period and is indicated in Hertz (Hz = cycles per second). The phase of an oscillation relates the relative position of a time point and can be expressed in degrees from 0° to 360°, or in radians from 0 to 2π.

Three different types of oscillatory activity can be distinguished: spontaneous, evoked, and induced respones (Galambos, 1992). Oscillations in the brain without relation to an external stimulus or event reflect spontaneous activity. Evoked activity occurs in response to an external event and is strictly time- and phase-locked to its onset in each trial repetition. Evoked responses can be extracted from noise in the time-domain by averaging the signal evoked in each trial. In contrast, induced activity after stimulation occurs with varying onset times and phase jitter and can therefore not be extracted in time domain of the averaged ERP. In this case, specific signal analysis methods have to be used. As one approach, the time-frequency analysis underwent a renaissance in the middle of the nineties, initiated by the work of Tallon-Baudry who studied EEG gamma-band oscillations and its role in object representation (Tallon-Baudry et al., 1996, 1997). Meanwhile it is generally accepted that the frequency characteristics of the scalp EEG reflect perceptual as well as cognitive processes of the brain (Başar et al., 1999, 2000; Klimesch, 1999).

The next paragraph will introduce the fundamental issues of signal analysis referring to neural brain oscillations and how one can extract meaningful information relating to time and frequency.

3.3.2 Time-frequency analysis

For the analysis of event-related oscillations and their temporal dynamics, EEG signals have to be transformed into a time-frequency representation. The conventional frequency domain analysis is based on the Fourier transform. During a Fourier transform, the time signal is decomposed in a series of sines and cosines, which are characterized by a frequency and an amplitude value. The representation of a signal depending on the frequency is termed as a spectrum. The main disadvantage of this analysis, however, is that it reflects only frequency information and neglects time information. Thus, the Fourier transform provides no information regarding the point of time at which specific spectral components appear.

The wavelet transform or wavelet analysis is probably the most recent solution to overcome the shortcomings of the Fourier transform. At the beginning of the eighties, the french geophysicist Jean Morlet developed an analysis technique, which enables a spectral analysis with a direct time resolution using frequency adapted basis functions (Morlet et al., 1982). Wavelet functions can be used to analyze non-stationary time series and give a distribution of power in two dimensions, namely time and frequency. Signals are described as non-stationary, if frequency portions vary over time. An example is the evoked gamma-band activity, being the main physiological signal presented in the thesis and showing a temporally closed circumscribed activity at a specific frequency range. In order to compute a wavelet transform, the measured EEG signal needs to be convolved with a so-called mother wavelet. As such a mother wavelet, a complex Morlet wavelet was applied in all analyses within this thesis. A Morlet wavelet is a complex sine wave multiplied by a Gaussian envelope, both in the time and frequency domain around the central frequency. A family of wavelets is obtained by shifting and scaling this mother wavelet, such that this set of functions adequately sample all the frequencies present in the EEG signal. As a result, wavelet analyses employ a different time window length for each frequency, with the longest windows applied to the lowest frequency and the shortest window to the highest frequency. However, the advantage of a finer temporal resolution with increasing frequency results in the disadvantage of a diminshed frequency resolution as frequency increases. This convolution procedure leads to a new signal of wavelet coefficients, which quantify the similarity between the original EEG signal and the wavelet function at a specific scale and latency. In the end, the result of this wavelet transform gives a collection of time-frequency representations of the signal.

To extract the phase-locked GBR, the wavelet transform is computed on the averaged evoked potential. In this procedure, the non-phase-locked activity is cancelled out. To identiy the non-phase-locked part, the wavelet transform is therefore applied to every single trial and the obtained absolute values are averaged subsequently. The calculated time-frequency representation contains the sum of phase-locked (evoked) and non-phase-locked (induced) activity and is therefore referred to as total activity. This procedure is illustrated in Figure 3.1. Finally, the frequency specific baseline activity in a prestimulus interval is subtracted to yield values that indicate the oscillatory amplitude (or power) relative to the baseline. Additionally, in all experiments the amount of phase-locking across trials is computed. The absolute value yields a number between 0 and 1, determining the degree of phase-locking, where 1 indicates perfect phase alignment across trials and values close to 0 reflect a high phase variability.

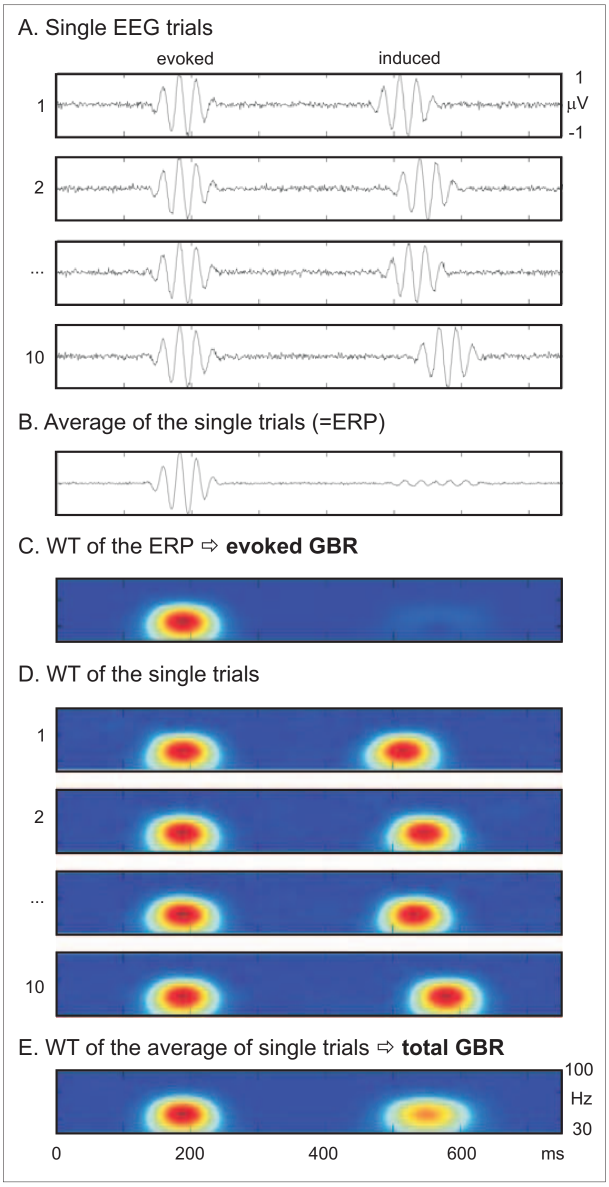

Figure 3.1: To analyze the evoked and induced portion of the GBR two different approaches are required. In (A) 10 simulated single EEG trials are displayed containing early evoked and late induced gamma-band bursts. (B) Averaging all single trials results in the ERP. (C) Computing the wavelet transform (WT) on the ERP yields only the evoked GBR, since the induced portions are cancelled out due to the phase jitter of appearance after stimulus onset. (D) Therefore, the WT is first applied to every single trial. (E) In the next step, the obtained time-frequency representations of each trial, containing both the evoked and induced activity, are averaged. The sum of evoked and induced activity is also referred to as total activity (Parts of the Figure are redrawn from Herrmann et al., 2004.).

4 Experiment I: Visual contrast modulates evoked gamma-band activity in human EEG

The experiment described in this chapter has been published in the Journal "International Journal of Psychophysiology" (Schadow et al., 2007b).

4.1 Introduction

Oscillatory responses of neuronal assemblies in the gamma range (30-80 Hz) have recently been described in the auditory, somatosensory, and especially in the visual modality (Başar et al., 2000). The investigation of modulating factors of gamma activity linked to sensory and cognitive aspects has attracted much interest from numerous research groups (refer to the review of Engel et al., 2001). In general, most studies distinguish between two types of GBRs: the early 'evoked' and the later 'induced' GBR (Başar-Eroglu et al., 1996, cf. Chapt. 3). The early gamma activity observed during the first 100 ms after stimulus onset was initially associated with sensory coding processes (Karakaş and Başar, 1998). Later, it was shown that early gamma activity might also reflect cognitive processes (Karakaş et al., 2001; Senkowski and Herrmann, 2002; Fell et al., 2003; Herrmann et al., 2004b; Busch et al., 2006). For a variety of paradigms, particularly in the visual modality in animals and humans, the late gamma activity around 200-400 ms after stimulus onset is closely related to top-down factors such as attention (Gruber et al., 1999; Müller et al., 2000; Keil et al., 2001a; Fries et al., 2001), task complexity (Posada et al., 2003), and perception (Tallon et al., 1995). Moreover, recent studies have highlighted a pivotal role for both types of gamma activity in memory processes (Herrmann et al., 2004b; Gruber et al., 2004). In the 'match-and-utilization model' memory is discussed as a global underlying mechanism for early and late GBRs (Herrmann et al., 2004c).

Several studies investigating gamma oscillations and their potential functional role in animals and humans reported difficulties in either detecting gamma-band activity or gamma modulations (Tovee and Rolls, 1992; Young et al., 1992; Menon et al., 1996; Lamme and Spekreijse, 1998), or pointed out discrepancies in the experimental findings between animals and humans (Menon et al., 1996; Juergens et al., 1999). Juergens et al. (1999) demonstrated a strong stimulus-related increase in gamma oscillations in monkeys, but no related GBR in humans in the same visual paradigm. Furthermore, some research groups failed to replicate former results regarding visual gamma modulations. The group of Roesler (cited in Juergens et al., 1999) tried to replicate the findings of an experiment on visual gamma modulation done by Tallon-Baudry et al. (1996) without success. These inconsistent findings could be attributed to the diverse methodological approaches concerning the analysis of gamma-band activity (Engel et al., 1992). One further possible explanation for the described difficulties in detecting gamma activity or gamma-band modulations might be differences in the experimental design and in the stimulation. Given the strong dependence of the GBR on stimulus properties, it is conceivable that negative results could have been obtained due to inappropriate stimulation.

Busch et al. (2004) demonstrated that stimulus properties such as size and eccentricity significantly influence gamma activity. The largest and most centrally presented stimulus evoked the highest GBR. Similar results for animals have been reported regarding the stimulus size. In recordings from cat retinal ganglion cells, large, but not small, stimuli elicited high-frequency oscillatory potentials (Neuenschwander et al., 1999). The same sizedependency was observed in frogs (Ishikane et al., 1999) and rabbits (Ariel et al., 1983). Bodis-Wollner et al. (2001) and Tzelepi et al. (2000) pointed out that the power in the gamma frequency range varies with spatial frequency as a further stimulus characteristic. Tzelepi et al. (2000) reported that responses were larger to 4 cycles per degree (cpd) grating stimuli than in response to 1 cpd stimuli, whereas Bodis-Wollner et al. (2001) observed the largest power to a spatial frequency of 5.5 cpd. Thus, the occurrence of evoked gamma activity seems to be most sensitive to stimulus properties such as size, eccentricity, and spatial frequency. Accordingly, we hypothesized that contrast, an additional characteristic of a stimulus, may influence the visual evoked GBR.

Such a modulation by contrast has already been described in event-related potential (ERP) studies of animals and humans (Tolhurst et al., 1981; Harnois et al., 1984; Campbell and Kulikowski, 1972; Bobak et al., 1987; Vassilev et al., 1994). Harnois et al. (1984) observed a dependence of the transient visual evoked potentials (VEPs) on contrast in rats. The latency of the P1 wave decreased linearly and the amplitude of the P1-N2 component increased with increments of contrast up to 55%. Similar results in visual cortical neurons of the cat were found by Tolhurst and colleagues (1981). At low contrasts, the response amplitude increased linearly with contrast, but a logarithmic rise might provide a better description for higher contrasts. However, saturation was observed at very high contrast levels above 50%. Human EEG studies confirmed the results described for animals. VEP latency decreased and amplitude increased as a monotonic function of stimulus contrast (Bobak et al., 1987; Vassilev et al., 1994).

In conclusion, a clear contrast modulation of VEPs was reported in all studies. The aim of the present study was to investigate the influence of contrast on the evoked GBR. We expected to find a similar modulation of gamma amplitude and to replicate results previously reported for VEP amplitudes and latencies.

4.2 Method

4.2.1 Participants

Twenty-one paid subjects (13 females, 8 males, mean age 26.2 ± 5 years) participated in the study. They had normal or corrected-to-normal vision and showed no signs of psychiatric or neurological disorders. All subjects received a written task instruction and gave informed consent to participate. Two subjects were excluded from the data analysis due to numerous eye artifacts. The ethical principles of the Declaration of Helsinki (1964) concerning human experimentation were followed.

4.2.2 Stimuli and Task

Sinusoidal gratings with a constant spatial frequency of 5 cpd at a size of 9 degrees of visual angle were generated using MATLAB 6.5. They were centrally presented on a TFT computer screen placed 115 cm in front of the subjects. The Michelson contrast of the grating pattern (C) is defined as

$$C = \frac{L_{max} - L_{min}}{L_{max} + L_{min}} * 100$$

where L_{max} is the maximum and L_{min} the minimum luminance (Bodis-Wollner et al., 1972). Gratings with three varying contrast levels (5%, 20%, and 50%) were created and presented on a grey background with mean luminance $(L_{max} + L_{min})/2$ (see Fig. 4.1). The present experiment was constructed as a forced-choice discrimination task. The frequent stimulus (80% of presentations) was oriented horizontally, whereas the infrequent stimulus had a vertical orientation. The experimental session consisted of 300 frequent stimuli (100 for each contrast) and 75 infrequent stimuli (25 for each contrast) which were presented in a pseudo-randomized order. Only the frequent stimuli were included in the present analysis. The presentation duration of each stimulus was 1000 ms with an interstimulus interval (ISI) between 1200-2000 ms. Participants were instructed to press a button with their right index finger in response to the infrequent stimuli and another button with their left index finger in response to the frequent stimuli. During the entire experimental session subjects were instructed to fixate a cross in the center of the screen to avoid eyemovement artifacts. Two breaks were included. The length of each break was individually determined by the participant.

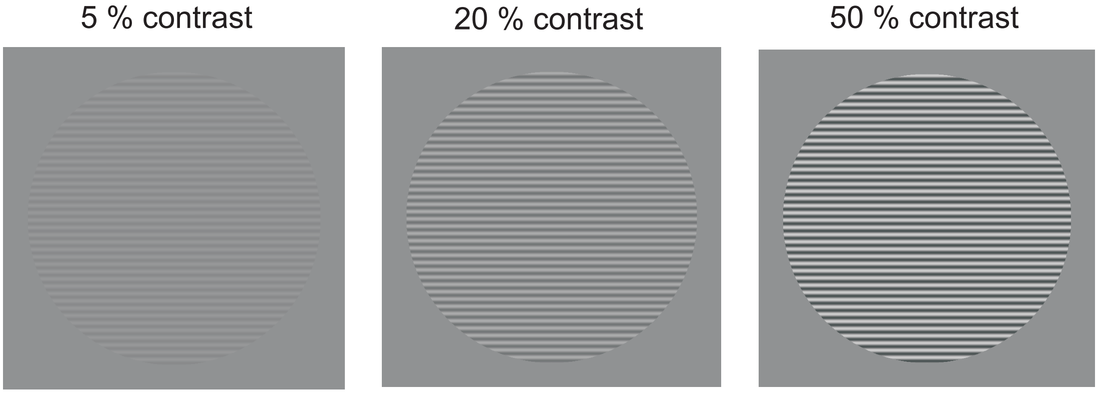

Figure 4.1: The horizontally oriented stimuli at three contrast levels.

4.2.3 Data acquisition

EEG was recorded with a BrainAmp amplifier (Brain Products, Munich), using 32 sintered Ag/AgCl electrodes mounted in an elastic cap (Easycap, Falk Minow Services, Munich) and placed according to the 10-10 system, with a nose-tip reference and ground electrode between Fz and Cz. Eyemovement activity was monitored with an electrode placed suborbitally to the right eye. Electrode impedances were always below 5 kΩ. Data were acquired with a band-pass filter of 0.016-250 Hz and a sampling rate of 500 Hz with an amplitude resolution of 16 bit, i.e. 0.1 μV resolution and $\pm$ 3.28 mV dynamic range. Stimulus markers and EEG were stored on hard disk for further analysis. The EEG was recorded while subjects sat in an electrically shielded, sound-attenuated room. The monitor was place outside this cabin behind an electrically shielded window. All devices inside the cabin were operated on batteries to avoid interference of the line frequency (50 Hz in Germany). Digitized EEG data were transferred to a computer outside the cabin with a fiber-optic cable. Averaging epochs lasted from 200 ms before to 1000 ms after stimulus onset for VEPs and evoked GBRs. Baselines were calculated in the interval from -200 ms to -100 ms and subtracted before averaging. An automatic artifact rejection was computed which excluded trials from averaging if the standard deviation within a moving 200 ms time interval exceeded 40 μV. All epochs were also visually inspected for artifacts and rejected when eyemovements occured, electrode drifts, or electromyographic activity. Whereas data analysis was performed on unfiltered data, VEPs are displayed low-pass filtered at 20 Hz.

4.2.4 Data analysis

Behavioral Data

Responses were scored as correct if the correct button was pressed within a time interval lasting from 200 to 2500 ms after the stimulus onset. False trials were rejected from the behavioral data analysis, as well as trials in which the reaction time (RT) exceeded two standard deviations from the mean.

Visual evoked potentials

The statistical analysis of evoked potentials was performed after selected channels were pooled into a posterior region of interest (ROI). Based on the inspection of the topographies, those electrodes that showed a distinct signal were chosen for the ROI (Cp1, Cp5, Cp6, Cp2, P7, P8, P3, P4, Pz, O1, O2). Two VEP components were defined as peak amplitudes in the time interval of 90 ms to 150 ms (P100) and 160 ms to 230 ms (N200). Amplitudes were analyzed using a repeated measures ANOVA with the factor CONTRAST (3 contrast levels) for each of the two components. Post hoc t-tests of specific comparisons of significant ANOVA effects were calculated. The Greenhouse-Geisser correction, an adjustment used in univariate repeated measures when the sphericity assumption is violated, was applied for all ANOVA models. All post hoc t-tests were Bonferroni corrected.

Early and late gamma-band responses

For the analysis of gamma-band activity, a wavelet transform with a width of 12 cycles based on Morlet wavelets was applied (Herrmann et al., 1999). To analyze the evoked GBR phase-locked to the stimulus, the wavelet transform was applied to the averaged event-related potentials. However, for the non-phase-locked portion of the GBR, each trial was first transformed in the frequency domain and then the resulting wavelet transforms were averaged. This measure represents the total activity, comprising the phase-locked and non-phase-locked part of the GBR. Additionally, the amount of phase-locking across trials was computed. The absolute value yields a number between 0 and 1, determining the degree of phase-locking, where 1 indicates perfect phase alignment across trials and values close to 0 reflect a high phase variability. The frequency used for this wavelet analysis was individually adapted by the time-frequency plane of the O1 electrode. The individual gamma frequency was defined as the highest peak in response to the 50% contrast stimulus in the time interval between 40 and 160 ms (early GBR) as well as 200 and 600 ms (late GBR) after stimulus onset in the gamma frequency range. If no clear GBR peak was visible, a frequency of 40 Hz was chosen for analysis (as done previously, e.g. Herrmann et al., 2004b). For the statistical analysis, early GBRs were defined as the peak amplitude of evoked gamma activity, the phase-locking and total gamma activity in the time-interval between 40 and 160 ms, which turned out to be the peak interval in the time-frequency planes. Thereby, channels were pooled into a ROI comprising the following seven parieto-occipital electrodes which exhibited the strongest responses after visual stimulation: P7, P8, P3, P4, O1, O2, and Pz. Late GBRs were defined as mean amplitude of total gamma activity in the timeinterval between 200 and 600 ms.

A repeated measures ANOVA was calculated for the factor CONTRAST (3 contrast levels). Post hoc t-tests of specific comparisons of significant ANOVA effects were calculated (50% vs. 20%, 50% vs. 5%, and 20% vs. 5%).

4.3 Results

4.3.1 Behavioral data

Participants performed the task with high accuracy (1.3 % errors). The ANOVA of the RTs yielded a significant main effect of CONTRAST ($F[2, 36] = 13.186, p = 0.001$). Responses were fastest for stimuli with the highest contrast (50%, mean RT = 488 ms), whereas subjects responded slowest to low contrast stimuli (5%, mean RT = 520 ms). Post hoc tests showed a significant difference between the conditions 50% vs. 5% ($t[18] = 3.802, p = 0.003$) and 20% vs. 5% ($t[18] = 4.162, p = 0.003$).

4.3.2 Visual evoked potentials

The VEPs of all conditions were characterized by a first positive peak at a latency between 90-150 ms (P100) followed by a negative peak between 160-230 ms latency (N200, Fig. 4.2). P100 amplitudes yielded a main effect of CONTRAST ($F[2, 36] = 16.078, p < 0.001$), indicating increasing amplitudes with increasing stimulus contrast in posterior electrodes (see the scalp topographies for the P100 in Figure 4.3A). Post hoc tests yielded significant effects for the 50% vs. 20% ($t[18] = -4.907, p < 0.001$) and for the 50% vs. 5% ($t[18] = -4.181, p = 0.003$) condition. An ANOVA on the P100 latencies revealed a main effect of CONTRAST ($F[2, 36] = 16.491, p < 0.001$). This result indicates that P100 latencies increase in posterior electrodes with decreasing stimulus contrast. Post hoc tests showed significant differences between all conditions: 50% vs. 20% ($t[18] = 2.854, p < 0.05$), 50% vs. 5% ($t[18] = 6.077, p < 0.001$), and 20% vs. 5% ($t[18] = 2.787, p < 0.05$). No significant modulation by stimulus contrast was obtained for N200 amplitudes or latencies. The scalp topographies of the N200 show a characteristic pattern after visual stimulation with pronounced activation peaks in more lateral posterior electrodes (see Fig. 4.3B).

4.3.3 Early and late gamma-band responses

The wavelet analysis revealed that evoked gamma activity increased when stimulus contrast was increased. Figure 4.4A depicts sample baseline-corrected time-frequency plots for each contrast condition at electrode O2 for one subject. The GBR showed a clear peak in a time window from 60 to 140 ms after stimulus onset for the 50% contrast stimulus. The ANOVA of the peak amplitudes of the evoked

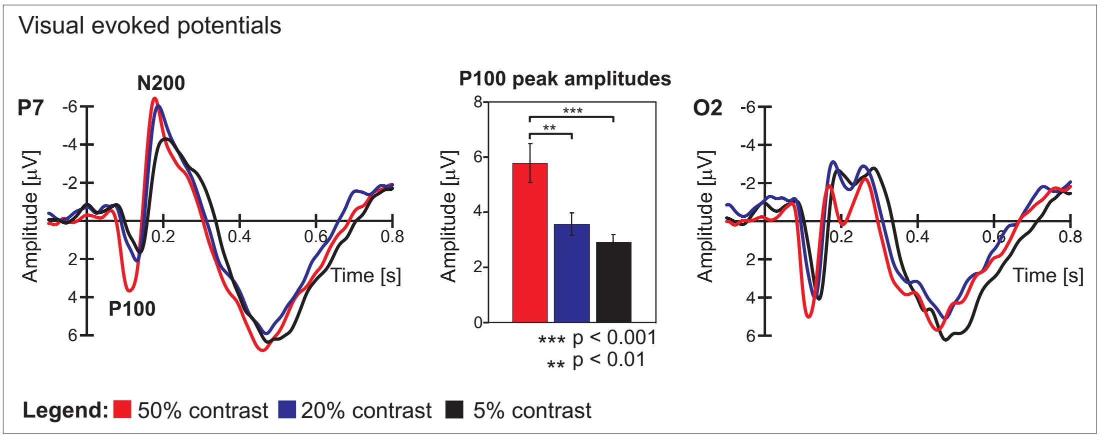

Figure 4.2: Grand average VEPs for all frequent contrast stimuli (50%, 20%, and 5%). Left: VEP waveforms at electrode P7. Middle: Peak amplitudes of the P100 and standard error for all electrodes within posterior ROI. Right: VEP waveforms at electrode O2.

GBR yielded a main effect of CONTRAST ($F[2,36] = 12.658, p < 0.001$; Fig. 4.4B) with larger amplitudes for stimuli with the highest contrast. Additionally, post hoc tests revealed significant differences between the following conditions: 50% vs. 20% ($t[18] = 4.834, p < 0.001$) and 50% vs. 5% ($t[18] = 3.777, p = 0.003$).

Figure 4.5 displays the variation in time of the evoked GBR, phase-locking, and total GBR averaged across all subjects at electrode O2. For this figure, peak frequencies of the individually identified evoked GBRs ranged from 25 Hz to 71 Hz (mean 45 Hz, SD=14.19 Hz). A frequency of 40 Hz was chosen for two participants, who showed no clear GBR peak (as done before, e.g. Herrmann et al., 2004b). Similar to the evoked GBR, we found a significant main effect of CONTRAST for the phase-locking ($F[2,36] = 16.789, p < 0.001$), whereas the analysis of the total GBR, an index of signal power, revealed no CONTRAST effect ($F[2,36] = 2.501, p = 0.101$). Thus, the increase in evoked GBR is most likely based on stronger phase-locking. Although evoked responses for high contrast stimuli occured slightly earlier (96 ms) than for the middle (104 ms) and low contrast stimuli (98 ms), GBR peak latencies did not differ significantly ($F[2,36] = 1.187, p = 0.314$). Figure 4.6 represents the topographies of the evoked GBR for each condition. The evoked GBR in response to the highest contrast stimulus shows a characteristic scalp distribution with a maximum at occipital and posterior electrodes, as reported in previous visual experiments (Busch et al., 2006).

For the late gamma-band activity in the time range between 200 and 600 ms after stimulus onset, the time-frequency planes did not reveal any activity that exceeded the noise level. Therefore, no further statistical analyses were

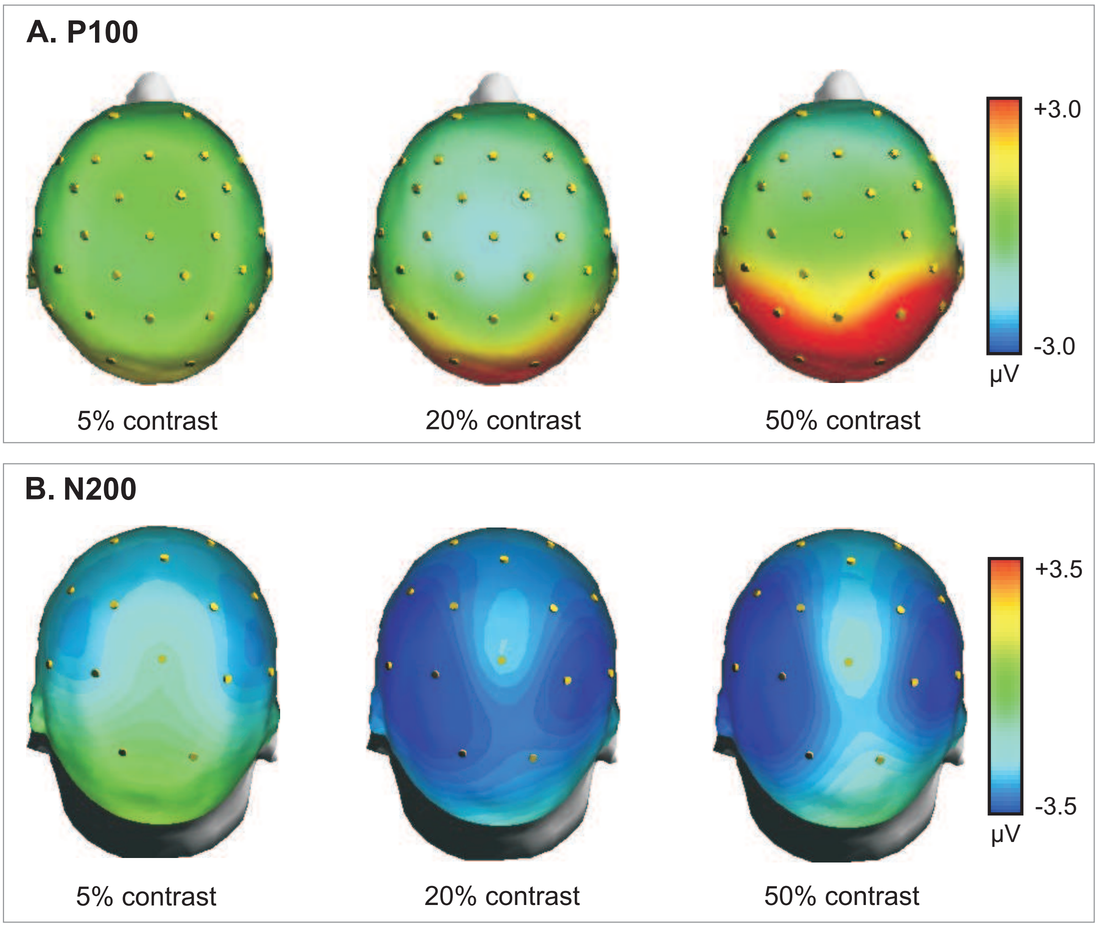

Figure 4.3: A. The first row depicts the scalp topographies of the P100 at its peak latency (112 ms) in the top view. B. In the second row scalp topographies of the N200 at the peak latency (170 ms) are displayed in the back view. Both rows represent the grand average of all subjects (n=19) for each contrast (5%, 20%, and 50%).

calculated.

4.4 Discussion

The goal of the present study was to investigate whether the visual evoked GBR is modulated by contrast as has been well demonstrated for VEPs. For this purpose, stationary sine wave gratings with three different contrast levels were presented.

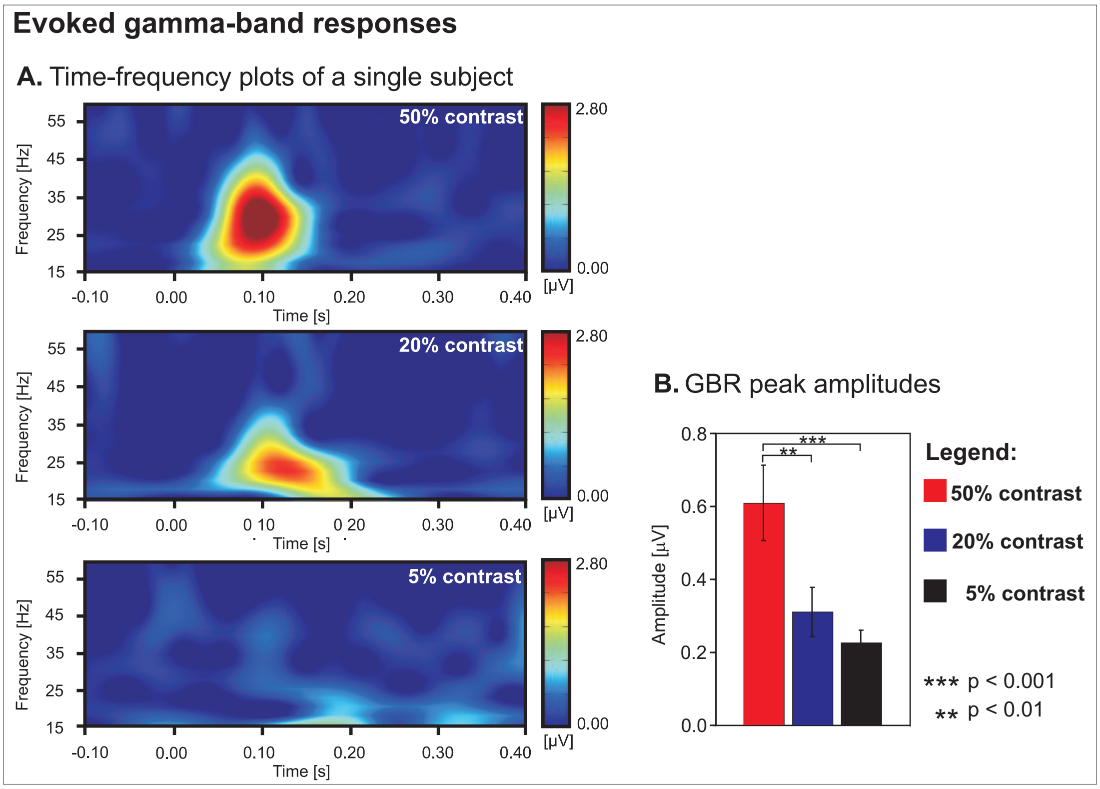

Figure 4.4: Evoked GBRs for all contrast stimuli (50%, 20%, and 5%). A. Sample time-frequency plots at electrode O2 for one subject. B. Peak amplitudes of the GBR and standard error for all electrodes within the posterior ROI.

4.4.1 Behavioral data

The behavioral data show that reaction times are significantly affected by contrast variation. Subjects' responses were shortened as the contrast level increased, which is in accordance with a number of previous experiments (Felipe et al., 1993; Vassilev et al., 2002; Chakor et al., 2005).

4.4.2 Early gamma-band responses

In the present study, gamma frequency oscillations revealed the strongest responses at occipital electrodes. Our results are consistent with findings showing evoked gamma-band activity in response to visual stimulation in a latency range of about 100 ms (Böttger et al., 2002; Senkowski and Herrmann, 2002; Busch et al., 2006). The data demonstrate that stimulus contrast strongly modulates the visual evoked gamma-band oscillations. High contrast stimulation (50%) enhanced the gamma amplitude, whereas the GBR, elicited by low contrast stimuli (5%), did not differ from noise level. In addition to the evoked GBR, we also analyzed the phase-locking and total response in the same time interval to de-

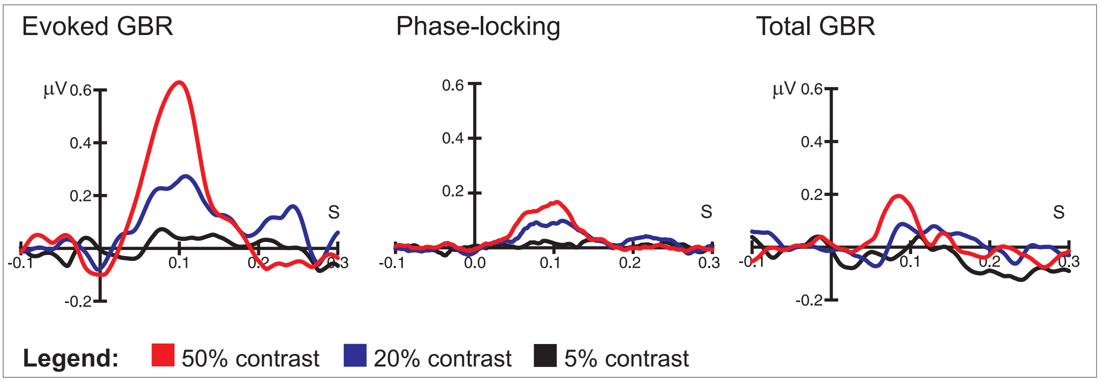

Figure 4.5: Time courses for the evoked GBR, phase-locking, and total GBR (containing the phase-locked and non-phase-locked parts of the GBR) at electrode O2 displayed for all contrast stimuli (50%, 20%, and 5%).

termine whether the contrast effect on evoked activity is caused by a stronger phase-locking to stimulus onset or by an increase in gamma-band power. In the present study, we observed a stronger phase-locking for high contrast stimuli with no significant effect on the total GBR. This result is in accordance with previous studies (Busch et al. 2004, 2006) which found that changes in bottom-up factors (e.g. stimulus properties such as size or contrast) mainly affected the phase-locking of early evoked GBR, while top-down effects (e.g. attention) on GBR derived from an increase in gamma-band power.

Our results are in agreement with recent studies in macaque monkeys that investigated the contrast effect in the gamma-band using local field potentials and multiunit activity (Logothetis et al., 2001; Henrie and Shapley, 2005). Whereas a human magnetoencephalograpic study reported a linear contrast dependency for the late induced gamma-band amplitude (Hall et al., 2005), the present study only observed effects for the early evoked GBR. This discrepancy might be related to the differences in recording as well as analysis methods, but it is also possible that the discrepancy is attributable to differences in the experimental setup (task, number of stimulus presentations). Whereas in the current experiment 100 stimuli per contrast condition were presented for 1000 ms with randomized ISIs to obtain a good signal-to-noise ratio, Hall et al. (2005) presented 25 stimuli per condition in an on-off mode at a frequency of 0.5 Hz where subjects were not required to respond to the stimuli. The employed task in our study required active involvement by the participants, ensuring active processing of the grating stimuli. Since gamma-band oscillations depend on active stimulus processing (Senkowski and Herrmann, 2002; Marshall et al., 1996), this might be one explanation for the differing findings of the two studies. The early GBR phase-locked to the stimulus is regarded as being most sensitive to processing demands (Yordanova et al., 1997). Moreover, we chose randomized ISIs to avoid task expectancy as a

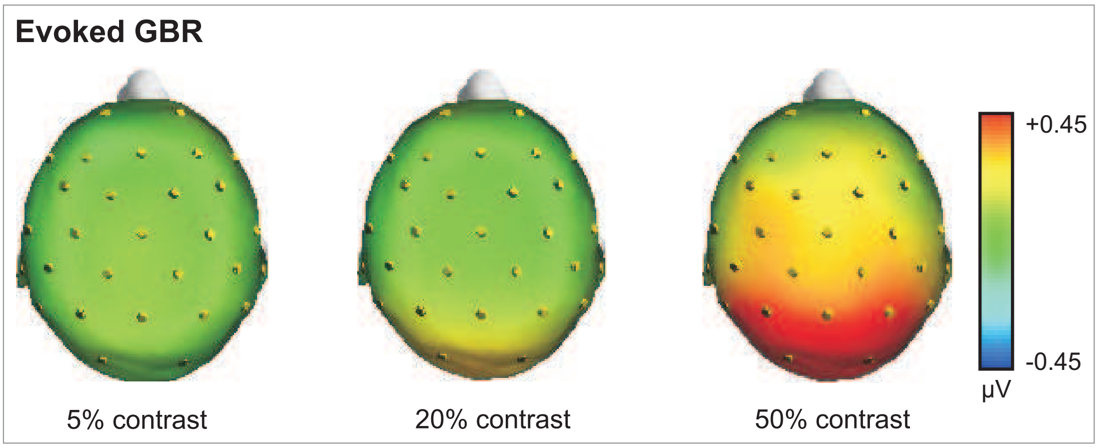

Figure 4.6: Grand averaged scalp topographies of the evoked gamma-band activity at the peak latency (98 ms) are displayed for each contrast (5%, 20%, and 50%).

confounding parameter because it has been demonstrated that the state of anticipation enhances the gamma-band power (Lee, 2003; Fitzgibbon et al., 2004). In addition to the contrast dependency, human studies have reported that oscillatory activity in the gamma range is modulated by changes along a variety of stimulus dimensions in the visual system. The size, eccentricity, luminance, and spatial frequency of a stimulus verifiably affect the magnitude of gamma activity (Busch et al., 2004; Rols et al., 2001; Tzelepi et al., 2000). To date it is still unclear, however, why some research groups failed to find gamma-band activity or gamma-band modulations (Menon et al., 1996; Juergens et al., 1999) and some did not. These conflicting results in the literature may be due to experimental designs in which variables like the aformentioned stimulus features are confounded with the independent variable. Stimulus contrast as one visual parameter is required to integrate stimulus features to form a global percept and segregate such a percept from its background or other elements. A large contrast appears as a very salient cue for segregation and indicates object borders. Hence, future visual studies that analyze early evoked GBRs should choose an appropriate stimulus contrast and control it across different conditions.

4.4.3 Visual evoked potentials

The strongest effects of stimulus contrast for the P100, elicited by grating stimuli, were found at posterior electrodes. As described in the results section, the first positive deflection showed the expected contrast dependency in amplitudes and latencies. While the P100 amplitudes exhibited an increase, the latencies decreased as a function of contrast. These findings are in accordance with both animal (Tolhurst et al., 1981; Harnois et al., 1984) and human studies (Campbell and Kulikowski, 1972; Spekreijse et al., 1973; Wright and Johnston, 1982; Bobak et al., 1987; Vassilev et al., 1994). However, most of these experiments applied a pattern revearsal, an onset-offset presentation, or a moving stimulation. Despite different stimulation settings, contrast variations yield a similar modulation of the visual evoked potentials, namely a monotonic increase of VEP amplitude with an increase in grating contrast. In particular, at low contrast levels Tolhurst et al. (1981) and Wright and Johnston (1982) postulated a linear amplitude increase with contrast, whereas a logarithmic function seems to provide a better explanation for the increased VEP amplitudes at higher contrasts. Regarding the negative component in the later time window between 160-230 ms, no significant contrast effect on amplitude and latency was observed. This result is in line with recent studies that reported a stronger contrast dependency on the P100, while the N200 is rather involved in, and modulated by, motion and form perception (Müller and Göpfert, 1988; Bach and Ullrich, 1997; Göpfert et al., 1998).

The different scalp distributions of the P100 and the N200 after visual stimulation indicated different underlying generators in the cortex (Herrmann and Knight, 2001). The P100 with an occipital topography is probably generated within the ventral part of the occipitotemporal cortex (Heinze et al., 1994; Yamazaki et al., 2000; Martínez et al., 2001; Di Russo et al., 2002). The subsequent negativity (N200) revealed a more distributed topography compared to the P100. Previous studies assumed that this negativity arises from activity in multiple brain areas within the extrastriate occipital and parietal cortex (Gomez Gonzalez et al., 1994; Di Russo et al., 2005).

4.4.4 Conclusion

The present study shows that visual contrast modulates the early evoked gamma-band activity and that the increase in evoked activity is mainly caused by stronger phase-locking. High contrast stimuli appear to be most suitable to elicit a strong response in the human scalprecorded EEG. Therefore, cognitive studies employing visual stimulus material should carefully match low level attributes of their stimulus material to avoid confounding GBR modulations.

5 Experiment II: Sound intensity modulates auditory evoked gamma-band activity in human EEG

The experiment described in this chapter has been published in the Journal "International Journal of Psychophysiology" (Schadow et al., 2007a).

5.1 Introduction

Synchronous neuronal firing in the range from 30-80 Hz appears to be involved in binding different features of an object so that it is perceived as a single, coherent one (Eckhorn et al., 1988; Singer, 1993; von der Malsburg, 1995). This phenomenon is well investigated for animals and humans in the visual modality (Gray et al., 1989; Singer and Gray, 1995; Tallon-Baudry and Bertrand, 1999). Furthermore, the indiviual stimulus features such as size, spatial frequency, and contrast have a noticeable influence on the human gamma activity (Busch et al., 2004; Tzelepi et al., 2000; Schadow et al., 2007b). The mentioned studies reported a systematic variation of gamma-band amplitude with changing stimulus features.

The auditory evoked GBR has been investigated with different methods in animals and humans (Başar et al., 1987; Pantev et al., 1991; Galambos, 1992; Başar-Eroglu et al., 1996). A number of studies argue about whether the auditory evoked gamma-band activity represents an independent brain response functionally distinct from the auditory middle latency response (MLR) and long latency response (e.g. N1) (Başar et al., 1987; Bertrand and Pantev, 1994; Pantev, 1995; Jacobson et al., 1998; Müller et al., 2001). Since several studies observed a similiar amplitude increase with an increasing interstimulus interval for evoked GBRs as shown for the MLR and long latency response (Makeig, 1990; Pantev et al., 1993), Başar et al. (1987) reasoned that the 40 Hz response is a consistent part of the auditory evoked potential. However, dipole localizations suggested that generators underlying the gamma-band field (GBF) are spatially distinct from those underlying the MLR Pa component as well as the N100 (Pantev et al., 1993). In this regard, the spatial separation of the GBF, MLR, and N100 provides evidence that they may arise from different processes in the auditory pathway (Pantev, 1995).

Animal studies with intracranial recordings have shown oscillations with a frequency around 40 Hz, both in the primary and secondary auditory cortex that occurred spontaneously and in response to sensory stimulation (Brett et al., 1996; Franowicz and Barth, 1995; MacDonald and Barth, 1995; Brosch et al., 2002). In humans, GBRs elicited by auditory stimulation were intensively studied in a variety of perceptual and cognitive tasks (Karakaş and Başar, 1998; Crone et al., 2001; Kaiser and Lutzenberger, 2005b; Karakaş et al., 2006). In different experiments, gamma-band activity was functionally related to Gestalt perception and attention as well as memory processing (Tiitinen et al., 1993; Yordanova et al., 1997; Knief et al., 2000; Debener et al., 2003; Kaiser and Lutzenberger, 2005a). However, the effects of auditory stimulus features on gamma-band activity such as loudness, pitch, timbre, or the combination of multiple frequencies have not yet been reported. Knowing and controlling such effects is nessecary even for investigations of auditory cognition in order to yield optimal GBRs and not to confound task (cognitive) effects with stimulus effects (see Busch et al. [2004] for a similiar discussion in the visual modality).

Processing of different sound intensities has already been investigated for auditory evoked potentials (AEPs). These studies consistently found a strong intensity dependency of the early AEP (Rapin et al., 1966; Beagley and Knight, 1967; Polich et al., 1996; Carrillo-de-la-Peña, 1999; Neukirch et al., 2002). All of them have reported a shortening of N1 latency and a pronounced increase of the N1-P2 peak-to-peak amplitude as the intensity of pure sinusoidal tones was increased. This loudness dependence phenomenon has also attracted much interest in psychiatric research, since several studies examined the serotonergic modulation of the cortical loudness dependency (Hegerl and Juckel, 1993; Hegerl et al., 2001; Debener et al., 2002). While Hegerl and colleagues stated that low serotonergic neurotransmission is associated with an enhancement in N1-P2 amplitude with increasing stimulus intensity, recent studies have demonstrated contradictory findings (Dierks et al., 1999; Debener et al., 2002; Massey et al., 2004). These studies manipulated the cerebral levels of serotonin by using tryptophan depletion and did not find significant effects of tryptophan depletion on intensity dependence of AEPs. Thus, it remains questionable whether the loudness dependency of AEPs is a specific biological marker of serotonergic activity.

The present study compared gamma-band activity in response to different sound intensity levels of a pure sinusoidal tone. This study represents a counterpart to the visual experiment analyzing the effects of stimulus contrast (Schadow et al., 2007b). We analyzed the GBRs in an early and late time interval. In the early time window, evoked and total GBR as well as the strength of phase-locking were calculated. Presenting the phase-locking values and the total GBR completes the description of the evoked GBR and might give an important explanation for amplitude differences in the early GBRs (Busch et al., 2006). These three measures might resolve the question of whether stronger evoked GBRs arise from stronger phase-locking of ongoing oscillatory activity or from signal increases. Based on the theoretical considerations, we expected to find enhanced GBRs with increasing intensity of the auditory stimulus. In addition, we aimed to replicate the aforementioned results for auditory evoked potentials.

5.2 Method

5.2.1 Participants

Twenty-one paid subjects (13 females, 8 males, mean age 26,2 ± 5 years) participated in the study. They had no history of hearing impairments and showed no signs of psychiatric or neurological disorders. All subjects received a written task instruction and gave informed consent to participate. Two subjects were excluded from the entire data analysis due to numerous eye artifacts. The ethical principles of the Declaration of Helsinki (1964) concerning human experimentation were followed.

5.2.2 Stimuli and Task

Two pure sinusoidal tones (2000 Hz, 4000 Hz) were generated using Adobe Audition V1.0 (Adobe Systems Inc., 2004) and delivered binaurally through insert earphones (EARTone 3A). The duration of each stimulus was 500 ms (10 ms rise and fall time) with a randomized interstimulus interval (ISI) between 1200-2000 ms. For each participant and each sine tone, the individual hearing threshold for the left and the right ear was determined in intensity steps of 1 dB. Based on the individual sensation level (SL), three intensities (30, 45, 60 dB) were selected for the high and the low frequency tone. A calibrated attenuator was used to control the sound levels (Tucker-Davis Technologies, model PA5). This attenuator has two channels - one for each ear. The attenuator is set before the presentation of every sinusoidal tone. Thus, we can adjust for each ear and each tone individually.

The present experiment was constructed as a forced-choice discrimination task. The frequent stimulus ($p=0.8$) was a 2000 Hz tone, whereas a 4000 Hz tone served as the infrequent stimulus. The experimental session consisted of 300 frequent stimuli (100 for each intensity) and 75 infrequent stimuli (25 for each intensity) which were presented in a pseudorandomized order. Only the frequent stimuli were included in the present analysis.

Since it has been demonstrated that stimulus-related motor activation modulates the GBR (De Pascalis and Ray, 1998; Yordanova et al., 2001, 2002), all stimuli required a motor response to avoid confounding effects. Participants were instructed to press a button with their right index finger in response to the infrequent stimuli and another button with their left index finger in response to the frequent stimuli. During the entire experimental session, subjects were instructed to fixate a cross in the center of the screen to avoid eye movement artifacts. Two breaks were included. The length of each break was individually determined by the participant.

5.2.3 Data acquisition

EEG was recorded with a BrainAmp amplifier (Brain Products, Munich), using 32 sintered Ag/AgCl electrodes mounted in an elastic cap (Easycap, Falk Minow Services, Munich). The electrodes were placed according to the 10-10 system, with a nose-tip reference and ground electrode between Fz and Cz. Eye movement activity was monitored with an electrode placed suborbitally to the right eye. Electrode impedances were kept below 5 kΩ. Data were acquired with a band-pass filter of 0.016-250 Hz and a sampling rate of 500 Hz with an amplitude resolution of 16 bit, i.e. 0.1 μV resolution and ± 3.28 mV dynamic range. Stimulus markers and EEG were stored on hard disk for further analysis. The EEG was recorded while participants sat in an electrically shielded, sound-attenuated cabin. The monitor was placed outside behind an electrically shielded window. All devices inside the cabin were operated on batteries to avoid interference of the line frequency (50 Hz in Germany). Digitized EEG data were transferred to a computer outside the cabin using a fiber-optic cable. Averaging epochs lasted from 200 ms before to 1000 ms after stimulus onset for AEPs and evoked GBRs. Baselines were calculated in the interval from -200 ms to -100 ms and subtracted before averaging. An automatic artifact rejection was computed which excluded trials from averaging if the standard deviation within a moving 200 ms time interval exceeded 40 μV. Afterwards, all epochs were also visually inspected for artifacts and rejected when eye movements, electrode drifts, or electromyographic activity occured. Whereas data analysis was performed on unfiltered data, AEPs are displayed low-pass filtered at 20 Hz.

5.2.4 Data analysis

Behavioral Data

Responses were scored as correct if the correct button was pressed within a time window lasting from 200 to 2500 ms after the stimulus onset. False trials were rejected from the behavioral data analysis, as well as trials in which the response time (RT) exceeded two standard deviations from the mean.

Auditory evoked potentials

The statistical analysis of AEPs was performed after channels which exhibited the strongest activity were pooled into a fronto-central region of interest (ROI) (F3, Fz, F4, Fc5, Fc6, Fc1, Fc2, C3, C4, Cz, Cp1, Cp2 - see the N100 scalp topographies in Fig. 5.1). Two AEP components were defined as peak amplitudes in the time interval from 60 ms to 160 ms (N100) and 290 ms to 400 ms (P340)[1]. Similiar to previous studies, the analysis of the loudness dependence phenomenon was based on the peak-to-peak amplitude of the N100-P340 complex. This peak-to-peak amplitude as well as N100 amplitude and latency were analyzed using a repeated measures ANOVA with the factor INTENSITY (3 intensity levels). F- and p-values were reported as well as effect sizes of selected comparisons (partial eta-squared - η_p^2)[2]. In order to ensure that all values that entered into the ANOVA were normally distributed, the Kolmogorov-Smirnoff test was applied. The analysis for each variable revealed p-values that were >.20. The Greenhouse-Geisser correction, an adjustment used in univariate repeated measures when the sphericity assumption is violated, was applied for all ANOVA models. Post hoc t-tests of specific comparisons of significant ANOVA effects were calculated. All post hoc tests were Bonferroni corrected for multiple comparisons.

Early and late gamma-band responses

For the analysis of the gamma-band activity, a wavelet transform with a width of 12 cycles based on Morlet wavelets was applied (Herrmann et al., 1999). To analyze the evoked GBR phase-locked to the stimulus, the wavelet transform was applied to the averaged event-related potentials. However, for the non-phase-locked portion of the GBR, each trial was first transformed in the frequency domain and then the resulting wavelet transforms were averaged. This measure represents the total activity comprising the phase-locked and non-phase-locked part of the GBR. Additionally, the amount of phase-locking across trials was computed. The absolute value yields a number between 0 and 1 determining the degree of phase-locking, where 1 indicates perfect phase alignment across trials and values close to 0 reflect a high phase variability. From the obtained time-frequency representations, the average from the baseline between 200-100 ms before stimulus onset was subtracted.

Since previous studies have shown that the frequency of oscillatory brain activity varies notably between subjects, the frequency used for the wavelet analysis was individually adapted by the time-frequency representation of the signal at Cz (Busch et al., 2004; Klimesch, 1999). The individual gamma frequency was defined as the highest peak in response to the 60 dB tone in a time interval between 20 and 90 ms (early GBR) as well as 200 and 600 ms (late GBR) af-

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[1] Note, that this ERP component ist referred to as P2 in many sensory experiments. The latency of the P2 component could extend to frequently presented stimuli, if the task requires a motor response to infrequent (target) stimuli (Starr et al., 1997). Thus, we designated this component P340 to account for the later latency.

[2] The η_p^2 is the proportion of the effect and the error variance that is attributable to the effect (Pierce et al., 2004).

ter stimulus onset in the gamma frequency range. However, the time-frequency planes did not reveal any late gamma-band activity in the selected time interval that exceeded the noise level. Therefore, further statistical analyses and the description of the results were only related to the early gamma-band activity. If no clear GBR peak was visible, a frequency of 40 Hz was chosen for analysis (as done previously, e.g. Herrmann et al., 2004b). This had to be done for two subjects in the early time interval. The peak frequencies of the individually identified evoked GBRs ranged from 26 Hz to 65 Hz (mean 42.6 Hz, SD=11.7 Hz). For the statistical analysis, early GBRs were defined as the peak amplitude of evoked gamma activity, the phase-locking and total gamma activity in the time interval between 20 and 90 ms, which turned out to be the peak interval in the time-frequency planes. Thereby, channels were pooled into a ROI comprising the following seven central electrodes which exhibited the strongest GBRs: FC1, FC2, C3, C4, Cz, Cp1, Cp2 (see the scalp topographies in Fig. 2). We performed a repeated measures ANOVA using the factor INTENSITY (3 intensity levels). The Kolmogorov-Smirnoff test applied to each variable revealed p-values that were $>$.20. Post hoc t-tests of specific comparisons of significant ANOVA effects were additionally calculated (60 dB vs. 45 dB, 60 dB vs. 30 dB, and 45 dB vs. 30 dB). For all ANOVA models the Greenhouse-Geisser correction was applied and post-hoc t-tests were Bonferroni corrected.

5.3 Results

5.3.1 Behavioral data

Participants easily performed the task with high accuracy (2.4% errors). The error rates were not influenced by sound intensity ($F[2, 36] = 1.702, p = 0.205$). The responses to the 45 dB tone (meanRT=421 ms) were somewhat faster than to the 60 dB (meanRT=439 ms) and 30 dB (meanRT=432 ms) tone, however, this difference was not signifcant ($F[2, 36] = 2.858, p = 0.097$).

5.3.2 Auditory evoked potentials

The AEPs of all conditions were characterized by a first negative peak at a latency at 100 ms (N100) followed by a positive peak at approximately 340 ms latency (P340, Fig. 5.1). For all conditions the strongest N100 responses were observed at fronto-central sites, while the P340 responses were strongest at posterior-central electrodes (see the scalp topographies for the N100 and P340 in Fig. 5.1). Peak-to-peak amplitudes of the N100-P340 were larger for higher stimulus intensities ($F[2, 36] = 6.441, p < 0.05, \eta_p^2 = 0.264$). Post hoc comparisons revealed a significant effect for the 60 dB vs. 30 dB tone condition ($t[18] = -3.004, p < 0.05$). Post hoc tests between 60 dB vs. 45 dB and 45

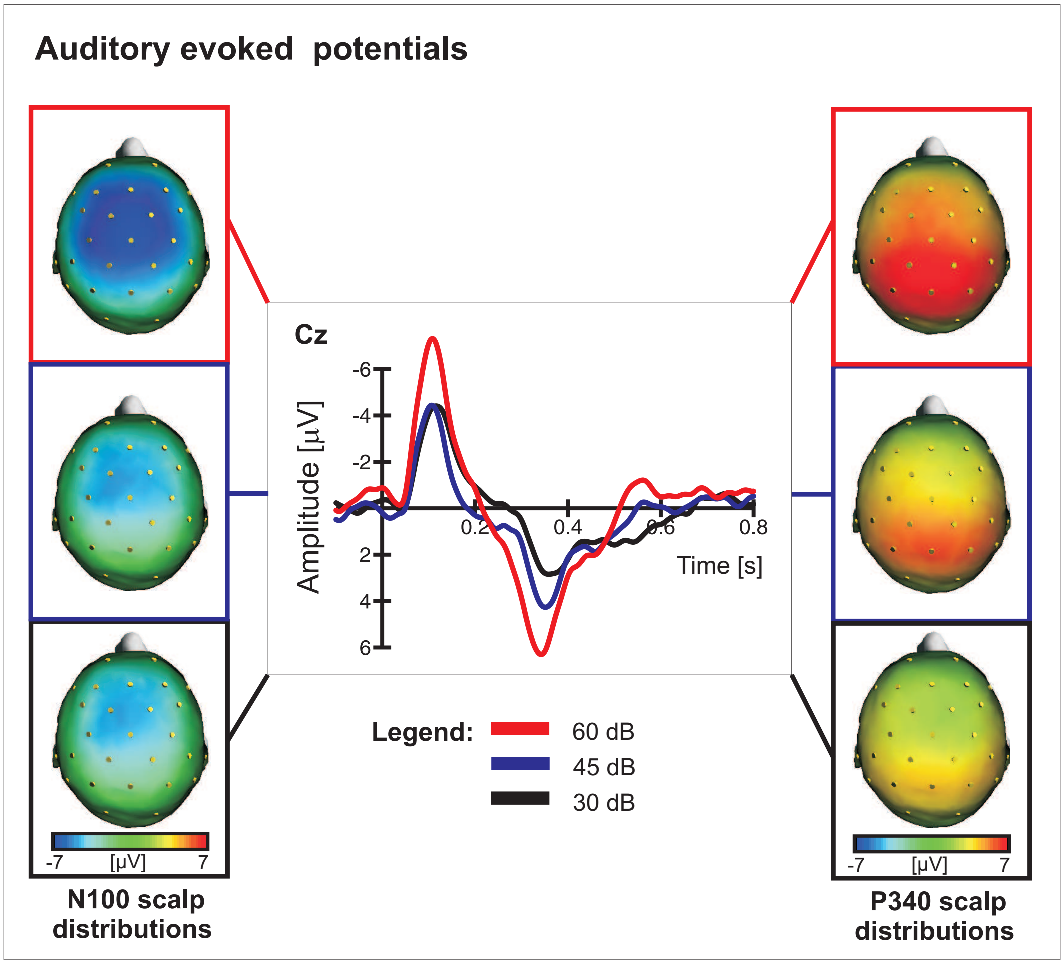

Figure 5.1: Left column: Scalp distributions of the N100 at its peak latency (108 ms). Middle column: Auditory evoked potentials at electrode Cz for 60 dB SL (red), 45 dB SL (blue), and 30 dB SL (black) sine tones. Right column: Scalp distributions of the P340 at the peak latency (342 ms).

dB vs. 30 dB revealed no significant differences, although the data showed a statistical trend for larger amplitudes at higher sound intensities. In contrast, no significant effect of stimulus intensity was found for N100 amplitudes ($F[2,36] = 0.122, p = 0.858, \eta_p^2 = 0.007$). Instead, N100 latencies were shorter for higher sound intensities ($F[2,36] = 4.574, p < 0.05$). Post hoc tests yielded only a significant effect between 60 dB vs. 30 dB ($t[18] = 3.265, p < 0.05$), but not for the remaining comparisons (60 dB vs. 45 dB and 45 dB vs. 30).

5.3.3 Early gamma-band responses

The wavelet analysis revealed an increase in evoked gamma-band activity for higher sound intensities. This is illustrated in Figure 5.2 by the baseline-corrected

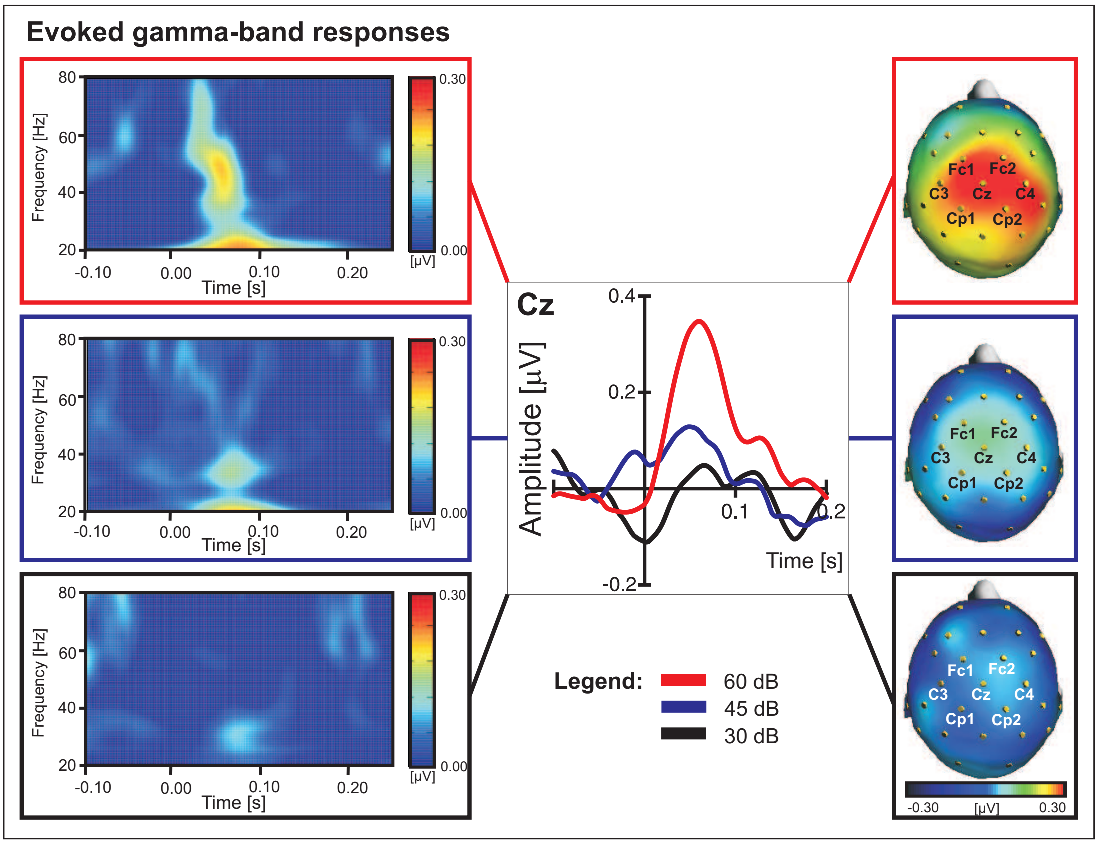

Figure 5.2: Left column: Time-frequency plots at electrode Cz for 60 dB SL (red), 45 dB SL (blue), and 30 dB SL (black) sine tones. Middle column: Time courses of the individually adapted wavelet transforms at electrode Cz. Right column: Scalp distributions of the gamma peak at 61 ms for all conditions.

time-frequency plots and the time courses of the individually adapted wavelet transforms for all intensity conditions. The ANOVA of the peak amplitudes yielded a main effect of INTENSITY ($F[2,36] = 9.276, p = 0.001, \eta_p^2 = 0.339$; Fig. 5.2) with larger amplitudes for stimuli with the highest sound intensity. Post hoc comparisons revealed significant differences between the 60 dB vs. 30 dB ($t[18] = -4.092, p = 0.003$) and the 60 dB vs. 45 dB ($t[18] = -3.039, p < 0.05$) condition, but not between the middle and the lowest intensity ($t[18] = -1,031, p = 0.948$). The electrode Cz and adjacent leads show the largest amplitudes compared to frontal and occipital areas. This is explicitly apparent for the middle and the highest intensity (see scalp distributions in Fig. 5.2). The analysis of the GBR peak latency revealed no significant main effect of INTENSITY ($F[2,36] = 0.812, p = 0.446$).
Figure 5.3 displays the time-course of evoked GBR, phase-locking, and total GBR (containing the phase-locked and non-phase-locked parts of the GBR) in comparison. For the evoked GBR, the amount of phase-locking was significantly larger

for sine tones with higher sound intensities ($F[2,36] = 5.997, p = 0.009$), whereas the analysis of the total GBR, an index of signal power, revealed no INTENSITY effect ($F[2,36] = 0.694, p = 0.506$). Thus, the increase in evoked GBR is most likely based on stronger phase-locking. Interestingly, in the grand average across all subjects the frequency of the evoked GBR was higher for the 60 dB tone (47 Hz) than for the 45 dB (35 Hz) and 30 dB tone (30 Hz). However, the ANOVA did not turn out to be statistically significant ($F[2,20] = 2.237, p = 0.140$).

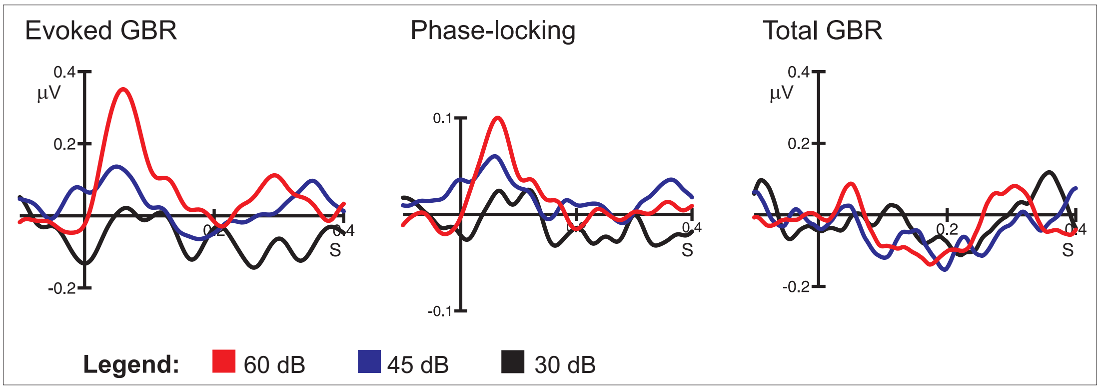

Figure 5.3: Time courses for the evoked GBR, phase-locking, and total GBR at electrode Cz. All displayed time courses were baseline corrected.

5.3.4 Comparison of AEPs and evoked GBRs

The effects of sound intensity level were compared for the N100, N100-P340 complex and GBRs. To this end, the amplitude value of the lowest sound intensity was set to 100%. Subsequently, the increase in response to the intermediate and the loudest stimulus relative to 30 dB tone was calculated (see Fig. 5.4). It stands out that the amplitudes of GBRs as well as all AEP components exhibit an enhancement with intensity of the sine tones. Nevertheless, a difference between auditory evoked potentials and gamma oscillations is apparent, indicating an enhanced intensity effect for the evoked gamma-band activity particularly with regard to the 60 dB SL tone. This is also reflected in the larger effect size of the evoked GBR ($\eta_p^2 = 0.339$) compared to the AEPs (N100-P340: $\eta_p^2 = 0.264$, N100: $\eta_p^2 = 0.007$).

5.4 Discussion

The purpose of the present study was to investigate the influence of sound intensity on gamma-band activity and to replicate existing reports of such effects on auditory evoked potentials.

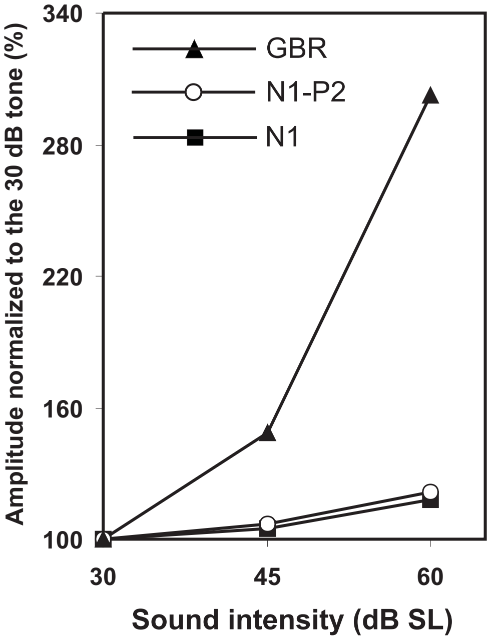

Figure 5.4: Increase of amplitude for AEP components (N100-P340 and N100) and auditory evoked GBRs with increasing sound intensity.

5.4.1 Auditory evoked potentials

We found the strongest response pattern for auditory stimuli at fronto-central electrodes, which is in line with previous studies of auditory evoked potentials (Woods, 1995). Dipole source analyses of the N1-P2 complex have explained this topography by two dipoles per hemisphere: a tangential dipole located in the superior temporal plane including the primary auditory cortex and a somewhat later activity of a radial dipole situated near the lateral temporal cortex (secondary auditory areas, Pantev et al., 1991; Hegerl et al., 1994; Scherg and von Cramon, 1985, 1986).

The AEP results of our study agree in most instances with those of Rapin et al. (1966), Beagley and Knight (1967) and Carrillo-de-la-Peña (1999). Similar to those studies, we found the expected enhancement of amplitude as a function of sound intensity. The results demonstrate a stronger intensity dependency of the peak-to-peak amplitude of N100-P340 compared to the N100. Contrary to our expectations and to previously mentioned studies, the enhancement of N100 amplitude did not reach statistical significance. One explanation, which Näätänen and Picton (1987) discussed in a review about the N100 wave, might be that the change in amplitude with increasing intensities varies greatly among subjects. This was also the case in our study. In some subjects, we observed an increasing N100 amplitude with enhanced sound intensity, whereas others showed no clear differences or the inverse effect in N100 amplitude, especially for the 45 and 30 dB sine tone. Therefore, some studies classified the subjects into "augmenters" and "reducers" and attempted to associate these groups with aspects of personality and psychopathology (Buchsbaum, 1976). Nevertheless, the augmenting/reducing approach and its functional relevance is still under debate (for more details refer to the critical review of Carrillo-de-la-Peña, 1992).

Moreover, our study confirmed the N100 latency dependence on stimulus intensity (Rapin et al., 1966; Beagley and Knight, 1967). Our data showed longer N100 latencies at low intensity levels. However, post hoc comparisons revealed only a significant effect between 60 dB vs. 30 dB, but not between the other sound intensities. One explanation for this result might be the frequency of the sine tone. Rapin et al. (1966) only observed a prolongation of N100 latency for low frequencies (250 Hz) but not for higher frequencies (1000, 6000 Hz). For the 1000 Hz tone the latency effect was extremly reduced and for the 6000 Hz tone there was no significant latency modulation by intensity. In our experiment, we chose a frequency of 2000 Hz for the frequent sine wave tone. This frequency lies exactly between the low and high frequency tones mentioned by Rapin et al. (1966). Hence, their finding might elucidate why we did not find such an obvious latency effect between the two highest sound intensities.

5.4.2 Evoked gamma-band responses

The present study demonstrates that auditory gamma activity in scalp-recorded human EEG can be detected using sine tones of a specific sound intensity and is additionally influenced by the stimulus intensity. It has been demonstrated that the processing demands of a task modulates the gamma-band activity (Yordanova et al., 1997; Senkowski and Herrmann, 2002; Simos et al., 2002). Thus, the fact that our participants had to perform a discrimination task might have contributed to our results. However, we assume that the intensity dependence also occurs in a fully passive listening condition. The evoked gamma-band activity following the highest intensity (60 dB SL) had a mean latency of 60 ms after stimulus onset with strongest responses at central electrodes. Given that auditory evoked potentials of this latency range stem from the auditory cortex and that generators in the auditory cortex result in maximum amplitudes over electrode Cz, it seems plausible to assume that the auditory evoked GBR is generated in or near the auditory cortex. This is in line with a previous study by Pantev et al. (1993), who reported that the generators of auditory gamma-band activity are located in the supratemporal auditory cortex which explained the strongest activity at central leads.

In contrast to the highest sound intensity (60 dB), lower ones (30 and 45 dB SL) evoked only very low GBRs. Three possible mechanisms could account for this result. Either more neurons might respond to the louder sound (i), or the same number of neurons with higher interneuron synchronization (ii), or the same number of neurons with higher synchronicity to stimulus onset (intertrial synchronization - iii). Both (i) and (ii) would result in an increase of total gamma-band activity which we did not observe. Only the last possibility (iii) is in accordance with the observed data. We found a higher phase-locking to stimulus onset for the high intensity stimulus. Thus, we assume, that the condition difference of sound intensity in the evoked time-domain signal results from increased phase-locking. This interpretation is in line with previous findings in the visual domain (Busch et al., 2006). In their study, bottom-up factors modulated only the phase-locking, whereas top-down factors modulated the power of the early evoked GBR. The intensity variation of our study represents such a bottom-up modulation. Therefore, it was to be expected to find the observed increase in phase-locking for higher sound intensities.

Phase-locking represents a measure across trials and cannot be seen in a single trial. This raises the question of which neural mechnism could modulate such an intertrial synchronization. Loud stimuli have been demonstrated to result in an earlier latency of the first spike that can be recorded in response to a stimulus (Heil, 2004). This so-called first-spike-latency is believed to be an important code for the brain. At the same time that first-spike-latency is reduced in response to loud stimuli, the standard deviation of latencies across trials decreases (Heil and Irvine, 1997). This is illustrated in Fig. 5.5 and offers a potential explanation for the increased phase-locking observed for loud stimuli: The standard deviation of the first-spike-latency represents the variability across trials, i.e. it represents a similar measure to our phase-locking. The more narrow the standard deviation becomes, the higher the synchronization of the first spike to stimulus onset must be. Other recordings have also revealed an increased phase-locking in response to loud stimuli, however for the first recordable spike. Therefore, it seems plausible to also expect such an effect for further measures such as evoked gamma activity. Even though we do not want to argue that the first spike in the auditory cortex would evoke a GBR that can be recorded at the scalp, it seems probable that subsequent stages of processing also reveal more narrow latency distributions in response to increased sound intensity if the first spike does. Thus, we believe that our enhanced phase-locking in response to loud stimuli is a result of shorter first-spike-latency, even though the latter cannot be recorded at the scalp.

While we think that our increase in evoked gamma-band activity in response to high intensity stimuli is due to enhanced phase-locking to the stimuli, other studies investigating sound level dependent processing found different phenomena. On the one hand, a larger number of neurons fire at higher sound intensities due to their tuning curves, which are narrow for low but wide for high intensities (Pickles, 1988). On the other hand, fMRI studies exhibited a systematic increase in the extent of activated voxels and BOLD signal intensity with enhanced sound intensity (Brechmann et al., 2002; Hart et al., 2003; Mulert et al., 2005), implying a larger number of neurons being active in response to higher intensity.

One type of neurons in the auditory cortex reveals a monotonic increase in their

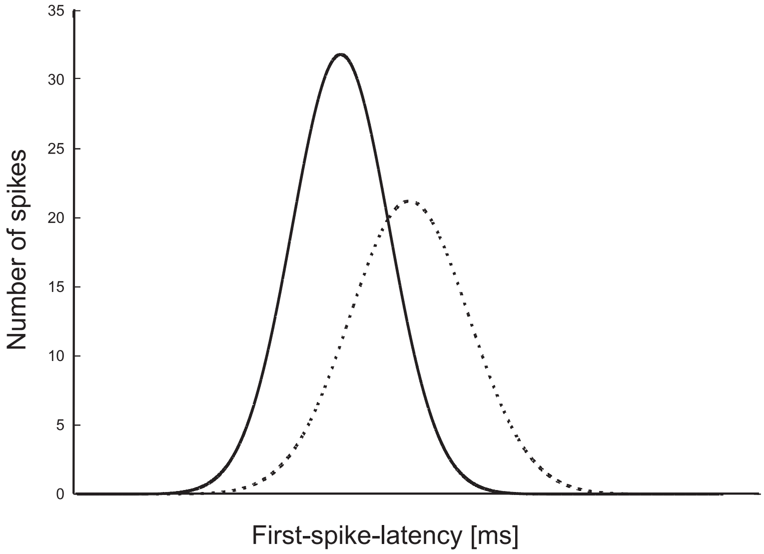

Figure 5.5: First-spike-latency of auditory neurons. In response to low-intensity sounds (dotted line), first-spike-latency is longer than in response to high-intensity sounds (solid line). At the same time, the standard deviation of latencies decreases. This potentially explains why we observed an increased phase-locking for high-intensity sounds.

firing rate in response to higher sound intensities and is therefore called monotonic neuron (Pfingst and O'Connor, 1981). Thus, one might expect the frequency of the GBR to increase at higher sound intensities. While this effect did not reach significance in our data, there was a tendency in this direction: 30 Hz, 35 Hz, and 47 Hz for 30 dB, 45 dB, and 60 dB, respectively.

Furthermore, the present study provides new contributions to the frequently discussed question of why some research groups failed to find any gamma-band activity (Menon et al., 1996; Juergens et al., 1999). A key factor that seems to be most important in eliciting a strong response in the auditory gamma-band is the sound intensity of stimuli. These results are supported by studies that investigated additional parameters affecting the auditory evoked GBR. First, the GBR decreases as a function of shortening the ISI (Pantev et al., 1993; Pantev, 1995). Auditory evoked GBR is best elicited with long ISIs around two seconds. Second, tone-burst stimuli evoked a GBR in as few as 33 percent of normal subjects, while noise-burst stimuli elicited a GBR in as many as 80 percent of normal subjects (Jacobson et al., 1998). Furthermore, Crone et al. (2001) investigated changes in the gamma-band during auditory tone and phoneme discrimination by electrocorticographic recordings. Those data showed a greater augmentation in gamma power during phoneme discrimination than during tone discrimination. Apparently, stimuli such as noise and speech contain more frequencies and temporal changes which have to be processed and therefore require a higher demand of integration of neuronal assemblies than processing pure tones.

According to the abovementioned findings, gamma oscillations seem to be very sensitive to experimental conditions. Hence, sound stimuli with a greater spectral and temporal complexity presented with a sound intensity of 60 dB SL or higher and an ISI around two seconds are most suitable to evoke a measureable GBR at the scalp. The present study cannot provide evidence about how the GBR amplitude is associated with intensity levels higher than 60 dB SL. Future research should consider more than three intensity levels across a wider range, which would yield more reliable results (Beauducel et al., 2000). Our results concerning sound intensity effects could be particularly important for auditory paradigms investigating top-down influences on gamma-band activity. Thus, potential confounds with bottom-up factors such as sound intensity are avoidable. Interesting in this context would be a study combining both bottom-up and top-down aspects to resolve the question under which circumstances top-down influences can be optimally observed in auditory GBRs. Such a study for the visual system was already conducted by Busch et al. (2006), who examined both stimulus size and attention in one task. The results indicated that attention effects on visual GBRs only occur if the stimulus covers a sufficiently large area.

5.4.3 Comparison of AEPs and evoked GBRs

When comparing the effects of stimulus intensity on GBRs and auditory evoked potentials, it is apparent that GBRs are modulated considerably stronger and earlier than AEPs. A similar pattern has been demonstrated in the visual domain (Busch et al., 2004), where visually evoked GBRs are modulated stronger and earlier by stimulus size and eccentricity than visual evoked potentials. This difference between GBRs and AEPs supports the notion, also proposed by Bertrand and Tallon-Baudry (2000), that both reflect independent neuronal and possibly functional mechanisms.

5.4.4 Conclusion

The present study revealed that the auditory evoked GBR is modulated by sound intensity and much more so than AEPs. It has been argued that gamma activity is essential for human cognition involved in binding, perception, and memory processes (Singer and Gray, 1995; Engel et al., 2001; Keil et al., 1999; Tallon-Baudry and Bertrand, 1999).

These findings may help to design future auditory experiments dealing with gamma oscillations as a central issue. Future experiments should clarify whether other auditory stimulus features affect 40 Hz oscillations. In addition, most natural sounds are not, however, well approximated by sinusoidal tones of a particular frequency as used in our study. Thus, it is of considerable interest to investigate spectrally more complex environmental sounds and their evoked responses.

6 Experiment III: Early gamma-band responses reflect anticipatory top-down modulation in the auditory cortex

The experiment described in this chapter has been published in the Journal "Neuroimage" (Schadow et al., 2009).

6.1 Introduction

We live in an extremely complex acoustic environment and are surrounded by simultaneously occurring sounds such as music, speech, and noises from multiple sources. Therefore, it requires a perceptual organization of this extensive mixture of sounds. The auditory system has to segregate and integrate different sounds into meaningful auditory units or objects, which is also known as auditory scene analysis (Bregman, 1994). Bregman (1994) distinguished the perceptual organization along a horizontal (time) and a vertical axis (frequency). The horizontal axis comprises the sequential grouping of sounds over time (e.g. melody), whereas the processing along the vertical axis involves the integration of simultaneous sounds (e.g. forming chords). These grouping processes are governed by both primitive automatic (bottom-up) and learned (top-down) constraints.

Recently, it was suggested that oscillatory activity in the gamma-range (30 - 80 Hz) is related to bottom-up and top-down factors as well as to the integration of both (Herrmann et al., 2004c). Thus, GBRs might provide additional insights regarding the basic sensory analysis of auditory information as well as the influence of this analysis by top-down processes. Generally, GBRs are divided in an early evoked and a late induced portion. While evoked activity is defined to be time- and phase-locked to an event, induced GBR is time-locked, but shows a high phase variability across trials (Galambos, 1992; Pantev, 1995). Phase-locked oscillatory activity has been reported to be modulated by physical stimulus properties during a very early time interval in the visual (at ∼90 ms; Tzelepi et al., 2000; Bodis-Wollner et al., 2001; Busch et al., 2004; Fründ et al., 2007a; Schadow et al., 2007b) and auditory modality (at ∼50 ms; Schadow et al., 2007a; Lenz et al., 2008). The later non-phase-locked GBR between 200 and 400 ms after stimulus onset is mainly associated with a more elaborated processing and is therefore linked to cognitive mechanisms such as attention (Gruber et al., 1999; Tallon-Baudry et al., 2004) and memory (Lutzenberger et al., 2002; Lenz et al., 2007; Busch et al., 2008). However, it has been shown that such top-down modulations can already occur much earlier and can be represented in the evoked gamma-band activity, too. Several visual and auditory experiments have shown an increase in the early evoked activity for target stimuli that capture a higher amount of attention than non-target stimuli (Tiitinen et al., 1993; Herrmann et al., 1999; Debener et al., 2003; Busch et al., 2006). Similarly, the match of a presented stimulus with a memorized template resulted in an enhanced evoked GBR compared to new stimuli (Herrmann et al., 2004d; Busch et al., 2008), which demonstrates a top-down modulation at the earliest stages of information processing. In addition to attention and memory resulting in a faster and more efficient analysis of the upcoming stimulus, most events in everyday life occur predictably for us. Thus, we often anticipate events and are therefore able to prepare a faster and more accurate behavior. Widmann et al. (2007) reported that visual symbolic information affect early auditory sensory processing at 42 ms after tone onset. The authors observed an increase of phase-locked evoked GBR in response to sounds that matched with a corresponding visual symbol and discussed the finding in relation with matching of incoming information against an expectation.

The present study aimed to investigate, whether anticipatory processes also result in such early modulation of the GBR. Therefore, we presented regularly ascending and descending tone sequences with six sinusoidal tones. These sequences reflected a good continuation of pitch, which also resulted in the buildup of an expectation for the upcoming stimulus by the listener during the presentation. However, some of the tone sequences contained a violation of the good continuation at the third or fifth tone position. Thus, the sequences violated the listener's expectation at different levels of expectation buildup. Gamma-band activity in response to regularly presented and deviant tones at the third and fifth position of each sequence was compared. If GBRs reflect matching with expectation, responses to regular tones within ascending/descending sequences should be larger than to deviating tones. We assume that regularly occurring tones might be processed by a pretuned population of neurons which is not the case for deviant tones.

Previous research has already revealed electrophysiological correlates of such mechanisms, e.g. the mismatch negativity (MMN), a component of the event-related potential (ERP) after about 150-250 ms (Näätänen, 1992; Näätänen et al., 2007), which is linked to processing of tone sequences and reflects a violation from the preceding stimulus or regularities in complex auditory information (Yabe et al., 2001; Kanoh et al., 2004; van Zuijen et al., 2004; Sussman and Gumenyuk, 2005; Kujala et al., 2007). The MMN operates basically at the sensory memory level and is an automatic process, irrespective of cognitive factors (e.g. attention, prior knowledge; Schröger, 1997; Näätänen and Winkler, 1999; Schröger et al., 2007). Hence, no behavioral task is needed to elicit a MMN. However, when stimuli are attended for example by a task, then the MMN is partially overlapped by the N2b. The N2b is linked to the expectation of regularly appearing stimuli and indexes deviance detection only if a deviant stimulus is attentively recognized (Näätänen et al., 1982; Novak et al., 1992; Eimer et al., 1996; Rüsseler and Rösler, 2000; Carrión and Bly, 2007). Therefore, we also expected a larger negative ERP response to deviant tones compared to regularly occurring tones within the sequence.

6.2 Materials and methods

6.2.1 Participants

Seventeen healthy volunteers (9 females, 8 males, mean age 25 ± 3.8 years) participated in the current study. They had no history of hearing impairments and showed no signs of psychiatric or neurological disorders. All participants received a written task instruction and gave informed written consent to participate. They received money or course credits for their participation. The experiment was conducted in accordance with the Declaration of Helsinki.

6.2.2 Stimuli and Task

Ten different sinusoidal tones with a duration of 500 ms (10 ms rise and fall times) and a frequency, ranging from 700 to 1177 Hz in semitone steps on the musical scale, were generated using Adobe Audition V1.0 (Adobe Systems Inc., 2004). Five ascending and five descending stimulus sequences, each comprising six tones, were composed. Some of these ascending or descending tone sequences were further modified either at the third or fifth position in their frequency to trigger a violation of the good continuation of the sequence. This sine wave tone deviated from the regularly presented tone about three semitone steps, either below for ascending or above for descending sequences (see Fig. 6.1). Consequently, we obtained three different categories of tone sequences:

A. tone sequences with a good continuation (= regular)

B. tone sequences with a violation at the 3^{rd} position (= irregular)

C. tone sequences with a violation at the 5^{th} position (= irregular)

All stimulus sequences were pseudo-randomly presented with a constant inter-tone interval of 1200 ms. The randomized interval between two adjacent tone

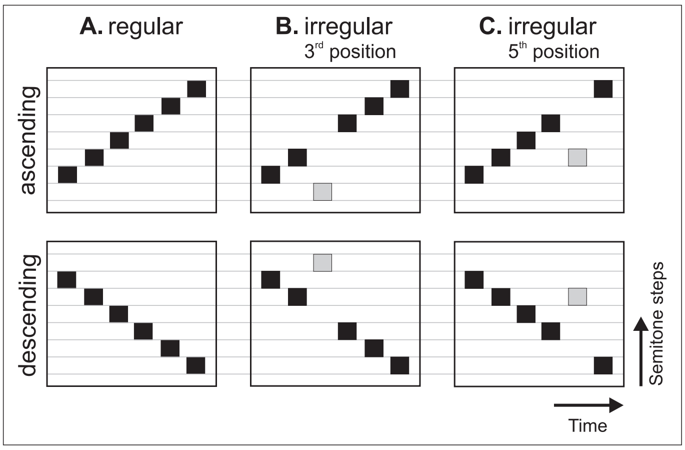

Figure 6.1: Schematic illustration of the paradigm. Black squares indicate tones that regularly fit in the ascending or descending sequence. In contrast, gray squares illustrate a violation either at the 3^{rd} or 5^{th} position of the sequence.

sequences was set between 1600 and 2000 ms. Sequences were repeated such that each of the three categories comprised the same number of trials (100 trials).
Auditory stimuli were applied to both ears by insert earphones (EARTone 3A). Before the experiment started, the individual hearing thresholds for the left and the right ear were determined by a staircase procedure in intensity steps of 2 dB for each participant and each sine tone. Based on the individual sensation level (SL), an intensity of 75 dB above the threshold was set for each tone. A calibrated attenuator was used to control the sound levels (Tucker-Davis Technologies, model PA5).
The present experiment was constructed as a discrimination task. Participants were asked to decide, whether the presented tone sequence is predominantly ascending or descending irrespective of a violation. Since it has been demonstrated that stimulus-related motor activation modulates the GBR (De Pascalis and Ray, 1998; Yordanova et al., 2001, 2002), all trials required a motor response to avoid confounding effects. Participants were instructed to press a button with the right index finger in response to descending sequences and another button with the left index finger in response to ascending sequences. Participants were asked to respond at the end of each sequence, which was signaled by a color change of the fixation cross from white to red. During the entire experimental session, participants were instructed to fixate the cross in the center of the screen to reduce eye-movement artifacts.

6.2.3 Data acquisition

EEG was recorded with a BrainAmp amplifier (Brain Products, Munich; Germany), using 31 sintered Ag/AgCl electrodes mounted in an elastic cap (Easycap, Falk Minow Services, Munich, Germany). The electrodes were placed according to the 10-10 system, with a nose-tip reference and ground electrode between Fz and Cz. Eye-movement activity was monitored with an electrode placed sub-orbitally to the right eye. Electrode impedances were kept below 10 kΩ. Data were acquired with a band-pass filter of 0.016-250 Hz and a sampling rate of 1000 Hz. Stimulus markers and EEG were stored on hard disk for further analysis. The EEG was recorded while participants sat in an electrically shielded, sound-attenuated cabin (IAC, Niederkrüchten, Germany). The monitor was placed outside behind an electrically shielded window. All devices inside the cabin were operated on batteries to avoid interference from the line frequency (50 Hz in Germany). Digitized EEG data were transferred to a computer outside the cabin using a fiber-optic cable. Averaging epochs lasted from 200 ms before to 800 ms after tone onset for event-related potentials and GBRs. Baselines were calculated in the interval from -200 ms to -100 ms and subtracted before averaging. An automatic artifact rejection was computed which excluded trials from averaging if the standard deviation within a moving 200 ms time interval exceeded 40 μV. All epochs were also visually inspected for artifacts and rejected in case of eye-movements, electrode drifts, or electromyographic activity. While data analysis was performed on unfiltered data, event-related potentials are displayed low-pass filtered at 20 Hz.

6.2.4 Data analysis

Behavioral data

Only trials with responses given between 150 and 2000 ms after the presentation of the red fixation cross were included in the analysis. False trials were excluded from the analysis of reaction times, as well as trials in which the reaction time (RT) exceeded two standard deviations from the mean. On average a number of 30 trials were excluded.

Event-related potentials

In order to test differences in the neural responses to regular and irregular occurring tones, we analyzed amplitudes of the early negativity in the time interval from 150 ms to 350 ms. The statistical analysis of this early negativity was performed after channels that exhibited the strongest activity in the critical time window were pooled into a posterior region of interest (ROI): CP1, CP2, P3, Pz, P4, O1, O2. The statistical analysis was conducted on the peak amplitude in this time interval and ERPs at the third and fifth position in response to regular and irreguar tone sequences were compared. Amplitudes were analyzed using a repeated measures ANOVA with the factors REGULARITY (regular vs. irregular) and TONE POSITION (3^{rd} vs. 5^{th}). The Greenhouse-Geisser correction, an adjustment used in univariate repeated measures when the sphericity assumption is violated, was applied where appropriate.

Evoked and total gamma-band responses

For the analysis of gamma-band activity, a wavelet transform was computed by convolving the raw EEG signal with a complex modulated Gaussian (Herrmann et al., 2004a). At 40 Hz, the wavelet had a time resolution of $2\sigma_t = 50$ ms and a frequency resolution of $2\sigma_f = 13$ Hz. The exact time frequency resolution of the wavelet depended on the analyzed frequency. Different methods of evaluation are required to assess evoked and induced GBRs. To analyze the evoked GBR, the wavelet transform was applied to the averaged event-related potentials. However, for the non-phase-locked portion of the GBR, each trial was first transformed to the frequency domain and then the resulting wavelet transforms were averaged. This measure represents the total activity comprising the phase-locked and non-phase-locked fractions of the GBR. Additionally, the amount of phase-locking across trials was computed. The values yield a number between 0 and 1 determining the degree of phase-locking, where 1 indicates perfect phase alignment across trials and values close to 0 reflect a high phase variability.

Previous studies have shown that the frequency of oscillatory brain activity varies notably between subjects (Busch et al., 2004; Klimesch, 1999). Therefore, wavelet analysis was performed for each frequency bin in the gamma-frequency range. The resulting time-frequency representations were averaged across electrodes in the fronto-central ROI (Cz, FC1, FC2, Fz) and across the four interesting conditions (regular and irregular at the 3^{rd} and 5^{th} position). Afterwards, the individual gamma frequency was defined as the frequency showing the highest amplitude in the time interval between 20 and 90 ms after stimulus onset. The peak frequencies of the individually identified evoked GBRs ranged from 20 Hz to 64 Hz (mean 42.4 Hz, SD=13.8 Hz). The peak amplitude for this individual frequency was used for further statistical analyses of the evoked GBR, the phase-locking, and total gamma activity in the respective early time interval. Channels were pooled into a ROI comprising the following four fronto-central electrodes which exhibited the strongest GBRs: Cz, FC1, FC2, Fz (see Fig. 6.4). We performed a repeated measures ANOVA using the factors REGULARITY (regular vs. irregular) and TONE POSITION (3^{rd} vs. 5^{th}).

The time-frequency planes did not reveal any late gamma-band activity in the typical time interval between 200 and 600 ms that exceeded the noise level. Therefore, further analyses and the description of the results are focused on the early gamma-band activity.

Dipole modeling of the evoked GBR

Source modeling of evoked GBRs was conducted using ASA 4 (ANT Software, Enschede, The Netherlands). A band-pass filter covering 10 Hz above and below the mean of GBR peak frequencies of all subjects was applied to the grand-average ERP (mean peak frequency: 42 Hz, filter-band: 32-52 Hz). There were no differences in the scalp topographies of evoked GBRs following regular tones at 3rd and 5th position. Therefore, further calculations were done on the average of both conditions. As we obtained no individual MRI data from our subjects, source modeling was performed using the standard MRI and headmodel data included in ASA. In order to verify the hypothesis that the sources of the evoked GBR lie in the primary auditory cortex, the scalp signal was modeled using two symmetrical dipoles placed within the left and right primary auditory cortex and fixed in position (AC-PC coordinates: x=-50, y=-7, z=7 (left dipole); x=50, y=-7, z=7 (right dipole)). Afterwards, the 'goodness-of-fit' (GOF) as a measure of the model accuracy was calculated for the time-window between 50 ms and 60 ms.

6.3 Results

6.3.1 Behavioral data

Participants performed the task with high accuracy (ascending sequences: 94%, standard deviation (SD) = 6% and descending sequences: 95% correct, SD = 5%). The reaction times to the ascending (441 ms, SD = 87 ms) and descending sequences (447 ms, SD = 97 ms) were nearly identical. Neither the accuracy [t(16) = -0.77, p = 0.455] nor reaction times [t(16) = -1.14, p = 0.271] were significantly influenced by the task.

6.3.2 Event-related potentials

Time courses and scalp topographies of the event-related potentials to regular and irregular tones at the 3^{rd} and 5^{th} position within the sequences are depicted in Figure 6.2. A distinct early negativity between 150 and 350 ms at posterior electrodes was elicited when an irregular tone was presented at both possible positions. Amplitudes in response to irregular tones were significantly larger than in response to regular tones (main effect of REGULARITY: F(1,16) = 89.85, $p < 0.001$). Although this difference tended to be larger at the 5^{th} than at the 3^{rd} position, the interaction of REGULARITY and TONE POSITION only shows a statistical trend [F(1,16) = 3.88, p = 0.066].

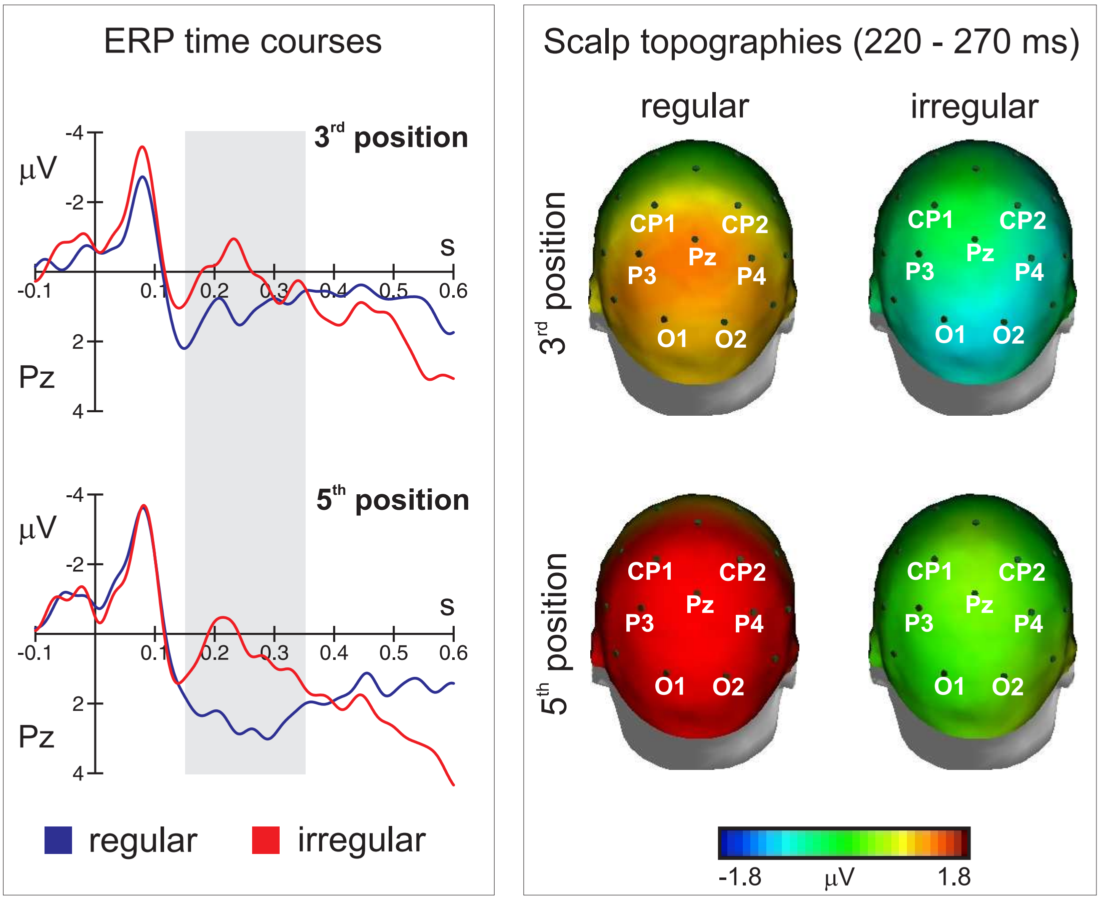

Figure 6.2: Time courses (left) and scalp topographies (right) of the event-related potentials for regular and irregular tones at the 3^{rd} and 5^{th} position of sequences are displayed. The gray bar highlights the statistically analysed time interval (150-350 ms) of the early negativity. Irregular tones elicited a larger negativity than regular tones. The potential maps were calculated over a narrower time window from 220 to 270 ms.

6.3.3 Evoked gamma-band responses

The wavelet analysis revealed an increase in the early evoked GBR for regularly presented tones. This is illustrated in Figure 6.3 by the baseline-corrected time-frequency representations. Regularly presented tones elicited significantly larger GBR amplitudes than irregular tones (main effect of REGULARITY: $F(1,12) = 14.604$, $p < 0.01$). This effect is mainly manifested in fronto-central electrodes, which is depicted in Figure 6.4. Source modeling of the evoked GBR based on bilateral dipoles in the primary auditory cortex yielded a GOF of 94.77% (see Fig. 6.5).

Since the ANOVA of mean baseline amplitudes between 200 and 100 ms before stimulus onset showed no significant effects of REGULARITY [$F(1,12) = 0.02$,

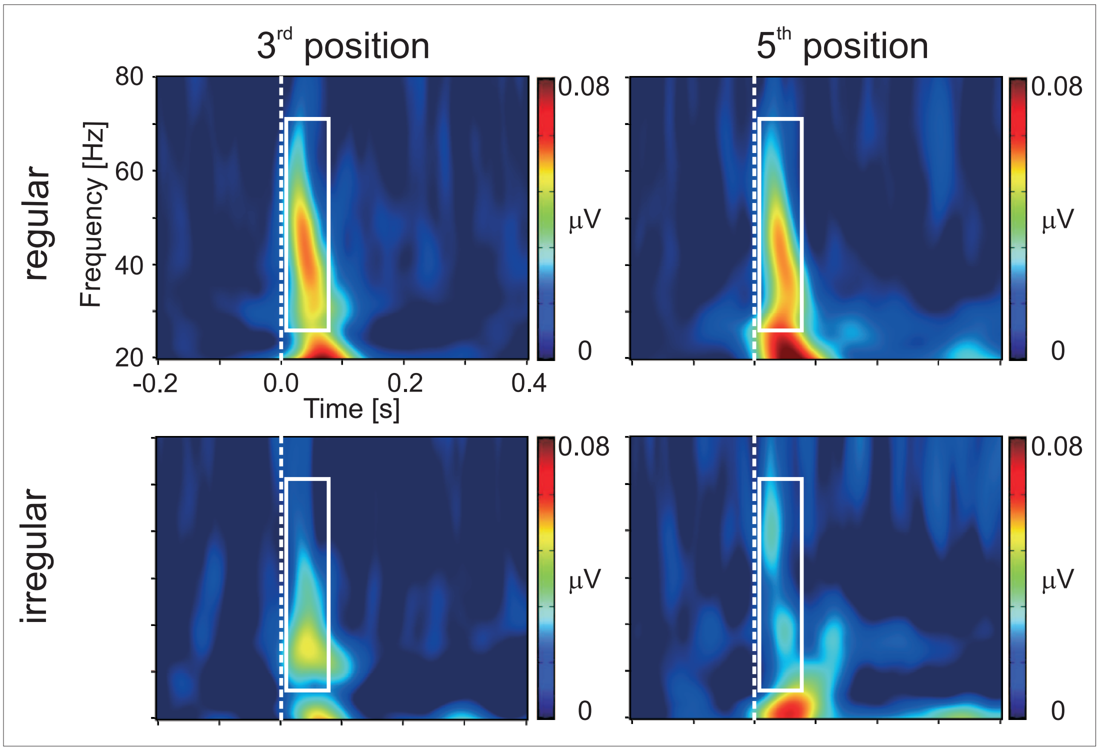

Figure 6.3: Time-frequency representations of the evoked GBR for regular and irregular tones at the 3^{rd} and 5^{th} position of sequences are displayed and averaged across the central ROI. The dashed white line highlights the stimulus onset (at 0 ms) and the rectangle indicates the range of the early gamma-band activity. Evoked gamma-band amplitudes were significantly enhanced in response to regular tones at both positions.

$p = 0.904$] and TONE POSITION [$F(1,12) = 0.46$, $p = 0.510$], the main effect of early GBR was not elicited by differences in the baseline. The analysis of the GBR latency revealed no significant effects at all.
Figure 6.6 displays the time courses of the evoked GBR, phase-locking, and total GBR in comparison. For the evoked GBR, the amount of phase-locking was significantly larger for regularly presented tones at both positions (main effect of REGULARITY: $F(1,12) = 16.910$, $p < 0.01$), whereas the analysis of the total GBR, an index of signal power, revealed no amplitude differences [$F(1,12) = 1.229$, $p = 0.289$]. Thus, the increase in the evoked GBR is most likely based on stronger phase-locking.

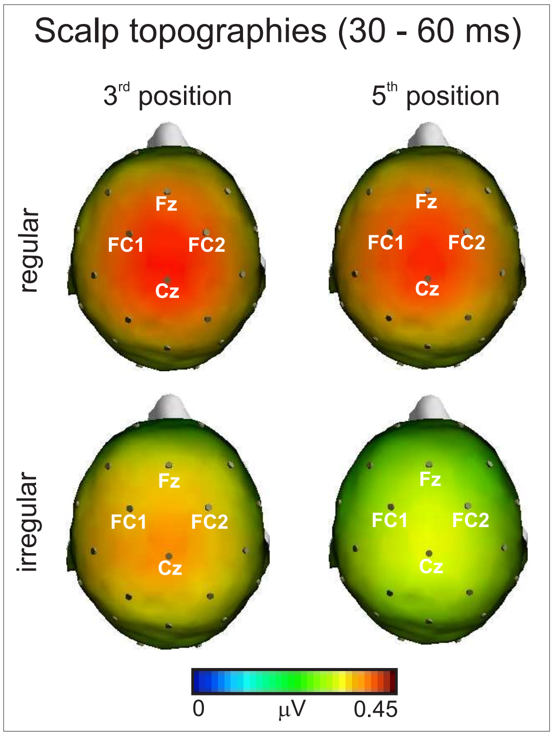

Figure 6.4: Scalp topographies (view from top, anterior is upwards) of the evoked GBR for regular and irregular tones at the 3^{rd} and 5^{th} position. Regular tones evoked stronger responses than irregular tones at fronto-central electrodes. The potential maps were calculated averaging signal values between 30 and 60 ms.

6.4 Discussion

6.4.1 Event-related potentials

The present study showed that irregular sounds within descending or ascending sequences elicited a larger negative deflection in the ERP than regular sounds. The main amplitude difference occurred in a time interval between 150 and 350 ms with an amplitude maximum at posterior scalp electrodes (relative to a nose reference electrode). This early negativity to irregular tones might reflect the ability of the auditory system to extract and apply sequential regularities. Previous research associated the detection of deviance with the mismatch negativity of the ERP without attentional modulation regarding simple (for a review, see Näätänen 2007) as well complex auditory stimuli (Brattico et al., 2006). The MMN usually peaks at 150 - 250 ms from stimulus onset with a frontocentral scalp distribution that reverses its polarity at mastoids. This, however, does not correspond to our findings. It has been reported that if participants attentively detect deviant stimuli, the MMN is partially overlapped by a further negative component, namely the N2b (Näätänen et al., 1982). We assume, that the early

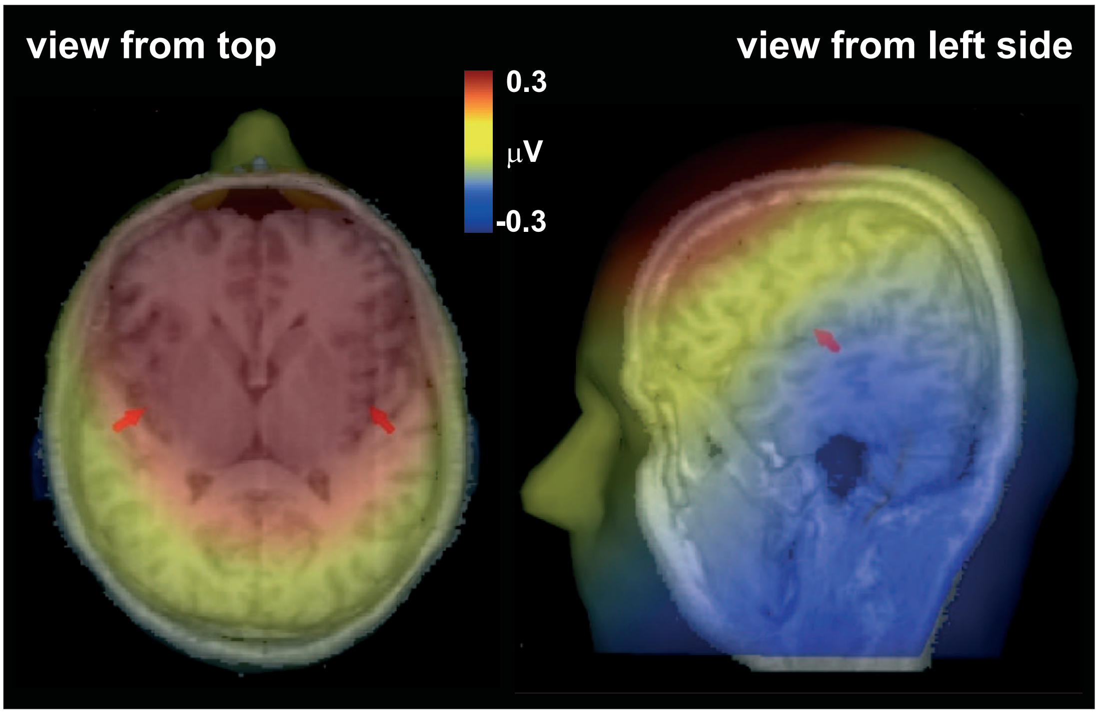

Figure 6.5: Source modeling of the evoked GBR for the grand-average of regular tones at the 3rd and 5th position was conducted using two symmetrical dipoles placed bilaterally in the primary auditory cortex. The dipoles are displayed as red arrows and the amplitude of the evoked GBR measured at the scalp is indicated by a color gradient from red to blue. The source estimation yielded a GOF of 94.77%, indicating that the sources are well in line with the measured scalp-data.

negativity in the current experiment might rather resemble an N2b response than a mismatch negativity. This is further supported by the finding that the N2b peaks later at ∼250 ms with a scalp distribution more posterior than that of the MMN (Alho et al., 1986). In contrast to other studies that reported a central scalp distribution for this negativity, we observed a scalp topography with a maximum at posterior electrodes. One possible explanation for this phenomenon might be the attended processing of the presented stimulus sequences in an active task. In this case, the early negativity seems to be intimately linked with a subsequent positivity waveform (P3, Snyder and Hillyard, 1976), which typically increases in magnitude at parietal electrode sites (Johnson, 1993) and is related to attentional processing (Polich, 2007). Furthermore, the P3 is discussed in conjunction with context-updating. If a new stimulus within a sequence is detected, attentional processes govern a change or 'updating' of the stimulus representation (Donchin and Coles, 1988; Polich, 2007). Thus, an overlap of N2b and P3 would be conceivable and might explain the posterior scalp distribution.
The processing of rules is also well investigated in language and music. Both, lan-

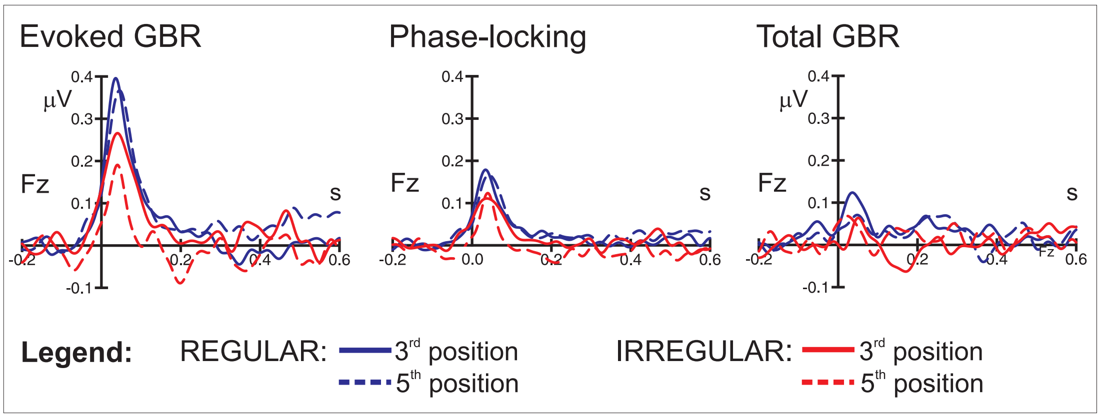

Figure 6.6: Averaged time courses of the evoked GBR, phase-locking, and total GBR at electrode Fz. Regular tones at the 3^{rd} (solid line) and 5^{th} (dashed line) position of sequences are displayed in blue, whereas irregular tones at the 3^{rd} (solid line) and 5^{th} (dashed line) position are shown in red. Since total GBRs do not show differences between conditions, the enhanced evoked GBRs for regular tones seem to be due to enhanced phase-locking.

guage and music are structured by complex syntactic rules and therefore evoke an expectation for upcoming events within a specific musical or linguistic context (Maess et al., 2001). In recent studies, the violation of regularities has shown to be reflected in an early right anterior negativity for musical stimuli (ERAN; Koelsch et al., 2002, 2007) and in an early left anterior negativity for linguistic stimuli (ELAN; Friederici, 1997, 2002) with an amplitude maximimum around 200 ms. In contrast to the N2b, these EEG components rather reflected initial and automatic neural mechanisms that were contributed to the processing of irregularities.

6.4.2 Evoked gamma-band responses

In the current study, we investigated in which way anticipation modulates early auditory gamma-band activity during listening to different tone sequences. Regularly presented tones matching the good continuation of a sequence elicited a considerably larger evoked GBR compared to irregular (deviant) tones with strongest responses at fronto-central electrodes. This corresponds very well to our source modeling of the evoked GBR. The dipole model with two bilateral dipoles in the primary auditory cortex accounted for 95% of the variance of the measured gamma-band activity. Previous investigations of the early evoked gamma-band activity also described the largest amplitudes in response to auditory stimuli at central electrodes and found the neural generators of this activity in the auditory cortex (Pantev et al., 1993; Mulert et al., 2007).

We observed this amplitude differences very early at 50 ms after stimulus onset. During anticipatory states, specific neuronal populations may be activated and further enhance subthreshold oscillations in sensory cortical areas (e.g. A1) before the actual stimulation (Engel et al., 2001). Matching of the bottom-up input with an internal prediction about the incoming stimulus therefore results in "resonance phenomena" and, thus, leads to enhanced evoked GBR in a very early time interval. Therefore, events or stimuli that match the expectancy expressed by coherent states of the neuronal network generate more salient and speeded brain responses than non-attended or unexpected stimuli. The top-down process whose modulatory influence we observe 50 ms after stimulus presentation has probably already started much earlier, i.e. when the previous tone was presented and a rule was generated in order to predict the upcoming stimulus. Such an early modulation during auditory stimulus processing has been also reported in an audio-visual integration study (Widmann et al., 2007). In that study, visual symbolic information served as a cue and preceded the auditory stimulus, while visual and auditory stimuli could be either congruent or incongruent. Only in the case of congruent stimulus presentations, where the prediction about the forthcoming sound matched the sensory input, an enhanced evoked GBR could be observed. The authors discussed their findings with respect to the "match-and-utilization" model (MUM) proposed by Herrmann et al. (2004c) for the visual modality. Hence, our results substantiate the findings of Widmann et al. (2007) and are further in line with the MUM. Herrmann et al. (2004c) stated that matching between an incoming stimulus and a memory template results in an enhanced evoked gamma-band activity. Thus, the early evoked GBR in the current study appears to reflect this matching mechanism. According to the model, attention represents a determining factor for enabling and facilitating the match. Applied to the present experiment, the regularity of the tone sequence has to be learned and memorized and thus, the participants built up an expectation for the forthcoming tone, which can result in a match or mismatch. During listening to the tone sequences, attended processing was also ensured, since the task required a behavioral response by the participant. Therefore, it is most likely that the larger gamma-band amplitude in response to regularly occurring sounds is due to the higher amount of anticipation or expectation of the listener.

A similar approach is suggested by the "adaptive resonance theory" developed by Grossberg (1999). Grossberg supposes that humans are always anticipating their next behavior and respective consequences. These expectations about the world are permanently matched against actually occurring events. It is assumed, that a match between the current sensory input with existing knowledge causes an amplification of a sensory response, whereas a mismatch leads to an extinction. Further, such top-down expectation can also sensitize or pretune specific cells and therefore prepare them to react quickly to bottom-up inputs that match the top-down prime (Grossberg, 2001). If this is the case, it is conceivable that top-down modulations on GBR already occur at 50 ms. These early influences on oscillatory activity in the gamma-range were previously observed for other cognitive features in humans such as attention- (Tiitinen et al., 1993; Yordanova et al., 1997; Herrmann et al., 1999; Debener et al., 2003; Busch et al., 2006) or memory-related stimulus processing (Herrmann et al., 2004b; Busch et al., 2008). Additionally, the status of anticipation or expectation and its influence on the processing of forthcoming stimuli was previously investigated with respect to oscillatory activity, too (Gonzalez Andino et al., 2005; Snyder and Large, 2005; Gómez et al., 2004). Visual GBRs were reported to precede the perceptual processing of a visual stimulus and correlated significantly with reaction times (Gonzalez Andino et al., 2005). This activity, occurring before stimulus onset, might facilitate the amplification of neural activity in sensory areas in response to the stimulus. This is not restricted to the visual modality: Snyder and Large (2005) studied the relationship between GBRs and the processing of rhythmic tone sequences. Here, induced GBRs appeared to predict tone onsets and persisted even for expected tones that were omitted. In contrast, the evoked GBR occurred in response to tones, but not to tone omissions. The authors concluded that the induced gamma-band oscillations might play a role in developing a mental representation of a temporally structured tone pattern, whereas the evoked activity reflects more stimulus driven aspects. We have previously demonstrated that auditory evoked GBR is modulated by stimulus properties such as sound intensity, too (Schadow et al., 2007a). However, we argue that evoked activity additionally reflects top-down aspects of stimulus processing. This is shown by the current results and earlier studies reporting strong effects of task difficulty (Mulert et al., 2007) and attention (Tiitinen et al., 1993; Debener et al., 2003) on the auditory evoked GBR. Furthermore, we reason that the status of anticipation during our task might affect even more strongly the matching process between the incoming tone and memory template than attentional parameters as was shown by Tiitinen et al. (1993). This seems very plausible to assume since the irregular or deviant tones within a sequence evoked significantly smaller GBR amplitudes than regular tone presentations although deviant stimuli are more powerful in attracting attention as indexed by the enhanced early negative ERP component. Our findings indicate that gamma-band oscillations are functionally more relevant for matching processes than for deviance detection, since regular tones that match the prediction of the listener evoked larger responses than deviant tones.

6.4.3 Conclusion

We conclude that the observed enhancement in early gamma-band activity reflects memory and anticipatory processes supporting the "match-and-utilization" model. Gamma-band oscillations were shown to be more relevant during matching processes than in detecting deviance. Our data suggest that early top-down modulation involves some of the first stages of auditory information processing (∼50 ms). The findings correspond to analogous studies in the auditory and visual system considering such early top-down influences.

7 General Discussion

In this Chapter, I will outline the main findings of the three presented studies according to the proposed hypotheses (see Chapter 2). I will summerize the results of the auditory as well as the visual experiments (7.1), discuss them within the framework of the match-and-utilization model (7.2) and emphasize similarities and differences between both systems within a low- and high-level perspective (7.3).

7.1 Summary and discussion of the main results

From the visual system, we already know that physical properties of visual stimuli affect electrophysiological markers of perception (Busch et al., 2004; Fründ et al., 2007a). According to these studies, I investigated the influence of a further important visual stimulus parameter, namely the stimulus contrast, on the GBR in a choice reaction task. Since the main concern of the dissertation is the comparison of processes in the visual and auditory system, I designed an analog auditory experiment. The most equivalent stimulus parameter to the stimulus contrast in the visual system might be the sound intensity for the auditory domain. Therefore, I have additionally studied, whether basic auditory perception operates in a similar way, showing a modulation of the auditory GBR in dependence on the intensity of a sound.

As expressed in Chapter 2, I examined the following hypotheses:
Hypothesis 1
The early evoked GBR is modulated by the contrast of visual stimuli.
Hypothesis 2
The early evoked GBR is likewise influenced by the sound intensity of sinusoidal tones.

Both hypotheses can be verified. The amplitude of the evoked GBR seems to be directly related to the physical properties of a visual or auditory stimulus: the higher the stimulus intensity (contrast as well as sound intensity) the larger is the evoked GBR. For both modalities, this increase in the evoked gamma-band activity can be explained by enhanced phase-locking to high intensity stimuli. The results are in accordance with studies demonstrating a dependence of gamma-band oscillations on stimulus parameters, and showing that the early evoked

GBR appears to be a signature of sensory processing mechanisms (Busch et al., 2004; Fründ et al., 2007a; Lenz et al., 2008). Furthermore, the current experiments extend the knowledge about the fact that processing of basic stimulus features in early sensory areas appears to be very similar in the visual and auditory modality.
This is an interesting result, since perception as well as processing of auditory and visual information strongly differs in some points. For example, the spatial resolution of vision exceeds the auditory localization abilities, whereas the temporal precision of the auditory system is far superior to that of the visual system (King and Nelken, 2009). For the auditory system, time is an essential variable of sensory inputs. While visual information (e.g. pictures) appears at once, acoustic signals (e.g. melody, speech, environmental sounds) are constantly changing as a function of time. The same time axis is also used by neural discharges throughout the auditory pathway. A further distinction between audition and vision is the temporal precision of sensory receptors and their peripheral representations. For the auditory system, the temporal precision is in the order of less than 1 ms, whereas it is in the order of 100 ms for the visual system (Wang, 2007). Despite of these differences, there is evidence that early processing of physical properties of simple stimuli happens comparably and is reflected in modulations of the same electrophysiological marker in the visual as well as the auditory system.

The question arises which possible mechanisms could account for these results. Either more neurons might respond to a more salient stimulus (i), or the same number of neurons respond with higher interneuron synchronization (ii), or the same number of neurons respond with higher synchronicity to the stimulus onset (intertrial synchronization - iii). Both (i) and (ii) would result in an increase of total gamma-band activity, which I did not observe in the current studies. Only the last possibility (iii) is in accordance with the observed data, as I found a higher phase-locking to stimulus onset for the high intensity stimuli in both modalities. Thus, the differences in the evoked GBR result from increased phase-locking following high intensity stimuli. This interpretation is in line with previous findings in the visual domain (Busch et al., 2006). In their study, bottom-up factors modulated only the phase-locking, whereas top-down factors modulated the power of the early evoked GBR.

Furthermore, both experiments were designed to answer the question why some research groups failed to find gamma-band activity or gamma-band modulations and some did not, or only observed GBRs in monkeys, but not in humans (Menon et al., 1996; Juergens et al., 1999). Different possible reasons were discussed to explain the aforementioned negative results. By means of the current experiments, I raise evidence that differences in the experimental design might account for negative results in measuring human GBR. The current findings emphasize the fact that the intensity of stimuli is essential for both the visual and auditory modality. The results show that stimulation with a low contrast grating or low intensity sound yields nearly undetectable evoked GBR in scalp measured EEG. Similar optimal stimulus characteristics have been reported, too (Busch et al., 2004; Fründ et al., 2007a; Lenz et al., 2008). Thus, an appropriate stimulation (high intensities for visual and auditory stimuli) should be guaranteed for a highly reliable measurement of evoked GBR in human EEG (Fründ et al., 2007b). The findings further implicated that stimulus parameters of stimuli belonging to different experimental conditions should be carefully matched. It appears probable that conflicting results in the literature could arise from experimental designs, in which variables like the aforementioned stimulus features confound the independent variable, making it hard to differentiate between a pure bottom-up effect or higher influences in a top-down fashion.

Within the framework of a methodical point of view, Experiment 1 and 2 yield the following main conclusions:
First, stimulus parameters should be matched within different experimental conditions, so that potential top-down effects are not confounded by differences in stimulus parameters (bottom-up). Second, for experimental stimulation, high intense stimuli (regarding the sound intensity or contrast) should be selected that evoke large responses differing significantly from background noise.

The third experiment investigated top-down effects on auditory processing, while assessing the role of evoked GBRs. I studied, in which way specific expectations of a listener influence the subsequent auditory stimulus processing and whether this is reflected in the early evoked gamma-band activity.

Therefore, I want to remind of the third working hypothesis (see Chapter 2):
Hypothesis 3
The influence of anticipation on the auditory stimulus processing is reflected in an increased early evoked GBR.

As the main result of this study, I observed larger evoked GBRs as early as 50 ms after stimulus onset for tones matching the good continuation of the sequence compared to tones violating the good continuation. Thus, the third hypothesis can also be verified. Indeed, a top-down modulation within 50 ms after stimulus onset is very fast, however, such early top-down effects were reported by other research groups as well (Tiitinen et al., 1993; Yordanova et al., 1997; Debener et al., 2003; Widmann et al., 2007). A recent audio-visual study even described a top-down effect by anticipatory processes (similar to my findings) at 42 ms after stimulus onset. During anticipatory states, specific neuronal populations may be activated and further enhance subthreshold oscillations in sensory cortical areas (e.g. A1) before the actual stimulation (de Oliveira et al., 1997; Engel et al., 2001). This corresponds very well to the current findings, since a dipole modeling with two bilateral dipoles in the primary auditory cortex accounted for 95% of the variance of the measured gamma-band signal.

Therefore, matching of bottom-up input and active prediction about the incoming stimulus match will result in enhanced evoked GBRs in a very early time interval. It was proposed that early evoked GBRs are a signature of this matching process (Herrmann et al., 2004c). Events or stimuli that match the expectancy, expressed by coherent states of the neuronal network, generate more salient and speeded brain responses than non-attended or unexpected stimuli. This is supported by a couple of studies investigating the relation between the electrophysiological markers of attentional orienting and the speed of responding (Talsma et al., 2007; Desimone and Duncan, 1995). Preparatory attention can bias the respective sensory system in advance to favor a certain kind of stimuli (e.g. task-relevant stimuli). Anticipatory activity is highly relevant in everyday life and exerts influence on two main subsequent processes: motor functions and perception. This implies: High anticipation results in a modulation of perceptual processing of such incoming stimuli on the one hand and improved task performance (e.g. shorter reaction times, higher accuracy) on the other hand.

Interestingly and therefore important to mention are the differences between observed ERP responses and evoked GBRs following expected and irregular (or deviant) sounds. Deviant sounds within the descending or ascending sequences elicited a larger negative deflection (N2b) in the ERP between 150 and 350 ms than expected sounds. This is in contrast to the early GBR where deviant sounds evoked significantly smaller amplitudes than expected sounds. Thus, the findings indicate that both electrophysiological responses reflect different processing levels. Further, evoked gamma-band oscillations are functionally more relevant during matching processes than in deviance detection that apparently reflects later, more elaborated processes.

Hence, two main conclusions derive from the results of Experiment 3:
First, early evoked GBRs appear as a neural correlate of anticipatory and memory processing in the auditory system. Second, the evoked GBRs reflect matching processes, whereas the later N2b component of the ERP is much more relevant during deviance detection.

According to the reported experimental results, I will now discuss them within the context of the MUM (Herrmann et al., 2004c).

7.2 Match-and-utilization model in the auditory modality

The proposed model, termed as "match-and-utilization model", attempts to explain cognitive functions with respect to high frequency oscillations (30-80 Hz) (see Fig. 7.1). The authors suggested that the GBR is a correlate of the comparison between sensory information and information stored in memory. Thus, if the sensory bottom-up input matches with templates previously stored in memory, this results in enhanced evoked gamma-band activity. A successful matching process initiates further so-called utilization processes, which are reflected by the late induced GBR in the model. This late gamma-band activity can be involved in selection of specific behavioral responses, memory updating, or reallocation of attention.

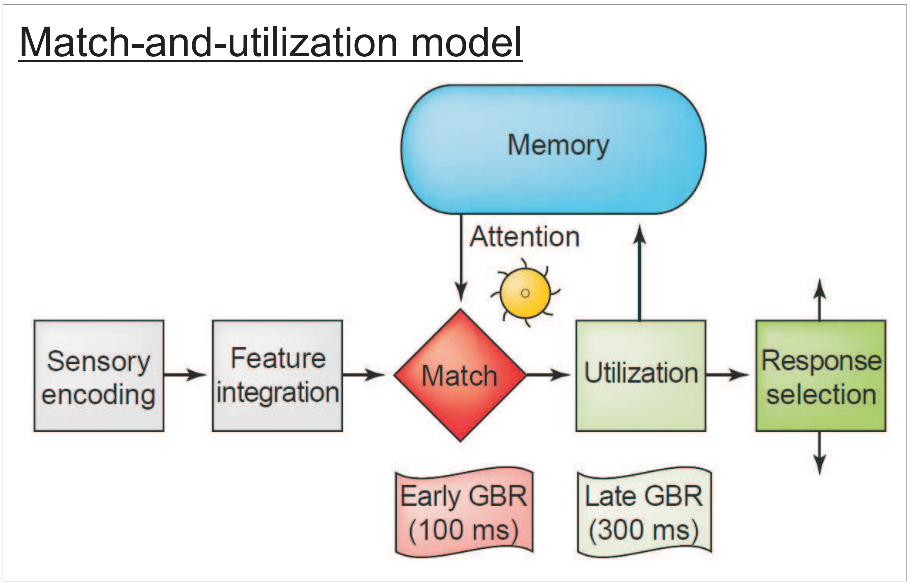

Figure 7.1: Illustration of the match-and-utilization model (The figure is redrawn from Herrmann et al., 2004.).

This model was mainly developed for integrating findings from the visual modality. Therefore, it would be interesting, if the model could also account for explaining cognitive functions in the auditory system. For early processing mechanisms, it appears plausible that the evoked GBR serves as the same mechanism in processing low level attributes of visual and auditory stimuli. Modulations of evoked GBRs by physical characteristics of a stimulus have been observed for both modalities in the first experiments and in previous studies (Busch et al., 2004; Fründ et al., 2007a; Lenz et al., 2008). Such sensory coding mechanisms provide the basis for further processing steps such as matching sensory input in-

formation with memory contents. The matching or this integration of bottom-up and top-down information only results in the aforementioned increase in early GBR, if stimulus characteristics are salient enough (Busch et al., 2006; Fründ et al., 2008b). So far, Lenz et al. (2007) reported that induced gamma-band activity in the time interval between 300 and 500 ms after stimulus onset reflects the matches between environmental sounds and their representations in auditory long-term memory. With respect to the time-scale, this result differs from what was reported for the visual modality. However, the late effect seems most likely and much more plausible: The perception of an environmental sound builds up over a time period which is very distinct from the perception of pictures. Changes in tone intensity or frequeny has to evaluated over a specific time in order to match with a stored representation.
However, in the third experiment, I was able to show that matching processes can occur as early as during the first 50 ms after stimulus onset. This early top-down modulation by anticipatory processes in the auditory system might be conceivable for two main reasons: First, sine wave tones as used in this experiment are very simple compared to the complex environmental sounds used by Lenz et al. (2007). Second, during anticipatory states, specific neuronal populations were sensitized even before stimulation and were therefore able to react faster after a successful matching process. A similar top-down modulation on the early gamma-band activity during the detection of target tone stimuli (sine wave tones) was reported by Debener et al. (2003). Target detection also resembles a matching process, since every incoming sound has to be compared with a memorized target template which is usually defined before performing the experiment. According to the first processing stages, described in the MUM, the following conclusion with respect to the aforementioned findings can be drawn: Basic building blocks of cortial processing are shared in bottom-up visual and auditory processing. Further, top-down driven matching processes of incoming information with a representation of an anticipated sound are reflected in the early evoked GBR and are well in line with MUM.

In the MUM, induced GBRs are associated with readout and utilization processes. To my knowledge, studies investigating induced GBRs in the auditory modality reported highly inconsistent results. The findings range from decreased activity in response to targets (Bertrand and Tallon-Baudry, 2000), no significant differences between target and non-targets (Debener et al., 2003), and to increased activity in response to deviants (similar to a target stimulus, Kaiser and Lutzenberger, 2005b). However, there are some findings which are in line with the model. During the active maintenance of specific auditory information in short-term memory, induced GBR was increased over putative sensory processing streams and frontal regions (Lutzenberger et al., 2002; Kaiser et al., 2003). Furthermore, the maintenance of relevant auditory information was accompanied by gamma-band coherence between higher order sensory and prefrontal areas.

This supports the notion of the study done by Widmann et al. (2007) that later processing stages are linked to integration of different information.
In conclusion, some of the reported findings regarding the auditory system are in line with the MUM and emphasize the induced gamma-band activity as an integration mechanism. However, other studies show a diverse pattern of results requiring a further systematic investigation of the functional significance of induced GBR during higher level auditory processes.

7.3 The visual and auditory modality in comparison

In this paragraph, I highlight basic similarities and differences during perceptual processes in the auditory as well as the visual system with regard to high frequency oscillations.

7.3.1 Low-level processing

As demonstrated in the Experiments 1 and 2 as well as reported in other studies, there is a clear evidence that both modalities share the same processing mechanisms during the first 100 ms reflected in the evoked gamma-band activity. This is interestingly, since stimulus material is very different, particularly it is processed in different time scales. A picture comprises various information at once, whereas the information of a sound has to be evaluated over time. Several facts related to anatomical (i) and functional (ii) commonalities could account for this:

(i) The cortex is organized in six horizontal layers running in parallel to the brain surface, while each layer differs in densitiy, size, form, function and synaptic circuits of neurons. This columnar organization appears to be relatively homogeneous across sensory cortices (Linden and Schreiner, 2003; Hirsch and Martinez, 2006), which is important as mainly primary sensory areas are thought to be the origin of evoked GBR (Pantev et al., 1993; Mulert et al., 2007). Previous investigations of the early evoked gamma-band activity described the largest amplitudes in response to auditory stimuli at central electrodes and found the neural generators of this activity in the primary auditory cortex (Pantev et al., 1993; Mulert et al., 2007). Up to now, there is no study examining neural generators of the visually evoked GBR. However, strongest visual-related GBRs were consistently observed over parieto-occipital electrodes suggesting the source of activity in primary visual areas (Busch et al., 2004; Schadow et al., 2007b; Fründ et al., 2008a). Nevertheless, a source localization of the visually evoked GBR would complement the findings from the auditory modality.

(ii) During the first steps of stimulus processing, different aspects of an event have to be extracted and then integrated to a unified percept. In the visual modality, this was reported to occur during the first 60 ms after stimulus onset (Roelfsema et al., 2007). In the auditory modality, the timing of feature integration depends on the duration of the sound. One central theme in both modalities is the processing in two parallel, but functionally specialized pathways: the 'what' and 'where' stream (Ungerleider and Haxby, 1994; Ahveninen et al., 2006; Altmann et al., 2007). In audition, the pathways were discussed in terms of a preferred processing of spatial features (e.g. sound localization) in caudal cortical areas, whereas non-spatial features are processed in more ventral cortical areas (Ahveninen et al., 2006; Altmann et al., 2007). Within the 'what' stream, grouping mechanisms are essential to develop or identify a useful concept of a visual or auditory object. Such grouping mechanisms are not only well-established in vision, but also in audition. One example for generating perceptual entities is the figure-ground segregation, which is illustrated for both sensory systems in Figure 7.2. During perception of the Rubin vase/face[1] (left part of Fig. 7.2), attention controls which figure is perceived and relegates all other information to the ground. If listeners are following an alternating tone sequence composed of two pure tones of different frequencies (ABAB...), two percepts are possible - depending on the frequency separation between the A and B tones (Bregman, 1994). When A and B have similar frequencies, listeners typically hear a single stream of sound with a galloping rhythm. However, when the A and B tones are more distinct, listeners perceive two streams and the gallop disappears. This latter phenomenon has become known as auditory stream segregation. In such tone sequences, the attended stream is subjectively louder than the unattended stream, leading to an auditory "figure-ground" percept (see right part of Fig. 7.2).

As already reported in the Introduction, some studies investigated the functional relevance of gamma-band oscillations in response to coherent object perception in both modalities (Tallon et al., 1995; Tallon-Baudry et al., 1996; Knief et al., 2000) and found different results. An increase in induced GBR has been demonstrated to coherent visual objects, whereas no induced effects were shown for respective auditory objects. However, the cortical sources of the evoked GBR for spectral and virtual pitches (comparable with the real and illusory triangle in the visual modality) were found to be closer together. The cortical source for the non-coherent tones was located more anterior to those of the coherent tones, suggesting that different cortical areas were active in processing spectral/virtual pitches and non-coherent tones. At first glance, it seems as if coherent object perception is reflected by different GBR responses in the studied sensory systems. Indeed, it cannot be ruled out, whether coherent object perception is

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[1] The picture of the Rubin vase/face was downloaded from the following website: http://www.uncleernest.com/fun_optical.html.

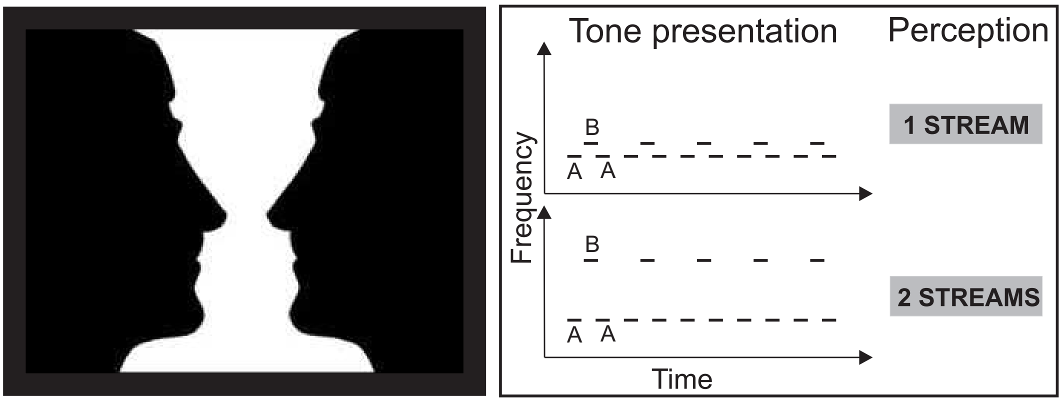

Figure 7.2: Figure-ground segregation - an example for a grouping mechanism by which perceptual entities are formed - is illustrated for the visual (left) and the auditory (right) system.

really reflected in comparable processes in audition and vision and whether these differences might be also caused by experimental requirements.

7.3.2 High-level processing

Higher levels of perceptual processing involves a more global view of the sensory input information, extracting the meaning by accessing concepts and making sense of situations at a conceptual level. This ranges from the recognition of objects to structuring of information by attention or expectations.

The results of Experiment 3, investigating the influence of expectation on auditory stimulus processing, support findings of a study addressing the same question for the visual system (Fründ et al., 2008b). In the visual experiment, oscillatory activity to natural images with respect to stimulus anticipation was investigated. Effects of such stimulus anticipation for the phase-locked response were observed in Experiment 3 and by Fründ et al. (2008b), whereby the effect for natural images was manifested in a somewhat lower frequency band (beta-band). A possible explanation might be the stimulus complexity which required an integration of information from remote cortical areas. This in turn needs to engage spectral components of lower frequencies (von Stein and Sarnthein, 2000).

Furthermore, memory processes have been examined in both modalities and revealed different findings caused by the aforementioned different time scales of stimulus processing. Whereas pictures (line drawings) that match with a long-term memory representation evoked early GBRs (Herrmann et al., 2004b; Fründ et al., 2008a), environmental sounds (also with a memory representation) induced a late GBR in a time window between 300 and 500 ms (Lenz et al., 2007). Interestingly, the memory-related effect was also reflected in the later induced GBR in the case of more detailed visual stimuli, while this effect was not present in case of simple line drawings (Fründ et al., 2008a). A very recent study investigated the personal significance of SMS handy tones on the GBR (Roye et al., 2009). The personally relevant tone stimulus elicited a strong evoked GBR during the first 60 ms after stimulus onset. Given that SMS tones are rather simple compared to everyday life sounds and that the personal significance prompts the formation of individual memory representations, memory-related effects on the GBR are possibly depended on the complexity of stimulus material.

Finally, attentional modulations on the GBR were shown very early in time, namely for the evoked response in the visual as well as auditory modality (Herrmann and Mecklinger, 2000; Debener et al., 2003). The authors emphasized the evoked GBR as a mechanism for object selective attention.

Comparing low-level and high-level processing in the visual and auditory system with regard to gamma-band oscillations as one underlying electrophysiological marker, the following conclusions can be drawn:
First, although the timing of sensory input is fundamentally different in vision and audition, early processing of stimulus features is equally reflected in the evoked GBR occurring with a latency between 60-100 ms after stimulus onset with generators in predominantly sensory cortices. Second, there is convincing evidence for similar operating memory matching mechanisms reflected in the evoked GBR, depending on stimulus complexity in case of auditory and visual stimulation: Here, top-down modulations by memory matching are either reflected in the early evoked (for simple stimuli) or late induced (for complex stimuli) GBR.

A Curriculum vitae

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Jeanette Schadow

B Danksagung

"Was lange währt, wird endlich gut."

Wahrscheinlich bin nicht nur ich überaus glücklich über die Tatsache, dass der letzte Satz in dieser Arbeit geschrieben und das Pamphlet nun eingereicht wurde. Es gab sehr viele Menschen, die mich durch diese Zeit begleitet, mich unterstützt und manchmal auch mitgelitten haben. Deshalb möchte ich mich an dieser Stelle bei all denen herzlichst bedanken.

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C Selbstständigkeitserklärung

Hiermit erkläre ich,

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dass ich die vorliegende Dissertationsschrift selbstständig verfasst und keine anderen, als die angegebenen Quellen und Hilfsmittel verwendet habe sowie wörtlich oder inhaltlich übernommene Stellen als solche gekennzeichnet habe.

Magdeburg, am 23. Juni 2009 Jeanette Schadow

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