Interactions of bottom–up and top–down processes in human evoked gamma–band activity

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Contents

The Unknown

As we know,
There are known knowns.
There are things we know we know.
We also know
There are known unknowns.
That is to say
We know there are some things
We do not know.
But there are also unknown unknowns,
The ones we don't know
We don't know.

Donald B. Rumsfeld, Feb. 12, 2002, Department of Defense news briefing

Chapter 1

Introduction

The analysis of event–related electroencephalographic (EEG) data by means of frequency or time–frequency analysis has become increasingly popular in recent years. The gamma frequency band (i.e. the frequency band from 30-100 Hz) has been of particular interest in empirical research as well as theoretical work, and a good deal of reports on this matter has been recently published in high–ranking journals. In spite of this popularity, however, many questions about the gamma–band have so far remained unanswered, and I believe that these open questions have indeed troubled a lot of research work, especially in the domain of human EEG. In this dissertation project I have attempted to come to understand some of these issues. In particular, I attempted to derive parameters for optimal stimulation in order to obtain reliable gamma–band signals of perceptual functions, identify the circumstances under which these functions can be modulated by cognitive processes, and suggest a general framework of top–down modulations of gamma–band activity which may serve to integrate a large body of literature.

1.1 Bottom–up and top–down

A working hypothesis of this thesis is that gamma–band responses can, at the same time, be modulated by both top–down and bottom–up influences. Hence, the terms “top–down” and “bottom–up” are among the key concepts of this thesis. They are, however, used with somehow different meaning by different authors and in different context, and, therefore, shall be described in more detail.

Representations of the outside world are shaped by two sources of information. Representations depend upon actions of the environment on the sensory organs, e.g. on the impact of light rays on the retina or on physical pressure on touch sensitive parts of the skin. However, the picture one sees is more than meets the eye. Our representation of the world outside is to a large extend influenced by internal processes. For instance, when looking at a crowd of people one would easily recognize the face of a friend (and later remember having seen him) whereas faces of unfamiliar people (that are physically highly similar) are likely to be ignored and forgotten. Yet another example is given by the images in Figure 1.1. Without knowing what they depict these images are hard to interpret. However, with the help of top–down processes provided by the undegraded images and explanations from Figure 1.2 the same physical stimulus and sensory input can be processed in a different way (e.g. figure ground segregation or later recognition).

In cognitive sciences the input from the environment is usually considered as “bottom–up” while influences on representations from within the cognitive system are referred to as “top–down”. Bottom–up and top–down can be understood in terms of brain anatomy and physiology. It is widely assumed that perceptual processes are hierarchically organized. This hierarchy consists of a set of multiple modules which are interconnected. In this system, there exist ”lower“ areas, which process simpler sensory features and are activated earlier (e.g. V1) than ”higher areas“ which process more complex or abstract information and are activated later (e.g. occipito–temporal cortex, cf. Grill-Spector and Malach, 2004). Bottom–up, in this respect, refers to a feedforward flow of information and top–down refers to a

Figure 1.1: Examples of stimuli that are hard to process when seen for the first time. However, with the bottom–up information provided by Figure 1.2 the same stimulus can be processed more efficiently. Stimuli were adapted from Goffaux et al. (2004), Schäfer (2001), and Snodgrass and Vanderwart (1980).

feedback flow of information along the hierarchy. An alternative conception refers more to conceptual principles rather than referring to anatomical systems such as ascending and descending projections. In this respect, processes which take information coming into the eye and make judgements about the nature of the visual world solely based on this information are termed “bottom–up” (sometimes referred to as “data–driven” processes). On the other hand, processes which use operations such as attention, expectation, belief, or experience to influence perception are referred to as “top–down” (or “information–driven”).

Theories of perception and cognition have been at odds on how these two ways of processing are related to one another. Some theories have considered visual sensory processing to consist mainly of the sequential extraction and recombination of features, leading to the veridical reconstruction of object properties. That is, cortical processing of sensory information has been thought of as being largely performed in a feedforward manner. The information about stimuli propagates through a bottom–up pathway from lower to higher cortical areas (e.g. Oram and Perrett, 1994). As a result, perception was believed to deliver an internal ”world

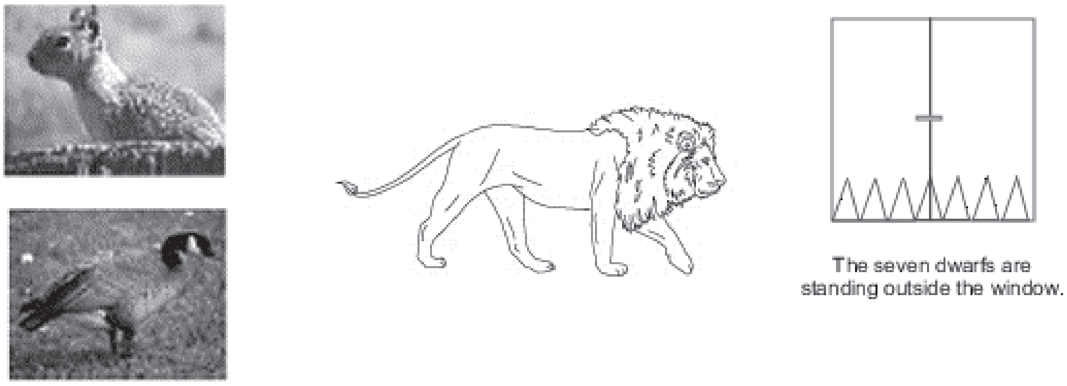


Figure 1.2: Undegraded version of and explanation for images in Figure 1.1.

model“ that provides general–purpose, context–invariant knowledge about the external environment. Subsequent cognitive or top–down processes could, then, operate with the input provided by theses world–models. This is largely a uni–directional bottom–up concept of visual perception in which sensory processes occur first and cognitive processes come into play much later. In contrast, the view favored in this thesis is that visual perception is subject to top–down influences, especially expectation and experience, even at anatomically and temporally early stages of processing. This implies that brain systems that express, for instance, target detection or familiarity are not necessarily separate from and involved later than systems responsible for sensory processes. Such a structure of visual cognition seems more appropriate to facilitate adaptive behavior than a context– and cognition–invariant model of the world that is established prior to and separate from cognitive operations. This is consistent with the notion of Engel et al. (2001, p. 705) who stated that ”... intelligent behavior presupposes that a cognitive system can detach itself to varying degrees from the current stimulus situation, and select (...) only those inputs that are meaningful for the control of action. (...) This seems to be possible only if the brain makes efficient use of top–down resources, allowing it to create predictions about forthcoming stimuli and to constantly match expectations against signals from the environment“. A similar idea has been put forward by Goodale (2000, p. 365) who stated that:

“Vision did not evolve to enable organisms to perceive. It evolved to provide distal control of their movements”.

One important example of models that describe interactions between bottom–up and top–down processes is the adaptive resonance theory by Grossberg (1999). The model assumes that feedback in sensory systems is necessary to stabilize important representations selectively in a rich environment, where only subsets of input signals are relevant. The theory assumes complementarity between ascending and descending pathways among sensory areas, the former allowing adaptive filtering of the input signals and the latter carrying predictive signals (templates of expected patterns that need to be matched by the current input). In this scheme, the lower area that is closer to the sensory periphery provides the interface where afferent data and learned feedback expectancies are compared. The assumption is that a mismatch between the two leads to extinction of the sensory responses in the early area, whereas a match causes their amplification, allowing broadcasting of the salient signals to other downstream areas. This models suggests that the comparison of sensory input with existing knowledge is essential for perception. In a similar manner, Herrmann (2002) pointed out that most experimental tasks require a matching of sensory input against representations or templates of behaviorally relevant stimuli. Other models considered cross–systems interactions and, in agreement with functional imaging (Frith and Dolan, 1997; Pollmann, 2004) and cellular data (Desimone and Duncan, 1995; Miller and Cohen, 2001), indicate that top–down influences originate in prefrontal and parietal cortical areas. For instance, Frith and Dolan (1997) distinguished the “sites” of interactions between sensory input and top–down modifications (located in sensory regions) from “sources” of these modifications (located primariliy in prefrontal and parietal cortex) which are supposed to be largely modality independent. As an elaboration of existing models, Engel et al. (2001) suggested that top–down effects (e.g. expectation of a task relevant stimulus) induce a particular pattern of subthreshold fluctuations in dendrites of the target population. These could be “compared” to temporal patterns arising from peripheral input by virtue of the fact that phase–shifted fluctuations will cancel each other, whereas in–phase signals will summate and amplify in a highly nonlinear way, leading to a salient postsynaptic signal. Hence, temporal patterning of oscillatory neural responses could provide a neural implementation of the mechanisms of amplification predicted by the Grossberg model. Incoming afferent signals induce some patterning of activity in cortical areas that arises from local computations operating on the input. These local patterns, however, are constantly subject to modulation by long–range interactions, both from other cell populations in the same area and from assemblies that are activated in other areas. These modulatory influences carry predictions about specific feature constellations. A successful match will result in the amplification of a specific pattern of synchronized neural discharges, which, in turn, will be broadcasted as a salient signal to other neuronal populations and support the stabilization of large–scale patterns of temporal coherence. As will be explained in Section 1.2.2 Engel et al. (2001) assume that oscillatory signals in the gamma–band are especially important for interfacing top–down and bottom–up processes. All the above–mentioned models stress the importance of constant comparisons between sensory input and stored representations of learned or expected stimuli. Moreover, these models assume that the interactions between bottom–up and top–down processes, e.g. in the form of a matching process, do not occur in particular “interaction areas”. Instead, these interactions are thought to be expressed in those areas providing the sensory input. Hence, it appears reasonable to assume that interactions occur at both anatomically and temporally early stages of visual processing. Moreover, it can be expected that an electrophysiological signal which reflects this interaction will also be susceptible to variations of the sensory input, e.g. by changing stimulus parameters.

1.2 EEG correlates of bottom–up and top–down

In order to test hypotheses on the early involvement of top–down processes in visual perception it is necessary to measure responses of the visual system that originate from an early stage of processing. Because of the superior temporal resolution of EEG, electrophysiological measures are a widely used tool for the investigation of sensory systems. Event–related EEG data is most commonly analyzed by averaging multiple data epochs related to the same experimental event. This is the event–related potential (ERP) which predominantly contains activity which is correlated to the event in question. Additionally, event–related EEG signals can be investigated in the frequency domain as event–related oscillations (EROs). It has been convincingly demonstrated that assessing specific time–varying frequencies can often yield insights into the functional cognitive correlates of EEG signals which may not be available from common ERP analyses (Başar et al., 2001; Makeig et al., 2004). ERPs and EROs are described in a more technical way in Chapters 2.1.2, 2.1.3, and 2.2. In the current chapter I will review studies that have provided insights into top–down and bottom–up modulations of ERPs and EROs. I will argue that oscillatory gamma–band responses are among the earliest responses of the visual system that can be measured in EEG and, therefore, are ideally suited to investigate early interactions of bottom–up and top–down processes.

In the field of electrophysiology a common terminology distinguishes between two different classes of electrophysiological responses. Again, the key idea is to distinguish between those components reflecting data driven and those reflecting cognition related processes, respectively. According to Coles and Rugg (1995, p. 15) "exogenous" components are "... a set of components whose characteristics (...) seem to depend on the physical properties of sensory stimuli. (...) It has been claimed that their characteristics are immune to variations in the subject's state and to the nature of the interaction between the subject and the stimulus — that is, that they are not influenced by "cognitive" manipulations". In contrast, endogenous components are conceptualized as phenomena that "vary as a function of such factors as attention, task relevance, and the nature of the processing required by the stimulus". It is commonly stated that this distinction is an oversimplification of the real state of affairs and that most ERP components are, in fact, intermediate between these two types (so–called mesogenous components) or should be conceived of as falling on an exogenous–endogenous dimension (Coles and Rugg, 1995; Proverbio and Zani, 2002). Nevertheless, this terminology is still widely used and it captures the fact that early EEG responses are more easily modulated by stimulus properties while subsequent responses are rather modulated by task–related processes. Thus, the concept of "exogenous" is very similar to "bottom–up" while that of "endogenous" comes close to "top–down".

Exogenous modulations especially of early ERPs and, to a lesser extend, of EROs have been demonstrated in several investigations. Obtaining detailed knowledge about these bottom–up modulations has been important for several reasons. First, covariation between stimulus attributes and ERP responses may give insights into the underlying physiology and functions. Moreover, knowing the physiological and sensory processes that give rise to a given EEG signal make it possible to use this component as a tool for the investigation of the intact sensory system and of its clinical disorders. Accordingly, early exogenous ERPs have been used extensively as tool for diagnosis of visual and auditory defects. Second, even for researchers interested in cognitive or affective processes it is important to consider putative exogenous influences on ERP data that might confound with endogenous effects. Accordingly, in a treatise on effective experimental design for ERP experiments Luck (2004, p. 29) suggested: "Whenever possible, avoid physical stimulus confounds by using the same physical stimuli across different psychological conditions". In other words, investigating exogenous modulations can yield important insights both from a theoretical and a pragmatical point of view. I will next review exogenous and endogenous modulations of event–related EEG patterns. I will focus on those components that are most relevant for the experiments reported in Chapters 4-6. These include the P1 and N1 component of the ERP which occur in a similiar time window as the evoked gamma–band response and the P3 component which has been reported to behave in a similar manner as the gamma–band response.

1.2.1 Event–related potentials

Exogenous modulations related to parameters of stimulation have been described for every sensory modality. I will focus here on the visual modality, since the experiments described in Chapters 4-6 are restricted to the visual modality, as well. It should be noted that the majority of studies investigating stimulus parameters and visual evoked potentials (VEPs) employed checkerboard or simple grating stimuli whereas experiments with a more "cognitive" background tend to use letters, geometric figures, or schematic or natural images. However, it is generally assumed that the same stimulus parameters affect visual evoked potentials no matter whether simple or more complex stimuli are employed. For a better understanding of exogenous effects it should be recalled that visual information is processed simultaneously via multiple parallel pathways or channels. There is a functional specialization in the visual system so that different attributes of the visual scene are processed in anatomically separate parts of visual cortex (Felleman and Essen, 1991; Zeki et al., 1991). Light increments and decrements, motion, spatial frequency, stereoscopic depth, color, shape etc. are processed separately and simultaneously. The functional specialization of separate anatomical areas is confirmed by the effect of selected lesions producing deficits limited to color, spatial perception, or movement. Because changes in certain aspects of visual stimulation are processed separately these different attributes of the visual scene can be isolated and studied by utilizing visual stimuli that preferentially activate one of these parallel channels. For instance, VEPs elicited from equiluminant chromatic (color) stimuli and VEPs elicited from moving dots have a different morphology and are distributed over the scalp in separate but overlapping topographical regions. VEPs to chromatic stimuli have a maximum distribution over temporal areas, whereas VEPs to movement are distributed over the parietal area (Aine and Stephen, 2002; Celesia, 2003). Early visual evoked potentials like the P1 and N1 component are also known to be modulated in both amplitude and latency by stimulus luminance, contrast (Wright and Johnston, 1982), size (Meredith and Celesia, 1982), eccentricity (Meredith and Celesia, 1982), field of stimulation (DiRusso et al., 2002), and spatial frequency (Celesia, 1993). Early ERP amplitudes decrease while latencies increase as pattern luminance is decreased, probably due to the reduction of the retinal illuminance (Johannes et al., 1995; Tobimatsu et al., 1993). Decreased contrast causes amplitude reduction and latency prolongation (Tobimatsu et al., 1993). P1 latency shows a U–shaped function against check size (Tobimatsu et al., 1993). Amplitudes and latencies of early ERP and event–related fields (ERFs), as measured in magnetoencephalography (MEG), increase with spatial frequency and decrease with contrast (Kenemans et al., 1993; Okada et al., 1982). In sum, early ERPs are correlated with visual functions and are modulated by variations in stimulus parameters affecting these functions.

ERPs also reflect aspects of information processing and cognition, that is, aspects of top–down processing. A comprehensive review of endogenous ERPs is beyond the scope of this introduction. Full length overviews on endogenous ERPs are available in the books by Rugg and Coles (1995) or Zani and Proverbio (2002). I will focus on those ERP components and processes that are most relevant for the experiments in this thesis, that is ERPs involved in selective attention and target detection. The earliest ERP components which show effects of top–down processes are the P1 and N1 components which are modulated by selective attention. When subjects are instructed to attend to one side of the visual field P1 and N1 amplitudes evoked by stimulation within the attended field are enlarged compared to stimulation in the unattended field (Luck et al., 2000). Hillyard and Anllo-Vento (1998) differentiated the attentional effects of visual P1 and N1, arguing that P1 might reflect a facilitation of early sensory processing for stimuli presented at an attended location (spatial–selective), whereas N1 might reflect the orienting of attention towards task–relevant stimuli (Hillyard and Anllo-Vento, 1998). In contrast, the earlier C1 component (50-90 ms), which was localized to primary visual cortex, is usually unaffected by manipulations of attention. In marked contrast with spatial attention, the selection of stimuli on the basis of nonspatial features such as color or shape is not associated with a modulation of the P1 and N1 components. Instead, stimuli having relevant or attended features elicit a broad negative ERP termed the “selection negativity” (SN), which begins between 140 and 180 ms poststimulus and persists for another 200 ms or more (Hillyard and Anllo-Vento, 1998). More specifically, the selective processing of nonspatial features reflected in the SN component is strongly dependent upon the prior selection for location, reflected in the P1 and N1 components. The different ERP configurations associated with spatial and nonspatial selections provided evidence that attention to location operates via qualitatively different mechanisms from attention to other stimulus features. Moreover, in a study by Johannes et al. (1995) effects of attention did not interact with effects of stimulus luminance suggesting that the sensory evoked ERPs and the attention effects occurring in the same latency range (i.e. bottom–up and top–down processes) as measured in the ERP reflect separate neural activities. One way to interpret the attention effects in the occipital Nl latency range is as a “selection negativity” that overlaps the sensory evoked components in this time period.

A further ERP component related to attention and target detection is the P3. The P3 is a positive deflection in the ERP which peaks around 300 ms after stimulus onset and is also called P300. It is the most prominent ERP component sensitive to cognitive processing. The P3 is elicited when subjects attend to a stimulus and when they discriminate the stimulus features, e.g. to differentiate them from similar stimuli. While early components like P1 and N1 in response to an auditory or visual stimulus will be generated in auditory or visual cortices, respectively, P3 amplitude and topography is largely insensitive to stimulus properties and modality. Hence, it is regarded as one of the classical endogenous components. The P3 is commonly investigated using the so–called oddball paradigm in combination with a target detection task. In this paradigm, a stream of stimuli is presented and rare target stimuli have to be detected among more frequent irrelevant standard stimuli. Task relevant targets usually evoke larger P3 amplitudes than irrelevant standard stimuli. The term P3b has been coined for the target P3 in order to differentiate it from an earlier positive component in response to novel stimuli, the P3a or novelty P3. Novelty P3s are observed in a target detection paradigm that involves three categories of stimuli: infrequent targets, frequent task irrelevant standards, and infrequent task irrelevant novel stimuli. The P3a occurs slightly earlier and has a more frontal scalp topography than the later P3b. P3b has been regarded as a sign of processes of memory access that are evoked by evaluation of stimuli in tasks that require some form of action like a covert or overt response (cf. Kok, 2001). The amplitude of the P3 reflects the categorization (Mecklinger and Ullsperger, 1993), probability and task relevance of a stimulus while P3 latency reflects the duration of stimulus evaluation (Herrmann and Knight, 2001). Comprehensive reviews on the P3 component are available in Herrmann and Knight (2001), Kok (2001) and Polich and Kok (1995).

1.2.2 Event–related gamma oscillations

Neural signals in the gamma frequency range (roughly 30-100 Hz) have received considerable attention in neuroscience for the past 15 years. Although the phenomenon of fast neuronal oscillations had been described as early as 1942 in animals (Adrian, 1959) and 1960 in humans (Chatrian et al., 1960) it started to attract major interest only in the late nineteen–eighties when synchronous firing of neurons at frequencies in the gamma range was shown to correlate with perceptual binding in animals (Gray et al., 1989). In a seminal experiment Gray et al. (1989) demonstrated that when two neurons are stimulated by one visual object which extends across both their receptive fields they fire in synchrony in the gamma range. If, however, the two neurons are activated by different objects they fire asynchronously. Hence, neural synchronization has been interpreted as a solution to the “binding problem”, as neuronal synchrony could selectively tag the responses of neurons that code for the same object, and demarcate their responses from those of neurons activated by other objects. These results have stimulated a lot of research work on gamma–band activity and a great deal of these studies has been conducted using human EEG. Comparing the literature on functions of gamma–band oscillations to the ERP literature described in Section 1.2.1 several differences are noteworthy. First, the terminology of exogenous vs. endogenous is usually not applied to gamma–band reponses. Second, the majority of studies on human gamma–band activity has clearly focused on top–down effects. Hence, compared to the comprehensive literature on exogenous effects on visual evoked potentials there is a paucity of reports for such effects on gamma oscillations in human EEG. Those few human and animal studies that tested for exogenous effects, however, demonstrated that gamma oscillations are highly susceptible to parameters of stimulation. Multi–unit activity and local field potentials in animal studies showed that gamma oscillations and synchronization are highly dependent on stimulus features such as orientation and direction of movement (Friedman-Hill et al., 2000; Frien et al., 2000; Siegel and König, 2003). Human EEG studies found gamma–band oscillations to depend on stimulus spatial frequency (Tzelepi et al., 2000) and quadrant of stimulation (Narici et al., 2003). The latter result indicates that gamma oscillations are generated in retinotopically organized visual areas. Other experiments have attempted to find effects of perceptual binding on gamma–band oscillations in human EEG. Experiments by Tallon–Baudry and collegues (Tallon et al., 1995; Tallon-Baudry et al., 1996) demonstrated that objects which induce the perception of an illusory figure, so–called Kanizsa figures, induced stronger gamma oscillations than stimuli that could not be bound into an illusory figure. Since these experiments contained task–relevance as a possible confound, Herrmann and collegues conducted a series of experiments in order to scrutinize the roles of perceptual binding and task relevance for gamma oscillations. They used four different stimuli to directly contrast visual feature binding and attention. Two of the stimuli were Kanizsa figures for which the constituent parts could be bound together while for the remaining two stimuli this was not possible. One out of the four stimuli was defined as a target and had to be detected. The experiments revealed that the attended target evoked significantly more gamma oscillations as compared to the three standards (Herrmann et al., 1999). In a further experiment Herrmann and Mecklinger (2001) used stimuli as targets which consisted of features that could not be bound together to coherent objects (a non–Kanizsa square). Nevertheless, this target also evoked the largest gamma activity of all four stimuli. Furthermore, the gamma responses evoked by the three standard stimuli varied in amplitude with the number of features (number of inducer discs and collinearity) which they had in common with the target. This indicated that attention towards a target stimulus is more important for the modulation of gamma activity than the feature binding required to bind together coherent objects. This interpretation is in agreement with numerous other studies demonstrating top–down modulations of gamma–band oscillations. For instance, selective attention has been shown to enhance oscillatory activity and synchrony in response to attended stimuli in monkeys (Fries et al., 2001b; Taylor et al., 2005) and humans (Tallon-Baudry et al., 2004; Tiitinen et al., 1993). Moreover, perception of speech signals also seems to modulate gamma oscillations (Crone et al., 2001a,b) as well as long–term memory processes (Gruber et al., 2004) or face perception (Rodriguez et al., 1999). Several detailed reviews about experiments on and interpretations of gamma–band activity are available (e.g. Herrmann and Knight, 2001; Kaiser and Lutzenberger, 2005). For the research project I want to present in this thesis it is important to point out that different publications revealed both perceptual as well as cognitive functions of gamma–band activity, in other words: both bottom–up and top–down modulations. Moreover, despite the extensive literature on gamma–band activity a common framework for interpretation of these very diverse findings is still missing (Bertrand and Tallon-Baudry, 2000). This stands in contrast with theories on functions of several of the ERP components, the most prominent example of which being the P3 (cf. Polich and Kok, 1995).

Despite this extensive body of positive results some authors have been more skeptical about the role of gamma oscillations. Part of the criticism is based on failures to find gamma activity at all (Juergens et al., 1999; Shadlen and Movshon, 1999; Tovee and Rolls, 1992). Some authors have even questioned that gamma oscillations are detectable at the scalp level (Menon et al., 1996). It can be speculated that many more negative results have been obtained but have remained unpublished. A second critical argument is focused on the functional role of a certain type of gamma oscillations. It refers to the common distinction between an early, phase–locked gamma response (approximately 100 ms after sensory stimulation), and a later non phase–locked or induced gamma response with a latency of 300 ms or longer (Başar-Eroglu et al., 1996). While most authors agree that the latter is a correlate of various cognitive processes some have argued explicitly that the early evoked gamma response is merely a refection of early sensory processes which is "pure of cognition" (Karakaş and Başar, 1998). Others have consistently found effects of cognition on induced gamma activity but reported no such effects on evoked gamma activity (e.g. Gruber et al., 2004; Tallon-Baudry et al., 1996). However, it should be noted that the "sensory nature" has been ascribed to evoked gamma–band activity not by demonstrating exogenous effects but by a failure to reveal endogenous effects.

In this thesis I attempt to encounter these points of critique. As will be described in more detail in Chapters 4-6 I argue that failures to find gamma activity may be due to inadequate stimulation. As the majority of gamma–band research has focused on top–down processes the possible importance of exogenous influences may have remained unnoticed. Moreover, I argue that evoked gamma–band activity is "mesogenous" in the sense that it represents sensory processes but some top–down processes may operate on this sensory representation. This is in line with the idea expressed by Engel et al. (2001) that interactions between bottom–up and top–down processes may not require "interaction areas" and separate neural substrates but may be expressed in those areas and by those processes providing the sensory input. This opens the question whether detecting these interactions in EEG may be dependent on some parameter of stimulation. Finally, I argue that a common process, inherent in most every experiment which has demonstrated top–down effects on gamma–band activity so far, is the comparison between sensory information and representations acquired by past experience or activated by expectation due to their task relevance.

Chapter 2

General methods

2.1 Electroencephalography

2.1.1 From cortex to electroencephalogram

Neuroscience's repertoire of methods used to explore brain function (besides neural stimulation, ablation, neuroanatomy, etc.) includes multiple techniques that measure brain activity. While several of these techniques image the brain's metabolism or chemistry a whole class of other methods including the electroencephalogram (EEG) exploits the electrical properties of neural responses. Cortical neurons fall into two main classes: pyramidal cells which represent approximately 80 % of all cortical neurons and non–pyramidal cells such as stellate or basket cells. Cortical pyramidal cells are considered to be the main generators of EEG. Although action potentials had been initially proposed as the phenomenon underlying the EEG signal, most researchers now agree that excitatory (EPSPs) and inhibitory (IPSPs) postsynaptic potentials generate the EEG (cf. Picton et al., 1995). Synaptic activation by either EPSPs or IPSPs results in a change of current flow through the synaptic and extrasynaptic membranes of a pyramidal cell. EPSPs cause an influx of NA^+ ions into the cell resulting in a change of the concentration of ions. NA^+ is reduced at the apical dendrite. Thus, the dendrite is negatively charged relative to the neuron's soma. The outward flow of positive charge leaves a relatively positive charge in the extracellular space. At this instant there is a dipole outside the dendrite, with a relatively negative charge at the apical dendrite (a current sink) and a positive charge closer to the cell body (a current source). Thus, an extracellular electrode placed near the end of the dendrite detects a negative potential. An electrode placed at the scalp cannot detect these electrical changes in a single neuron because the potentials are small in magnitude (due to the low extracellular resistance), and there is considerable distance from the cell to the scalp surface. However, two principles of cortical organization permit the recording of brain potentials at the scalp. First, pyramidal neurons in cortex are arranged in parallel to one another and orthogonal to the cortical surface. Second, most cortical functions involve the synchronous activation of a large number of neurons, so–called cell assemblies. Therefore, the electrical dipoles of single cells contained in a cell assembly all have a similar dipole orientation, and their postsynaptic potentials can summate over time and space. The resulting electrical fields are strong enough to be measured extracellularly, even from a distance of several centimeters. It can be measured even at the scalp, even though the signal is considerably attenuated and spatially distorted by brain tissue, meninges, skull and skin. It should be noted, however, that not all neural activity is measurable by means of scalp–recorded EEG. Problems arise especially when sources are too distant from the scalp, have a so–called closed field structure (i.e. cells are not arranged in parallel), or when neural activity is not sufficiently synchronous (see Proverbio and Zani, 2002, for an overview). The first measurements of scalp EEG were conducted by the German neurophysiologist Hans Berger in the 1920s with his son Klaus Berger participating as the first human subject in EEG history.

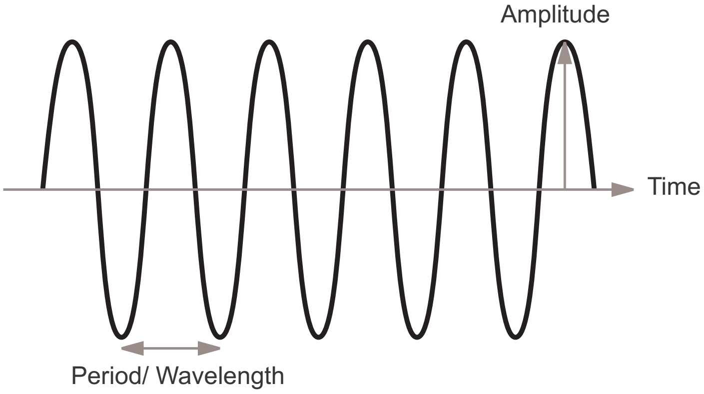
EEG is recorded as electrical potential differences between one or several active electrodes placed over sites of supposed neural activity and a common reference electrode placed over a neuro–electrically inactive site. Electrode locations are usually chosen in accordance with a standardized electrode placement system such as the international 10–20 system (Jasper, 1958) or the extended 10–10 system (Nuwer et al., 1998). In both systems electrodes are labelled according to their proximity to certain anatomical landmarks. Electrode labels consist of a single or multiple letters (Fp: frontal pole; F: frontal; C: central; T: temporal; P: parietal; O: occipital), combined with a number. Combinations of two letters indicate intermediate locations. Electrodes on the left are numbered odd, electrodes on the right are numbered even, and electrodes on the midline are appended with the letter z. Electrodes near the midline have the smallest numbers, and they increase towards the side.

2.1.2 From EEG to event–related potentials

While raw EEG contains mainly spontaneous activity which is — in a broad sense — related to the general state of the brain, most researchers are interested in brain activity related to experimental events and perceptive or cognitive functions. Brain responses elicited by experimental events can be regarded as signal whereas ongoing EEG is unrelated to these events and, hence, can be regarded as noise. In EEG noise usually has considerably larger amplitudes than signals. A standard method for extracting event–related activity from ongoing EEG is the computation of event–related potentials (ERPs). Earliest attempts to derive ERPs were based on the photographic superposition of several time–locked EEG traces. However, the popularity of ERPs did not start before the advent of digital computers in the 1960s (c.f. Fabiani et al., 2000). The most common procedure involves averaging samples of EEG that are time–locked to repeated occurrences of the experimental event in question. Because all those aspects of the EEG that are not time–locked to the event are assumed to vary randomly from sample to sample, the averaging procedure results in a considerable attenuation of noise. The resulting signal (the ERP) usually contains a series of positive and negative deflections, which are then subjected to a variety of measurement operations.

ERP peaks are generally described in terms of their characteristic scalp topography, polarity, and latency. For instance, the label P300 refers to a positive peak with a mean peak latency of 300 ms. Alternatively, ERP peaks can be labelled by the average latency of the component. Thus, P3 refers to the third positive peak in the waveform.

Although analyzing EEG data by means of the averaging procedure described above appears to be intuitive and straightforward, this technique relies on several critical assumptions. First, the ERP signals are assumed to be constant over trials. Signal variations between trials (e.g. due to latency jitter) tend to attenuate or distort the signal in the average waveform. Hence, signals that are not time– or phase–locked to the experimental event should be analyzed prior to averaging (see Sections 2.1.3, p. 25, and 2.2, p. 27). Second, background noise is required to be random across trials and, third, ERPs have to be independent from background noise. These assumptions are typically not satisfied, either. Although violations of these assumptions may not compromise most ERP experiments alternative frameworks for EEG research have been proposed (e.g. Makeig et al., 2004). Finally, it is usually assumed that the peaks and troughs of the ERP waveform represent so–called components. Although the term "component" is frequently used in EEG literature it is rarely defined explicitly and some authors even refer to it as "one of the most important but most nebulous concepts in ERP research" (Luck, 2004, p. 17). A common conception of ERP components assumes a close correspondence between the peaks and troughs of the ERP waveform on the one hand and neural sources and cognitive components on the other. This conception bears several critical issues some of which are especially relevant for the investigations reported here. First, conventional ERP analysis is restricted to a few ERP peaks of large amplitudes such as the P1, N1 or P3. In the frequency domain these signals correspond to slow frequencies below 30 Hz (cf. Makeig et al., 2004). Since signal frequency is inversely related to amplitude signals of higher frequency such as gamma–band responses are usually neglected or deliberately filtered out with high–pass filters. Second, an ERP measured at



Frequency:	**Name:**
0-4 Hz	Delta
4-8 Hz	Theta
8-12 Hz	Alpha
12-30 Hz	Beta
30-80 Hz	Gamma

Figure 2.1: Schematic depiction of an oscillation and denomination of frequency bands.

the scalp is likely to be generated not by a single neuronal process but, instead by several neuronal processes that overlap in time and (due to volume conduction) space. One possibility to overcome the restriction to the low frequency fraction of the ERP and to disentangle different components of the ERP is to analyze event–related EEG activity in the time–frequency domain. By means of time–frequency analysis the entire frequency range of the EEG signal may be analyzed and processes that overlap in time but not frequency may be distinguished.

2.1.3 Event–related oscillations

Oscillations are signals that exhibit a repeated regular fluctuation. These signals are characterized by several parameters (see Figure 2.1). The parameter amplitude gives the “strength” of an oscillation while the wavelength or period describes the velocity at which the signal oscillates. Oscillations are often described in terms of frequency rather than wavelength, where frequency (measured in Hertz) is the inverse of one wavelength. For instance, an oscillation with a wavelength of 25 ms has a frequency of 40 Hz. The phase of an oscillation relates the relative position of a time point and is usually given as an angle or a number between 0 and 2π in the waveform.

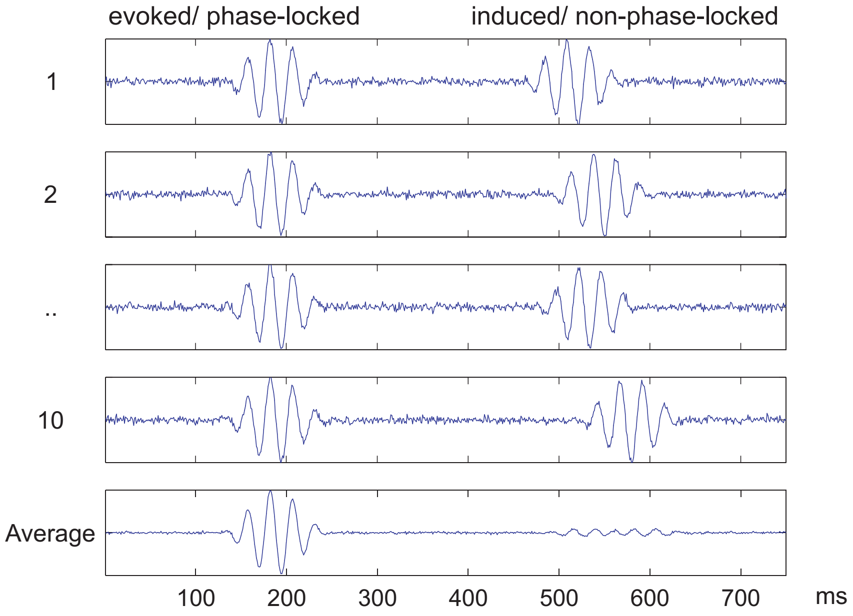


Figure 2.2: If oscillations occur at the same latency after stimulus onset and occur with the same phase relative to stimulus onset in multiple trials (rows 1-4), they are considered evoked by the stimulus (left). If latency or phase jitter relative to stimulus onset, the oscillations are considered to be induced by the stimulus (right). Evoked activity sums up in the average (bottom row, left), while induced activity is almost cancelled out (bottom row, right).

Oscillations were the very beginning of EEG research when the neurophysiologist Berger (1929) first observed the dominant oscillations of approximately 10 Hz recorded from the human scalp. Berger coined the term “alpha” frequency for activity in this frequency range by using the first letter of the Greek alphabet. Berger dubbed the second type of rhythmic activity that he found in the human EEG as “beta”, which is now considered to be the frequency range of approximately 12-30 Hz. Following this consecutive ordering, Adrian (1942) referred to oscillations around 40 Hz (more general 30-80 Hz) observed after odor stimulation in the hedgehog as “gamma” waves. Neuronal oscillations are often observed in response to experimental events.

A terminology of brain oscillations has been proposed by Galambos (1992).

This terminology refers to the regularity by which the oscillation occurs within subsequent experimental trials, i.e. to their degree of phase–locking to the stimulus. First, some spurious oscillations in the gamma frequency range happen to be present in the human EEG without correlation to experimental conditions during and in between stimulation periods. This activity is considered to be spontaneous and usually cancels out completely if an averaged ERP is computed across enough stimulus repetitions. In this framework, spontaneous activity is completely uncorrelated with the occurrence of an experimental condition. Second, oscillatory activity in EEG can be phase–locked to the onset of an experimental stimulus, as it starts at approximately the same latency and phase after stimulus onset for every repetition of the stimulus. In this case, the activity is called evoked, sums, and is visible in the averaged ERP. Figure 2.1 (left) illustrates this outcome. Third, oscillations occuring after each stimulation but with varying onset times and/or phase jitter are considered as being induced by the stimulus rather than evoked and are not visible in the averaged ERP, as illustrated in Figure 2.1 (right). Special methods have to be applied to analyze this type of activity (see Section 2.2).

2.2 Wavelet analysis

As outlined in Section 2.1.2 one of the drawbacks of conventional ERP analysis is its neglect of the frequency content of the EEG signal. The broadband ERP is basically a time–amplitude representation, yet sometimes distinguished information is hidden in the frequency content of the EEG signal. The first approach to frequency analysis of time series was developed by the French mathematician Joseph Fourier in the 1820ies. Fourier proved mathematically that any time series can be accurately represented as the sum of a number of sinusoidal variations of different frequencies, amplitudes and phases. Accordingly, the Fourier transform (FT) and its modern elaboration, the fast Fourier transform (FFT) decompose the EEG signal into frequency components. FFT assumes, however, that the signal be stationary, i.e. that the frequency content be constant over time. As a consequence, FFT does not provide any information about the temporal domain, i.e. at what times which frequency components exist. Regarding the assumption of stationarity this is actually not necessary because in a stationary signal all frequency components are present at all times. The assumption of stationarity, however, is commonly violated in natural signals such as the EEG. In fact, the experimental strategy pursued by cognitive neuroscience seeks to identify *changes* in brain dynamics induced by experimental events.

An intuitive extension of FFT is short time Fourier transform (STFT). STFT assumes that merely some portion of a non–stationary signal be stationary. In STFT the signal is divided into several small segments where these portions of the signal can be assumed to be stationary. A window function is then shifted across the time segments and FTs are computed for every time window. The problem with STFT (and time–frequency analysis in general) is related to what is known as the Heisenberg–Uncertainty–Principle. This principle, originally applied to the momentum and location of moving particles, can be applied to time–frequency information of a signal. Simply, this principle states that one cannot know the exact time–frequency representation of a signal, i.e., one cannot know with absolute precision what spectral components exist at what instances of times. What one can know instead are the *time intervals* at which certain *bands of frequencies* exist, which is a resolution problem. Wavelet transform can be thought of as an extension of STFT that was developed to overcome some resolution related problems of STFT. The major drawback with the STFT is the fixed window size that is used for every frequency. Long time windows lead to impaired temporal resolution and may violate the assumption of stationarity while short time windows lead to impaired frequency resolution, especially for lower frequencies.

Although this trade–off between time and frequency resolution applies to the wavelet transform as well, wavelet analysis is optimized by using analysis windows of variable length, depending on the frequency analyzed. In order to compute a wavelet transform, the original signal needs to be convolved with a so–called

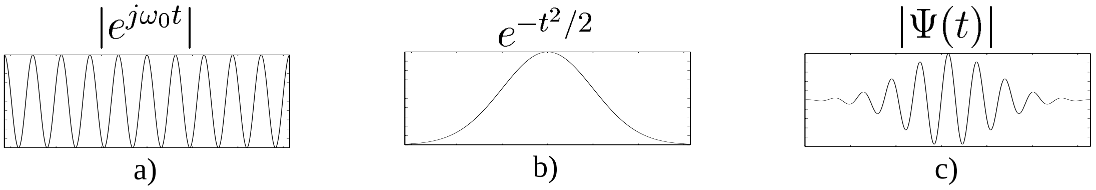


Figure 2.3: Multiplying a sinusoidal function (a) with an envelope function (b) results in a wavelet (c).

wavelet. In the case of the Morlet wavelet used here the mother wavelet is calculated according to the formula

$$\Psi(t) = e^{j\omega_0 t} \cdot e^{-t^2/2}$$

where j denotes the imaginary unit, $\sqrt{-1}$, and ω_0 is 2π times the frequency of the unshifted and uncompressed mother wavelet. Figure 2.3 shows how these mathematical terms construct such a wavelet. These wavelets can be compressed by a scaling factor a to obtain wavelets of different frequencies (substitute t by $\frac{t}{a}$, where $a = compression\ factor$). The mother wavelet ($a = 1$) has the same frequency as the sampling frequency (f_s) of the signal. Wavelets of lower frequencies are computed by increasing a (e.g. for $a = f_s$ the wavelet has a frequency of 1 Hz). Additionally, wavelets can be shifted in time by a parameter b.

Convolving compressed and time shifted wavelets with signals (e.g. EEG signals) results in a new signal (the convolution) which can be interpreted as the similarity between the wavelet and the original signal at a specific frequency and latency. The convolution is computed as

$$s_a(b) = A \int \overline{\Psi}\left(\frac{t-b}{a}\right) \cdot x(t)\ dt$$

where $\overline{\Psi}$ is the conjugate of the complex wavelet and $x(t)$ is the original signal at time t. These new signals $s_a(b)$ are usually computed for different scales a. The scaling factor $A = \frac{1}{\sqrt{a}}$ is used to scale the wavelet prior to convolution.

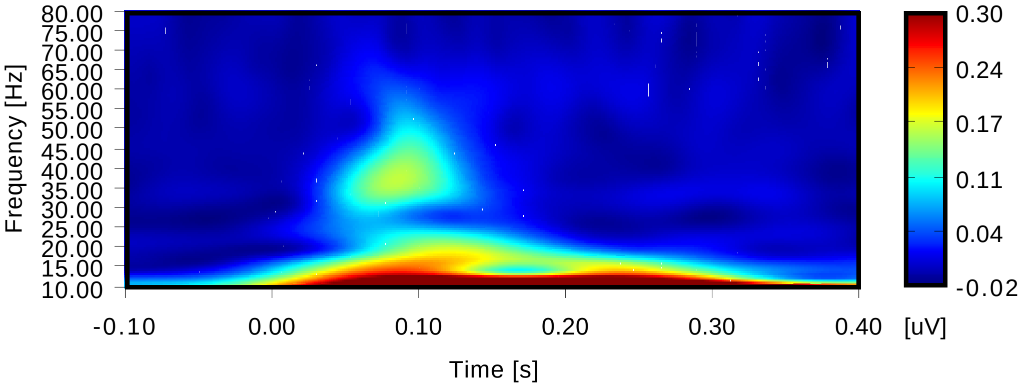


Figure 2.4: Wavelet convolutions of multiple scales (frequencies) can be color–coded and mapped in a single time–frequency-plot.

The convolution of an EEG with a wavelet results in a new signal, as depicted in Figure 2.3c. These wavelet convolutions can be computed for multiple frequencies and the amplitudes of the convolutions can then be color– or gray–scale–coded in one single diagram. This is shown in Figure 2.4 and is called a time–frequency representation.

Morlet wavelets can be thought of as "band–pass filters", with a Gaussian shape both in the time domain and in the frequency domain around their central frequency. Usually, the characteristics of a wavelet are denoted as $2\sigma_t$ and $2\sigma_f$. The standard deviation σ_t of the Gaussian temporal envelope is reciprocally related to the frequency ($\sigma_t \approx \frac{1}{f}$). The standard deviation in the frequency domain is given by $\sigma_f = \frac{2\pi}{\sigma_t}$. The time resolution of this method thus increases with frequency, whereas the frequency resolution decreases with frequency. Accordingly, a wavelet with a center frequency of 40 Hz employed in the studies reported in this thesis had a wavelet duration of $2\sigma_t = 50ms$ and a spectral bandwith of $2\sigma_f = 12.71Hz$ (see Figure 2.5). Besides this general trade–off between temporal and frequency resolution wavelets also allow to adjust their temporal and spectral width for any given center frequency. By using a wavelet with more cycles the frequency resolution increases, since the frequency can be determined via more time points. Of course the temporal resolution decreases at the same time. Using fewer cycles has the opposite effect. All analyses reported here employed wavelets

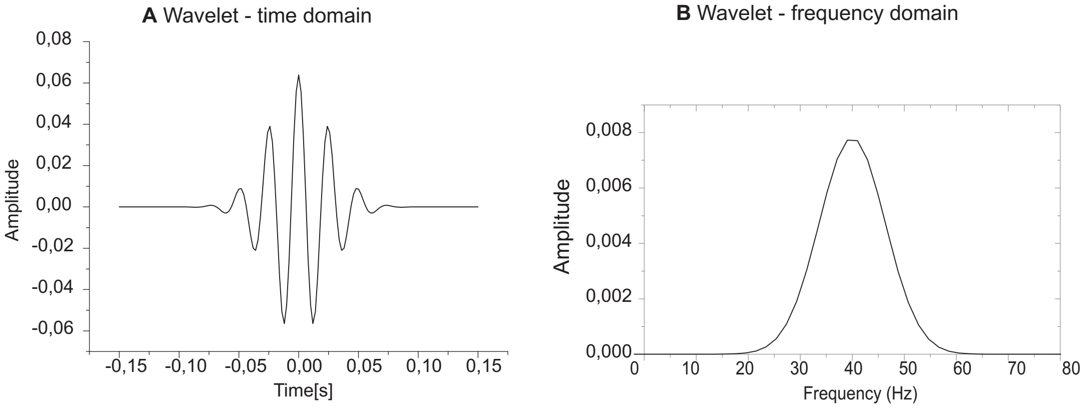


Figure 2.5: Characteristics of a 40 Hz wavelet in the temporal (A) and spectral domain (B).

with a length of 12 cycles.

To represent phase–locked (evoked) activity, the wavelet transform is computed on the average over the single trials, i.e. the ERP. This is denoted by the formula WTAvg (Wavelet Transform of Average). Since the wavelet transform returns complex numbers, the absolute values are calculated.

$$\mathrm{WTAvg} = \left| A \quad \int \overline{\Psi}\left(\frac{t-b}{a}\right) \cdot \frac{1}{n}\sum_{i=1}^{n} \mathrm{eeg}_i(t) \quad dt \right|$$

The baseline of the raw data in a time interval prior to stimulation (e.g. -200 - 0 ms) needs to be subtracted from each EEG epoch prior to averaging. Also, after calculating the activity of a certain frequency, the frequency–specific baseline activity can be subtracted to yield values which indicate amplitude relative to baseline. When wavelet convolutions are computed, the convolution peaks at the same latency as the respective frequency component in the raw data, but the width of the peak will be smeared. Therefore, the baseline should be chosen to precede the stimulation to avoid the temporal smearing of post–stimulus activity into the interval directly preceding the stimulus. To avoid distortions by the rectangular window function which results from “cutting out” a single epoch from continuous raw data, the convolution should start and end one wavelet length before the baseline and after the end of the investigated time interval, respectively.

The above time–frequency representation (WTAvg) contains only that part of the activity which is phase–locked to stimulus onset. In order to also compute the activity which is not phase–locked to stimulus onset (and is therefore canceled out in the average), the sum of evoked and induced activity can be computed. To calculate the sum of all activity at one frequency, the absolute values of the wavelet transforms of the single trials are averaged (AvgWT). This means that each single trial is at first transformed and the absolute values are averaged subsequently.

$$\text{AvgWT} = \frac{1}{n} \sum_{i=1}^{n} \left| A \quad \int \overline{\Psi}\left(\frac{t-b}{a} \right) \cdot x_i(t) \quad dt \right|$$

This new time–frequency representation contains all activity of one frequency that occurred after stimulus onset, no matter whether it was phase–locked to the stimulus or not. As above, activity in a pre–stimulus interval can be subtracted in order to get a relative measure. Other authors refer to this sum of evoked and induced activity simply as induced activity. This may be a legitimate approximation, since the absolute amount of evoked activity is small compared to the much higher absolute values of the summed activity. Detailed introductions to wavelet analysis of EEG data a available in Herrmann et al. (2004b, 1999) and Samar et al. (1999).

Chapter 3

Working hypotheses and outline of experiments

The theoretical and methodological background was described in Chapters 1 and 2. In this chapter I will shortly describe the working hypotheses, and how the hypotheses lead to the empirical questions pursued in the three experiments. The hypotheses will be explained in more detail in Chapter 4-6. In the present project it was assumed that

- gamma–band activity is generated by feature selective neuronal assemblies in early visual cortex,
- activity of these assemblies can be modulated by changes in stimulus properties (bottom–up modulation),
- but also by cognitive operations (top–down modulation),
- the most common being memory matching.

As outlined in Chapter 1 several reports failed to find gamma–band activity. As the question of how gamma–band activity in the EEG is modulated by stimulus properties has hardly been adressed before, it is conceivable that previous studies have been conducted using non–optimal stimulation. To overcome this problem we conducted a first experiment in which properties of visual stimulation (stimulus size, eccentricity and duration) were systematically modulated in order to find out whether these bottom–up factors exert any influence on the gamma–band response. The possible existence of such exogenous influences bears implications for effective experimental design of future studies and for interpretation of the functional significance of the gamma–band response. It was expected to find exogenous effects in the gamma–band that parallel those described for early ERPs.

As described in Chapter 1 most investigations of the human gamma–band response have been focused on effects of top–down processes on gamma–band activity. We conducted a second study in which we varied both a top–down aspect (stimulus relevance) and a bottom–up aspect of the stimulus (stimulus size), in order to investigate whether these different sources of modulation behave in an interactive or additive manner. It has been demonstrated that ERP effects of selective attention do not interact with bottom-up processes, but instead are additive to early ERPs in form of a selection negativity (Johannes et al., 1995). In contrast, from the hypothesis that stimulus evoked activity of feature selective cell assemblies can be modulated by top–down processes it was deduced that bottom–up and top–down effects should manifest in an interactive effect.

Study 2 as well as numerous other studies demonstrated that gamma–band activity is related to various cognitive processes (see Chapter 1). So far, no attempt has been made to assign a unitary function to gamma–band activity. On closer inspection, most previous studies had in common that the experimental task requires a comparison between a stimulus and memory contents, e.g. in order to discriminate targets vs. standards, faces vs. non–faces, or words vs. non–words (Eulitz et al., 1996; Herrmann et al., 1999; Rodriguez et al., 1999). Interestingly, most of the studies agree in that the condition providing the best match with memory contents (e.g. faces as opposed to non–faces) elicits stronger gamma–band responses than the non–matching condition. Hence, we hypothesized that the concept of a matching process might serve as a common unifying framework for interpretation of results on gamma–band activity. Therefore, in a third study we compared gamma–band activity evoked by pictures of meaningful objects as well as nonsense objects, in order to test the hypothesis that matching between a stimulus and memory contents enhances gamma–band responses.

Chapter 4

Experiment 1: Bottom–up modulations of gamma–band activity

The experimental results presented in this chapter have been published in the journal Clinical Neurophysiology (Busch et al., 2004).

4.1 Introduction

In recent years there has been a growing interest to complement the classical analysis of EEG and event–related potentials (ERPs) with various approaches of analysis in the frequency domain (Engel et al., 2001; Pfurtscheller and Lopes da Silva, 1999). The EEG frequency spectrum is usually subdivided into different frequency bands. Although the denotation of frequency bands is by no means standardized throughout the EEG literature, the most prevailing terminology distinguishes the delta (<3 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (13-20 Hz), and gamma (30-80 Hz) bands.

High frequency oscillations in the gamma–band have been investigated in numerous experiments in humans and animals (see Chapter 1). Under visual stimulation a strong increase in evoked oscillations near 40 Hz over posterior areas with a latency of approximately 100 ms and a later increase in induced activity with a latency around 300 ms can be observed. I will refer to both types of these responses as gamma–band responses. Such gamma–band responses have been found to be modulated by task variations and hence cognitive processes including visual feature binding (Tallon-Baudry et al., 1997), target detection (Herrmann et al., 1999), voluntary attention (Debener et al., 2003; Gruber et al., 1999; Herrmann and Mecklinger, 2001), memory (Tallon-Baudry and Bertrand, 1999), and emotional arousal (Keil et al., 2001). However, despite the growing interest in the gamma–band response some authors have been rather critical about the functional role of gamma–band oscillations (Jürgens et al., 1995; Shadlen and Movshon, 1999; Tovee and Rolls, 1992). Numerous attempts to investigate gamma–band oscillations in human EEG have failed to find gamma–band activity at all (Juergens et al., 1999) and some authors questioned that gamma oscillations are detectable at the scalp level (Menon et al., 1996). Considering these discrepancies which may, at least in part, result from differences in experimental settings, stimulus design, or method of data analysis, it seems important to investigate also noncognitive factors that influence the amplitude of the gamma–band response and, hence, its detectability (Lutzenberger et al., 1997). The influence of visual stimulus properties, for instance size, luminance, or spatial frequency, is well known and well examined in the ERP literature (see Chapter 1). Early ERP components that are strongly influenced by such physical properties of the eliciting stimulus are often called “exogenous” while the later components, which are more under the influence of cognitive processes, are termed “endogenous” (Coles and Rugg, 1995). Components that are influenced by both factors are sometimes termed “mesogenous”, a prominent example of which is the N1. While this terminology is commonly used for ERPs it has not been applied to event–related oscillations so far. Nevertheless, some evidence suggests that early event–related oscillations are subject to modulation by rather unspecific factors such as task difficulty (Senkowski and Herrmann, 2002) and subject's age (Böttger et al., 2002). In addition, Rols et al. (2001) showed that stimulus parameters like luminance influence the amplitude of the gamma–band response in electrocortical recordings in the macaque monkey. By using sinusoidal gratings as stimuli Tzelepi et al. (2000) demonstrated increased gamma–band responses for gratings of higher spatial frequency. Accordingly, early event–related oscillations like the gamma–band response could be conceptualized as mesogenous as well.

The present study was conducted to further investigate the impact of visual stimulus properties on gamma–band activity. Such influences are presumably relevant to most experimental paradigms used for the study of relations between cognitive processes and the gamma–band response. In order to properly argue that a difference in amplitude or latency of the gamma–band response between experimental conditions is attributable to cognitive processes it is, first, essential to elicit a significant response at all (which is not as trivial as it may sound). Second, it should be ruled out that differences are simply due to different stimulus properties. Two of such stimulus characteristics are size and eccentricity (i.e., how lateral the stimulus is presented). In addition we varied the presentation duration of the stimuli to investigate whether onset– and offset–related components of the gamma–band response superimpose at short stimulus durations. If ON and OFF responses merge together this could constrain interpretation when comparing experimental conditions with different presentation durations. Our choice of stimulus properties was based on typical stimulus dimensions used in many cognitive ERP experiments (e.g. Barcelo et al., 2000; Gomez Gonzalez et al., 1994; Rugg et al., 1985). Exogenous effects on visually evoked potentials have been investigated predominantly using checkerboard stimuli or sinusoidal gratings in a steady–state paradigm (Celesia, 1993). However, studies designed to investigate cognitive processes usually employ figural stimuli which are presented only once per trial. In order to provide a setting comparable with most cognitive experimental paradigms we used simple geometric shapes as stimuli that were presented transiently in a choice reaction task.

4.2 Materials and Methods

4.2.1 Subjects

23 subjects participated in the study (mean age 25; range 20-34 years, 16 female), all were paid for participation. Subjects gave informed consent prior to start of the experiment. All subjects had normal or corrected to normal vision and were free of current or past neurological or psychiatric disorders.

4.2.2 Stimuli and Procedure

Black circles and squares on a white background were used as stimuli. Subjects were required to press a button with the thumb of one hand if the stimulus was a circle and to press a button with the other hand if it was a square. Response hands were counterbalanced across subjects. Both types of stimuli appeared with equal probability in a pseudo–randomized order. Stimulus presentation was followed by a variable inter–stimulus interval ranging from 1000 ms to 1400 ms. Stimuli were presented on a computer monitor placed at a distance of 105 cm in front of the subject. Monitor refresh rate was 100 Hz. In three separate blocks we manipulated one of the stimulus parameters size, eccentricity or duration, the order of which was counterbalanced across subjects. In the size–block stimuli had a size of 1.5° (small), 4° (medium) or 8° (large) of visual angle and were presented centrally for a duration of 250 ms. In the duration–block a stimulus with a size of 4° visual angle was presented centrally for 50 ms (short), 150 ms (medium) or 250 ms (long). In the eccentricity–block a stimulus of 4° visual angle was presented for 250 ms either centrally or with an eccentricity of 4.3° (medium eccentricity) or 8.6° (high eccentricity) to the right side of the fixation cross. Subjects were required to always remain central fixation. Each block comprised 90 trials per type of stimulus (circles and squares) and level of size, duration or eccentricity, resulting in a total number of 540 trials per block. Two breaks of one minute duration were given in each block and an additional break occurred between two consecutive blocks.

4.2.3 Data acquisition

EEG was recorded using a high impedance 64 channel Net Amps 200 system (Electrical Geodesics, Inc. Eugene, Oregon) with Ag/AgCl–electrodes placed in an electrode cap (Easycap, Falk Minow Services, Munich) and a nose–tip reference. Sensor impedances were maintained below 20 kΩ prior data acquisition (Ferree et al., 2001). EEG was analog filtered from 0.1 to 100 Hz, digitized at 500 Hz, and stored on harddisk for off–line analysis. Recordings were made while subjects sat in a dimly lit, sound–attenuated and electrically shielded cabin. Averaging epochs lasted from 200 ms before to 600 ms after stimulus onset. Baselines were computed in the interval from 200 to 100 ms prior to stimulus onset. An automatic artifact rejection was computed which excluded trials from averaging if the standard deviation within a moving 200 ms time interval exceeded 30 μV. In addition, all epochs were also visually inspected for artifacts and those with remaining artifacts were rejected. While data analysis was performed on unfiltered data, ERPs are displayed low–pass filtered digitally at 20 Hz (3dB edge frequency = 15.05 Hz, steepness of roll–off = 14 dB/octave).

4.2.4 Data analysis

In order to avoid a loss of statistical power (Oken and Chiappa, 1986) we first computed ERPs and wavelet transforms for the single electrodes and then collapsed selected electrodes into nine regions of interest (ROIs) for all subsequent analyses (Oken and Chiappa, 1986). ROIs and corresponding electrodes were anterior left (5, 13, 14, 15, 23, 24), anterior midline (1, 3 , 6, 7, 8, 16), anterior right (9, 17, 18, 19, 26, 27), central left (22, 30, 31, 32, 42, 43), central midline (25, 33, 34, 35, 44, 45, 46), central right (28, 36, 37, 38, 47, 48), posterior left (40,

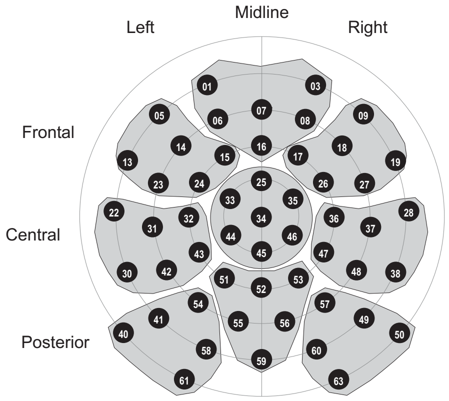


Figure 4.1: Channel layout used for statistical analysis. Regions of interest are indicated by grey shaded areas.

41, 54, 58, 61), posterior midline (51, 52, 53, 55, 56, 59), and posterior right (49, 50, 57, 60, 63). Electrode positions are displayed in Figure 4.1. Those electrodes were plotted in the figures at which effects were most pronounced.

Regarding oscillatory activity, it is important to distinguish between evoked and induced oscillations since they are assumed to reflect different processes. Evoked oscillations exhibit a strict phase–locking to the experimental event (e.g., stimulus presentation) whereas induced oscillations are (by definition) not phase–coupled to a stimulus, and show a certain degree of phase–jittering. Therefore, by averaging across trials these oscillations tend to cancel out and hence are only detectable by appropriate ways of analysis, e.g., by a single–trial based wavelet analysis with subsequent averaging (see Chapter 2.2). Therefore, we employed a Morlet based wavelet transform with a “width” of 12 cycles in order to provide a continuous measure of the amplitude of a frequency component (for details refer to Chapter 2.2 or to Herrmann et al., 2004b). The main advantage of this approach, compared to the short–term Fourier transform approach (Makeig, 1993), is that the duration of the window of analysis depends on the frequency band: the higher the central frequency, the shorter the window duration and the wider the frequency band. This method thus provides a better compromise between time and frequency resolution. To reveal the evoked fraction of gamma activity the wavelet transform was performed on the averaged evoked potential. In order to analyze also activity which is not strictly phase–locked to the stimulus, the wavelet transform was performed for each single trial, and the absolute values of the resulting transforms were averaged. This measure reflects the total activity for a certain frequency range, irrespective of whether it is phase–locked to the stimulus or not. We will refer to this measure as "total gamma–band activity" in order to make explicit that it comprises both the evoked and induced part of the gamma response. However, the same measure has been used previously for the estimation of only the induced part (Tallon-Baudry and Bertrand, 1999). While that may be a legitimate approximation, we prefer to stick to the precise differentiation. The frequency of gamma activity used for the wavelet analysis was individually determined via the time–frequency plane of electrode 34 (equivalent to CZ) in response to the largest stimulus in the size–block (as done before by Senkowski and Herrmann, 2002). This approach assumes that frequencies do not depend on stimulus properties. In fact, it might be speculated that the frequency of the early evoked gamma–band response is dependent on stimulus size, i.e. on the size of the cortical area involved. According to the temporal correlation hypothesis (Singer, 1993) such a relationship might be expected: "As the rhythm slows down, (...) binding by synchrony can be achieved over larger distances and between more cells." (Singer, 1993, p. 367). If assemblies coding bigger stimuli relied on lower frequencies this would broaden the time window during which events can be classified as synchronous. Therefore, in a first step we tested whether frequencies of evoked gamma–band responses differed between the three size conditions. One subject was excluded from this and all further analyses of evoked gamma activity because he did not show a significant response in the gamma–band (for criteria see below). Although there was a trend towards lower frequencies for bigger stimulus sizes this effect did not reach significance (F(2,42)=3.121, P=0.059). It might be interesting, however, to further investigate this effect in a separate analysis. In a second step individual maxima of evoked gamma activity were defined as the highest evoked activation peak in the frequency range of 30-80 Hz between 60-140 ms. The individual frequencies of total gamma–band responses were defined as the highest total activation peak

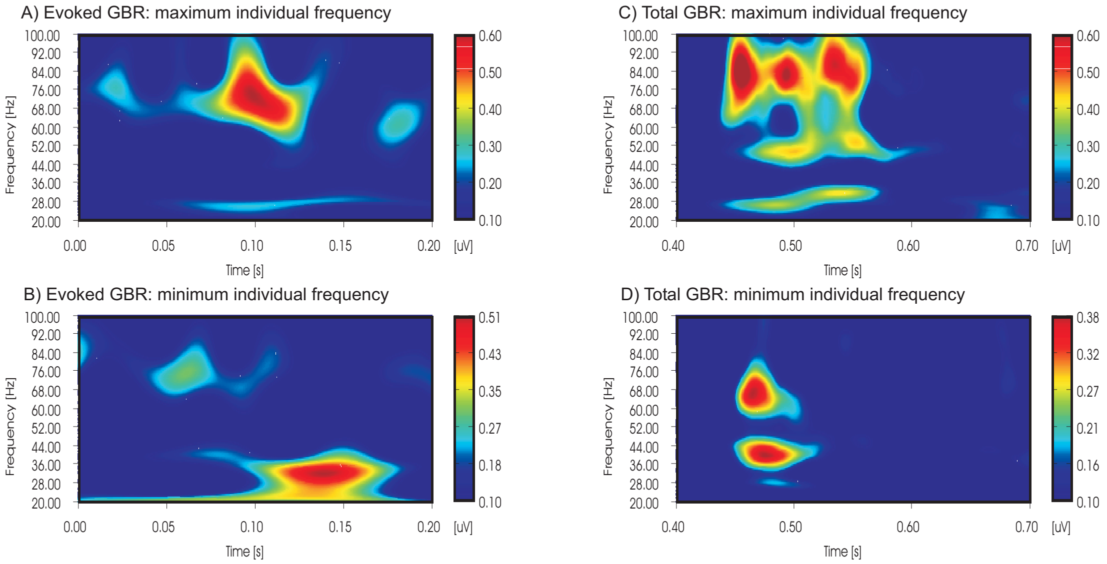


Figure 4.2: Time–frequency plots for the single subjects with the maximum and minimum individual evoked gamma–band response (72 HZ and 32 HZ, respectively) and the maximum and minimum individual total gamma–band response (89 Hz and 39 Hz, respectively).

in the frequency range of 30-90 Hz between 420-560 ms. Using this definition the peak frequencies of individually identified evoked gamma–band responses ranged from 32 to 72 Hz (mean 44.09 Hz, SD=10.04 Hz). The individual peak frequencies of total gamma–band responses were considerably higher with an average frequency of 65,52 Hz (SD=14.41 Hz) and a range from 39 Hz to 89 Hz. Data from the four subjects with the highest and lowest evoked and total gamma–band activity are plotted in Figure 4.2.

For the statistical analysis of ERP responses we used peak amplitudes in the time intervals between 50-130 ms (P1) and 130-200 ms (N1), respectively. P1 and N1 amplitudes and latencies were analyzed for posterior regions only. Statistical analysis of evoked gamma activity was performed on peak amplitudes and latencies of the individually adapted wavelet transforms in the time interval between 60-140 ms. Analysis of total gamma activity in the individually determined frequency was performed using the peak amplitudes and latencies in a time interval of 300-600 ms. The gamma–band response was investigated in all nine ROIs. All time windows were chosen on the basis of the grand mean average.

In a first ANOVA we tested whether the gamma–band response was modulated by stimulus type (circles vs. squares). Since no such effect was observed data was combined across squares and circles for all subsequent analyses . Thus, the repeated measures ANOVA of ERP effects comprised the factors stimulus (three levels of size, duration, or eccentricity, respectively) and laterality (posterior left, posterior midline, posterior right). The repeated measures ANOVA of the gamma-band activity comprised the factors stimulus, laterality (left, midline, right) and caudality (anterior, central, and posterior). The repeated measures ANOVA of reaction times comprised the factor stimulus (three levels of size, duration, or eccentricity, respectively). Greenhouse–Geisser correction was used where appropriate. Uncorrected degrees of freedom and corrected P–values are reported.

In order to visualize the impact of stimulus manipulations on ERPs and gamma–band responses, we plotted the change in amplitude for medium and large size as well as medium and high eccentricity relative to the amplitude of small and central stimuli, respectively (Figure 4.8). In the figures we plotted those electrodes at which effects were most pronounced.

4.3 Results

Stimulus presentation evoked a P1 (mean peak latency 100 ms) followed by an N1 (170 ms; Figures 4.5A, 4.7A, 4.3A). Stimulus disappearance resulted in an OFF response which was superimposed on a P3. The latency of the OFF responses varied with stimulus duration. However, neither the ERP OFF responses nor the P3 component were the focus of the present study and, hence, were not subjected to further analysis. The analysis of the individually identified gamma–band responses revealed a prominent evoked ON response (mean peak latency 86 ms; Figures 4.5B, 4.7B, 4.3B). Stimulus offset resulted in an evoked OFF response with a mean latency of 100 ms after stimulus offset. Additionally, stimulus offset resulted in a total gamma–band response which was observed at an average latency of 232 ms (for stimuli which were presented for 250 ms) after stimulus offset (Figure 4.6). This response was not visible in the evoked activity.

4.3.1 Size–Effects

Reaction times showed a main effect of size (F(2,44)=9.979, P<.001). Responses were fastest to medium sized stimuli (441 ms) while small and big stimuli did not differ significantly with respect to reaction times (457 ms and 451 ms, respectively; F(1,22)=1.70, P=.206).

The ANOVA of P1 amplitudes in the size–block yielded a main effect of size (F(2,44)=9.856, P=.001) with larger amplitudes for bigger stimuli (Figure 4.3A). A main effect of laterality (F(2,44)=11.816, P<.001) indexed smaller P1 amplitudes in the posterior midline ROI than in the lateral ROIs. No interaction of size and laterality effects was observed. P1 latencies showed a main effect of size (F(2,44)=18.092, P<.001) with longer latencies for smaller stimuli. N1 amplitudes were not significantly modulated by size. A main effect for laterality (F(2,44)=5.363, P=.014) indicated smaller N1 amplitudes in the posterior midline ROI compared to the lateral ROIs. Analysis of N1 latencies yielded a main effect of size (F(2,44)=13.587, P<.001) as well as laterality (F(2,44)=13.378, P<.001), and a significant size x laterality interaction (F(4,88)=3.805, P=.014) indicating longer latencies for smaller stimuli at lateral ROIs.

For the peak amplitudes of the evoked gamma activity in the size–block the ANOVA yielded a main effect of size (F(2,42)=11.124, P<.001; Figure 4.3B) with larger amplitudes for bigger stimuli. Peak latencies of the evoked gamma–band response were not influenced by stimulus size. Peak amplitudes of the total gamma–band response were not modulated by size (Figure 4.4A). Total gamma peak latencies were longer for bigger stimuli (F(2,44)=4.522, P=.016).

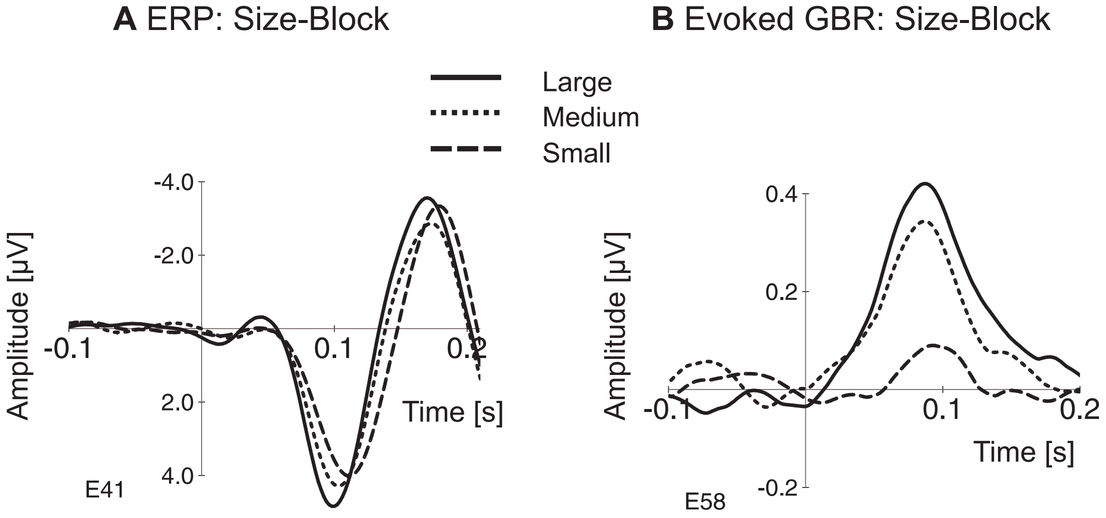


Figure 4.3: ERPs and individually defined evoked gamma–band responses in the size–block for large (solid line), medium sized (dotted line), and small stimuli (dashed line) for representative electrodes. Note the considerable effect of stimulus size on gamma–band amplitude, which was less clearly observed for the ERPs. Data represent the grand mean average across 23 subjects.

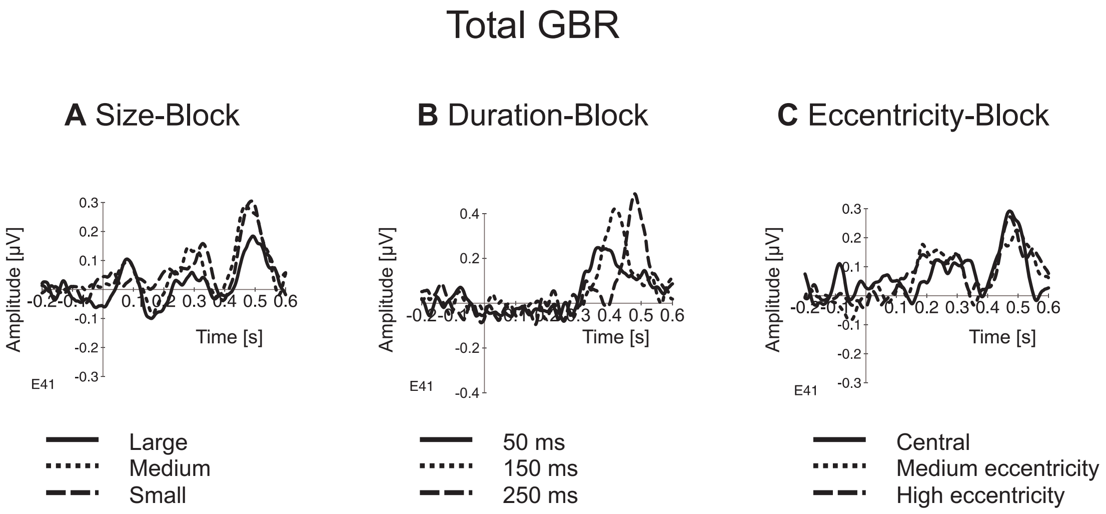


Figure 4.4: Individually defined total gamma–band responses in the size–, duration–, and eccentricity–block.

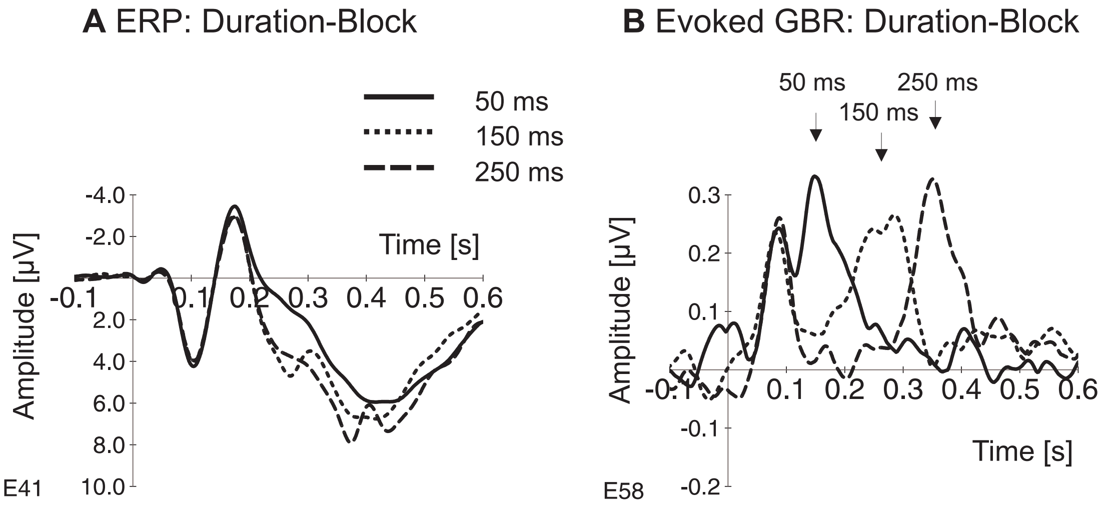


Figure 4.5: ERPs and individually defined evoked gamma–band responses in the duration–block for 50 ms (solid line), 150 ms (dotted line), and 250 ms presentation time (dashed line) for representative electrodes. For ERPs the OFF response was superimposed on the prominent P300 and thus no big differences are visible. For gamma–band activity, however, the OFF response was clearly affected by stimulus duration.

4.3.2 Duration–Effects

Reaction times showed no effect of duration (438 ms for short, 436 ms for medium, and 446 ms for long durations, respectively).

Neither P1 nor N1 amplitudes or latencies were affected by stimulus duration (Figure 4.5A).

Stimulus offsets elicited an evoked gamma–band OFF response. The latency of the evoked gamma OFF responses were 148 ms for 50 ms stimulus duration, 248 ms for 150 ms stimulus duration, and 350 ms for 250 ms stimulus duration (Figure 4.5B), i.e. the evoked OFF response appeared approximately 100 ms after stimulus offset (Figure 4.6). For the shortest stimulus duration evoked ON and OFF responses merged together, resulting in a larger evoked OFF response peak. The ANOVA of evoked gamma–band response peak amplitudes yielded a significant caudality x duration interaction (F(2,44)=3.756, P=.020). Subsequent analysis

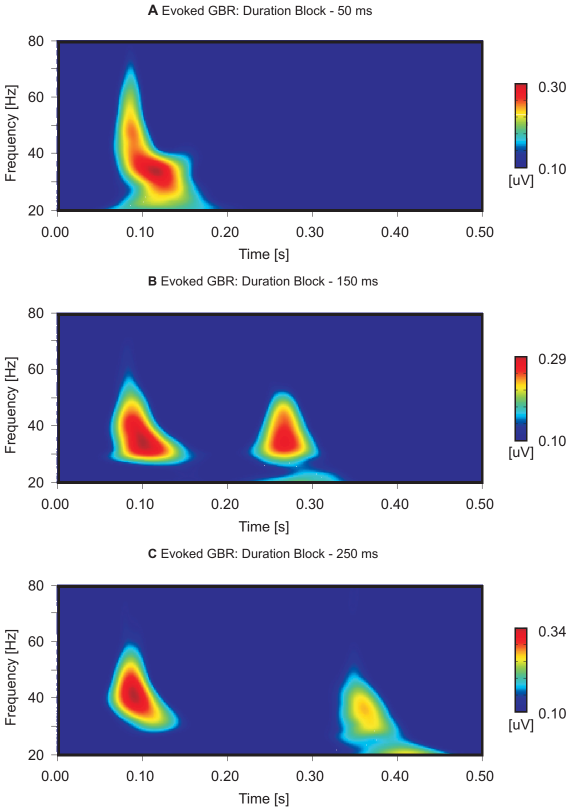


Figure 4.6: Time–frequency plots for the three different stimulus durations (50, 150, and 250 ms) at electrode E34. For the shortest stimulus ON and OFF responses merged together while in the other conditions a clearly dinstinguishable OFF response appears approximately 100 ms after stimulus offset.

revealed an effect of stimulus duration at posterior electrodes (F(2,44)=6.007, P=.006) indicating larger amplitudes for short stimulus durations. This effect probably resultet from a superposition of evoked ON and OFF responses.

Total gamma–band response amplitudes were modulated by duration with larger amplitudes for longer stimulus durations (F(2,44)=6.898, P=.004; Figure 4.4B). Total gamma activity peak latencies also varied significantly with stimulus duration (F(2,44)=14.438, P=.020) with longer latencies for longer stimulus durations (382 ms for short, 412 ms for medium and 482 ms for long durations).

4.3.3 Eccentricity–Effects

Reaction times showed no effect of eccentricity (454 ms for central, 452 ms for medium, and 457 ms for high eccentricity).

P1 amplitudes were modulated by eccentricity (F(2,44)=26.069, P<.001, Figure 4.7A) with larger amplitudes for central stimuli. Amplitudes also varied between ROIs, reflected by a main effect of laterality, (F(2,44)=12.753, P<.001), indicating smaller P1 amplitudes at the posterior midline ROI. Additionally, the analysis yielded an eccentricity x laterality interaction (F(4,88)=10.3, P<.001) indicating smaller P1 amplitudes for eccentric stimuli on the contralateral (left) side. P1 latencies were also influenced by eccentricity (F(2,44)=6.102, P=.012) and laterality (F(2,44)=11.966, P<.001). An eccentricity x laterality interaction (F(4,88)=7.281, P<.001) indicated longer P1 latencies for eccentric stimuli at the ipsilateral (posterior right) ROI but shorter latencies for eccentric stimuli at the contralateral (posterior left) and the posterior midline ROI. The analysis of N1 amplitudes yielded a main effect for laterality (F(2,44)=5.239, P=.009) with smaller amplitudes at the posterior midline ROI. N1 latencies also varied with laterality (F(2,44)=18.0, P<.001) with shorter latencies at the posterior midline ROI. An eccentricity x laterality interaction (F(4,88)=6.595, P<.001) indicated longer N1 latencies for eccentric stimuli on the ipsilateral (right) side.

The amplitude of evoked gamma activity was modulated by stimulus eccentricity (F(2,44)=4.692, P=.025; Figure 4.7B) with bigger amplitudes for central stimuli. The analysis also yielded a main effect of caudality (F(2,44)=3.752, P=.044) and a caudality x laterality interaction (F(4,88)=3.349, P=.025), indicating larger amplitudes in the central midline ROI. Gamma-band response latencies were not influenced by eccentricity. Neither peak amplitudes nor latencies of the total gamma–band response were modulated by eccentricity

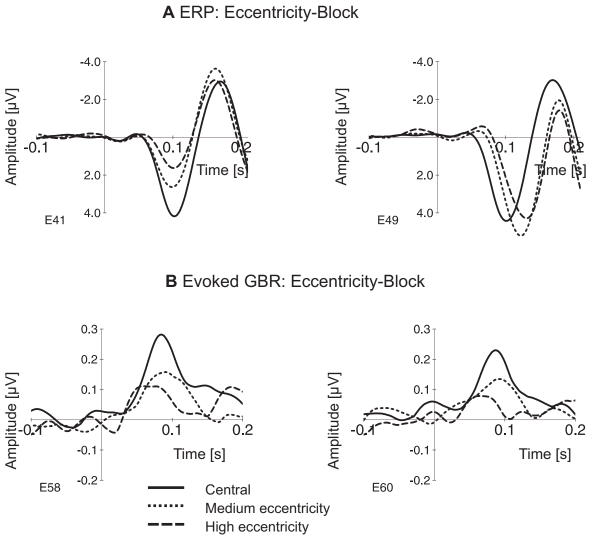


Figure 4.7: ERPs and individually defined evoked gamma–band responses from the eccentricity–block for central (solid line), medium eccentric (dotted line), and highly eccentric stimuli (dashed line) at four representative electrodes (E41 and E58: contralateral; E49 and E60: ipsilateral).

4.3.4 Relative amplitude changes

ERPs and evoked gamma–band responses were differently influenced by stimulus size and eccentricity (see Figure 4.8). While P1 and N1 amplitudes were only moderately modulated by stimulus size, evoked gamma amplitudes were more than doubled for large compared to small stimuli. In the eccentricity block P1 and evoked gamma–band response amplitudes moderately decreased with stimulus eccentricity, while again N1 amplitudes were almost unaffected.

4.4 Discussion

The present study investigated effects of stimulus properties on event–related potentials and oscillations in the gamma–band. ERPs revealed the expected modulation of P1 and N1 with stimulus properties, i.e. larger ON responses for larger and central stimuli. In addition, it was obvious that P1 and N1 OFF

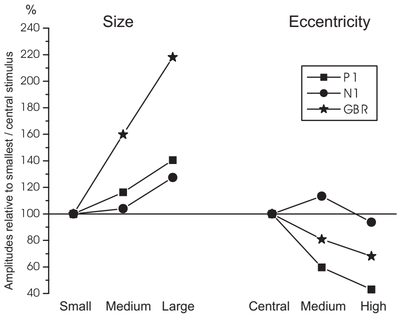


Figure 4.8: Amplitudes of P1, N1 and evoked gamma–band response expressed as percentage of amplitudes elicited by the small and central stimulus, respectively

responses were evoked by stimulus offset which appeared superimposed on late ERP components (P3). Therefore, it seems advisable to present stimuli longer than the largest latency of any ERP component which shall be analyzed. Otherwise a superposition of P1 and N1 could affect the quantification of later ERP components.

The gamma–band response has been used as a tool to study a large variety of cognitive processes and has proven to be a valuable complement to traditional ERPs (cf. Kaiser and Lutzenberger, 2005; Sannita, 2000; Tallon-Baudry and Bertrand, 1999). It has become a common practice to differentiate between early versus late gamma responses. Within this framework, early gamma responses are usually evoked by a stimulus while late ones are induced. Numerous previous experiments have focused on demonstrating top–down modulations of both evoked and induced gamma-band activity. Our results show that both fractions of the gamma–band response can be also strongly modulated in a bottom–up fashion by stimulus properties.

4.4.1 Influence of stimulus properties on evoked gamma–band activity

The amplitude of evoked gamma–band activity seems to be directly related to the size of the stimulus, which probably results from bigger stimuli activating larger cortical areas in retinotopic visual cortices than smaller ones. For small and peripheral stimuli the amplitude of evoked gamma–band activity hardly exceeded the noise level (Figures 4.3B and 4.7B). The present data also show that the eccentricity of visual stimuli modulates the amplitude of the evoked gamma–band response. While the central visual field is represented in the calcarine fissure near the occipital pole, the periphery is represented more anteriorly (Grill-Spector and Malach, 2004). Thus, peripheral stimuli evoke responses in neural tissue which is more distant from the scalp electrodes. If the early evoked gamma–band response is generated in early visual areas and follows a retinotopic mapping, this could explain the observed eccentricity effect. Electrocorticogram recordings in monkey V1 (Rols et al., 2001) did not reveal effects of eccentricity on the gamma–band response. This may, however, be due to the subdural recording methodology and to the fact that a large part of V1 in macaque monkeys is represented on the lateral surface of the occipital pole. Therefore, in the study by Rols et al. (2001), the electrodes were always close to the signal–generating sites for all investigated eccentricities.

4.4.2 Influence of stimulus properties on induced gamma–band responses

In addition to the early evoked gamma–band response we found a later gamma response which was only present in total gamma–band activity and must therefore reflect non–phase–locked activity. The latency of this response varied with presentation duration and, hence, was probably related to the stimulus offset. Such an induced offset response has been described before by Tallon-Baudry et al. (1998). It seems noteworthy that both in their as well as in our experiment the latency of the induced OFF response was markedly later than the evoked OFF response in our experiment (350 ms for evoked and 480 ms for induced gamma–band responses for a stimulus with 250 ms duration). Previous experiments revealed that the late induced gamma response in human EEG can be modulated by top–down processes such as memory (Gruber et al., 2004), attention (Gruber et al., 1999), auditory working memory (Kaiser and Lutzenberger, 2005), and object recognition (Rodriguez et al., 1999). These findings are supported by studies investigating local field potentials in monkeys (Fries et al., 2001b; Woelbern et al., 2002). However, our present study clearly demonstrates that also bottom–up factors like the duration of a stimulus modulate induced gamma–band responses.

4.4.3 Amplitude changes versus phase resetting

In principle, post–stimulus increases in the evoked gamma–band response might result from two different underlying mechanisms. On the one hand, the amplitude of the gamma oscillations could be amplified relative to pre–stimulus activity. In this case, the evoked and the total gamma response would both show an increase after stimulation. This situation was actually found in previous experiments, e.g by Tallon-Baudry et al. (1996). On the other hand, it is possible that the amplitude of the gamma oscillations does not change due to stimulation while only the phases of the oscillation is reset by each stimulus. This would mean that phases occur randomly before stimulus onset while the phase would show a stable value for all trials after stimulation. Such an effect has previously been observed for alpha oscillations (Brandt, 1997; Makeig et al., 2004). In this case, only the evoked response would show an increase after stimulation but no change would be visible in the total gamma response. The latter case describes the present data where only the evoked but not the total gamma response showed an early increase after stimulation. Thus, we argue that in our experiment the presentation of a visual stimulus mainly affected the phase of a early evoked gamma oscillations rather than its amplitude. In contrast, late induced gamma–band responses occurred without an accompanying increase in evoked activity, suggesting that they were mainly non–phase–locked. This finding suggests that late induced gamma–band activity represents an increase in amplitude rather than a change in the phase of the oscillation.

4.4.4 Differences between ERPs and evoked gamma–band responses

Our data revealed an interesting difference regarding the impact of stimulus eccentricity on ERPs and evoked gamma–band responses. ERP latencies were found to covary with eccentricity on the side ipsilateral to stimulus presentation. This delay for eccentric stimuli at ipsilateral sites has been observed before and was explained with interhemispheric transfer (Rugg et al., 1985). According to this hypothesis, information from the peripheral visual field needs to be relayed across the corpus callosum while no such transfer is necessary for central stimuli. Thus, latency differences between central and eccentric stimuli at electrodes ipsilateral to stimulus presentation may reveal the transfer time between the two cortical hemispheres. Interestingly, we found no such latency difference for the evoked gamma–band response. In a similar paradigm Başar-Eroglu and colleagues reported a reduced time for interhemispheric transfer from the contralateral to the ipsilateral hemisphere for beta frequencies compared to alpha and theta frequencies and ERPs (Nalcaci et al., 1999). The authors hypothesized that transfer of different frequency bands relies on callosal fibers with different conduction velocities (cf. Aboitiz et al., 1992). The present data might indicate a similar effect for the gamma–band.

4.4.5 Origin of the evoked gamma–band response

The results raise the question of where in the hierarchy of visual processing the generators for the early evoked gamma–band response reside. Early ERPs like P1 and N1 are known to be modulated by stimulus properties as well as cognitive factors like spatial attention. Their sources have been located in occipito–temporal and occipito–parietal areas (DiRusso et al., 2002; Gomez Gonzalez et al., 1994). In our study the mean peak latency of early evoked gamma activity was shorter than P1 latency (86 ms and 102 ms, respectively) suggesting that the source of the evoked gamma–band response is located earlier in the visual hierarchy. This interpretation is supported by the fact that early evoked gamma activity was even stronger influenced by stimulus properties than early ERPs. Findings from animal studies investigating local field potentials and multi unit activity corroborate this view (Eckhorn et al., 1993; Engel et al., 1991; Frien et al., 1994). These investigators found synchronous oscillations in early visual areas of cats and monkeys. The factor exerting the strongest impact was stimulus size, but stimulus eccentricity also led to modulations in the evoked gamma–band response. Due to the differential effects of experimental manipulations on latency and amplitude of ERPs and the early evoked gamma activity, these two measures might reflect partly different neuronal processes. Despite its short latency and its probable generation early in the visual hierarchy, the evoked gamma–band response has shown to be also under the influence of top–down cognitive mechanisms, a property that is not commonly associated with early visual processing. Recent models of the visual system, however, assume that visual processing relies on the interaction of feedback and feedforward connections already at a very early stage (Bullier, 2001; Lamme and Roelfsema, 2000; Taylor, 2002). Thus, this framework of early visual processing makes it plausible how a signal as early as the evoked gamma–band response can be modulated by bottom–up as well as top–down factors simultaneously.

4.4.6 Implications for studies of gamma–band responses

It should be emphasized that even the smallest stimulus size and the highest stimulus eccentricity employed in the present study are common in and sufficient for ERP experiments. The susceptibility of evoked gamma–band responses to exogenous influences might explain why other researchers failed to observe evoked gamma–band activity in their experiments. Therefore, the present findings are of practical importance for the design of experiments on gamma–band oscillations. First, since for small and peripheral stimuli the amplitude of the gamma–band response is diminished, stimuli should expand over at least 4° - 5° visual angle and should not be presented too peripheral in order to elicit a significant gamma–band response at all. Second, interpretation of cognitive effects in the gamma–band is difficult if conditions employed stimuli of different size or eccentricity. Also, for short stimulus durations one may not be able to distinguish between ON and OFF responses. If such a short stimulus duration was employed in only one condition one might mistake the superposition of onset and offset response as a larger amplitude due to the experimental manipulation. One would run the risk of confounding task effects with stimulus effects. Also, given the small amplitude of the gamma–band response compared to ongoing noise one should take care about technical issues during data recording and analysis (Lutzenberger et al., 1997). For instance, it seems advisable to use a high amplifier gain and ensure a sufficient electrical shielding of the recording environment.

4.4.7 Conclusion

It is well known that early ERPs are susceptible to stimulus properties like stimulus size or eccentricty. Here we were able to demonstrate that fast oscillatory EEG activity is even more susceptible to these parameters. While previous studies showed that evoked as well as induced gamma–band responses are modulated by top–down influences our data demonstrated that both types of gamma–band activity are also modulated by bottom–up influences. While evoked gamma–band responses were modulated by stimulus size, eccentricity, and duration, induced gamma–band responses were influenced by stimulus duration only. The fact that the evoked gamma activity was significantly modulated by the size of stimuli indicates that it is generated by a retinotopic area in early visual cortex. Since the present study employed a rather simple choice reaction task, subsequent studies should investigate the interaction of both bottom–up and top–down influences in the gamma–band. An interesting question would be, for instance, to what extend modulation of evoked gamma activity by stimulus size and by top–down attention interact. Also, the bottom–up effects on total gamma–band activity should be investigated more closely using longer stimulus durations and manipulating further stimulus properties (e.g. stimulus contrast or spatial frequency).

Chapter 5

Experiment 2: Interaction between bottom–up and top–down processes

The experimental results presented in this chapter are currently under review at the journal Neuroimage (Busch et al., 2005).

5.1 Introduction

5.1.1 Gamma–band activity

Oscillatory processes have been the focus of many recent electrophysiological studies. The so–called gamma–band, i.e. the frequency range from 30-80 Hz, has recently attracted the interest of many researchers (Herrmann et al., 2004c; Kaiser and Lutzenberger, 2003; Sannita, 2000; Tallon-Baudry, 2003). Numerous studies demonstrated that gamma oscillations are involved in many perceptual and cognitive functions such as feature binding (Tallon-Baudry and Bertrand, 1999), selective attention (Fries et al., 2001b), long–term memory (Gruber et al., 2004; Herrmann et al., 2004a), or speech perception (Crone et al., 2001a,b). This evidence has been obtained using a wide range of recording methods ranging from single cell recordings in animals to electrocorticograms, MEG, and scalp–recorded EEG in humans. Moreover, neurologic and psychiatric disorders have been demonstrated to be correlated with gamma–band abnormalities. In epileptic patients increased gamma–band power can be observed during the inter–ictal phase between two epileptic seizures and just prior to the onset of an epileptic seizure (Willoughby et al., 2003). Schizophrenic patients in general display reduced amplitudes of gamma–band responses as well as reduced gamma–band phase–locking, but abnormalities of these measures are also correlated with the extent of positive or negative symptomatology (Gallinat et al., 2004; Lee et al., 2003; Spencer et al., 2003, 2004). Despite this extensive body of positive results some authors have been more skeptical about the role of gamma oscillations. Part of the criticism is based on failures to find gamma activity at all (Juergens et al., 1999). It can be speculated that many more negative results have been obtained but have remained unpublished. A second critical argument is focused on the functional role of a certain type of gamma oscillations. It refers to the common distinction between an early phase–locked gamma response (approximately 100 ms after sensory stimulation) and a later non–phase–locked or induced gamma response with a latency of 300 ms or longer (cf. Başar-Eroglu et al., 1996). While most authors agree that the latter is a correlate of various cognitive processes some have argued explicitly that the early evoked gamma response is merely a reflection of early sensory processes (Karakaş and Başar, 1998) which is “pure of cognition”. Others have consistently found effects of cognition on induced gamma activity but reported no such effects on evoked gamma activity (e.g. Gruber et al., 2004; Tallon-Baudry et al., 1996). In a series of studies we were able to demonstrate that the strength of gamma oscillations is related to many non–specific factors like subjects’ age (Böttger et al., 2002), task difficulty (Senkowski and Herrmann, 2002) or stimulus properties (Busch et al., 2004). Hence, the failure to find gamma activity, especially in scalp–recorded EEG, does not speak against the existence of this phenomenon but, instead, may reflect an inappropriate experimental setup (cf. Lutzenberger et al., 1997). Similarly, one might ask whether (cognitive) condition effects on the early evoked gamma–band response also might be conditional upon a certain experimental setup or stimulation.

5.1.2 Top–down and bottom–up modulations

Previous studies revealed that early gamma–band responses are strongly modulated by stimulus features and, hence, are most probably involved in the neural representation of the stimulus. Multi–unit activity and local field potentials in animal studies revealed that gamma oscillations and synchronization is highly dependent on stimulus features such as orientation and direction of movement (Friedman-Hill et al., 2000; Frien et al., 2000; Siegel and König, 2003). Human EEG studies also found gamma–band oscillations to depend on stimulus parameters. Larger gamma–band responses have been obtained for larger stimuli and for central as compared to peripheral stimulation (Busch et al., 2004). Larger gamma–band responses have been also found for higher spatial frequency (Tzelepi et al., 2000). Quadrant of stimulation modulates the topography of gamma–band responses similar to ERP topography, with an inverted high–to–low and left–to–right distribution (Tzelepi et al., 2000). This pattern is similar to ERP topography (although sources were located in different locations) and is compatible with visual system organization (Grill-Spector and Malach, 2004). In this respect, the behavior of early gamma–band responses resembles that of so–called “exogenous” ERPs (Busch et al., 2004). Hence, if cognitive factors do exert an influence on early gamma–band responses these would most probably result in an interaction between top–down and bottom–up processes. Models of such interactions have been formulated (Herrmann et al., 2004c; Siegel and König, 2003). One example is the match–and–utilization–model proposed by Herrmann et al. (2004c). The model rests on the observation by Fries et al. (2001a) that ongoing LFP fluctuations (subthreshold oscillations) in the gamma–band in the cat visual cortex are highly coherent for cells with similar but incoherent for cells with different orientation preference. According to Herrmann et al. (2004c) top–down signals which express, for instance, selective attention towards a certain stimulus feature, synchronize subthreshold oscillations of feature selective assemblies. Other populations that do not code for the expected stimulus would not be primed by means of synchronized subthreshold oscillations, and would therefore have lower amplitude in the EEG after stimulus presentation. Thus, stimuli that meet the “expectancies” (e.g. target stimuli) expressed by coherent states of the network generate more salient responses than non–attended or unexpected stimuli (e.g. standard stimuli). This idea is consistent with findings from animal studies which demonstrated that feature selective attention modulates the sensitivity of feature selective neurons for orientation (McAdams and Maunsell, 1999), contrast (Reynolds et al., 2000), or color (Motter, 1994). In addition, selective attention enhances oscillatory activity and synchrony towards attended stimuli in monkeys (Fries et al., 2001b; Taylor et al., 2005) and humans (Tallon-Baudry et al., 2004). This implies that the more assemblies process an aspect of the stimulus that is subject to top–down influences the more assemblies will be modulated. EEG measurements at the scalp level do not pick up responses from individual neural assemblies, but instead, average responses of a large number of assemblies (cf. Chapter 2). Hence, the wider the attended feature is distributed across the stimulus and the more assemblies are modulated the more salient the difference between attended and unattended stimuli (i.e. the target–standard difference) will appear at the scalp.

5.1.3 Present study

The present study attempts to resolve the question whether evoked gamma–oscillations can be influenced by top–down processes and under which conditions these effects can be obtained. Resolving this question would be of both practical and theoretical interest. Previous failures to find top–down influences on gamma–band responses could be explained on the basis of the present study. Moreover, knowing the circumstances under which top–down influences can be optimally observed could guide the effective design of future investigations. This would foster the importance of the gamma–band response as a research and clinical tool. To this end we analyzed ERPs and gamma activity in a visual target detection ("oddball") paradigm and hypothesized that target detection modulates early gamma oscillations only if the physical difference between targets and standards is distributed over a large area. In the oddball paradigm a stream of stimuli is presented and rare target stimuli have to be detected among more frequent irrelevant standard stimuli. Subjects have to respond to the targets, e.g. by pressing a button or counting the occurrence. This task specifically requires target detection the classical electrophysiological correlate of which is the P300, a late positive deflection of the ERP which is larger for targets than for standards (Herrmann and Knight, 2001; Kok, 2001; Polich and Kok, 1995, see Chapter 1.2.1). Furthermore, phase–locked gamma–oscillations have been demonstrated to be similarly modulated by attention directed towards targets approximately 100 ms after stimulation (Debener et al., 2003; Herrmann et al., 1999; Stefanics et al., 2004). Some studies, however, could not replicate these findings (e.g. Karakaş and Başar, 1998). We therefore chose the visual oddball paradigm for the purpose of the present study because it is an acknowledged test of top–down cognitive processes and the inconsistent results exemplify the controversy about the functions of gamma oscillations as outlined above. The reasoning of the present study is summarized in Figure 5.1.

We compared two conditions using the same stimulation but with different instructions. Grating stimuli were presented that consisted of a small part in the center and a large part surrounding the center. The overall stimulus size employed in this study was adopted from the previous experiment (cf. Chapter 4) in which we observed strong gamma–band responses evoked by stimuli subtending 8° visual angle but no gamma responses evoked by small stimuli. Due to cortical magnification of the representation the foveal part of the visual field is significantly larger than the cortical representation of the periphery (Cowey

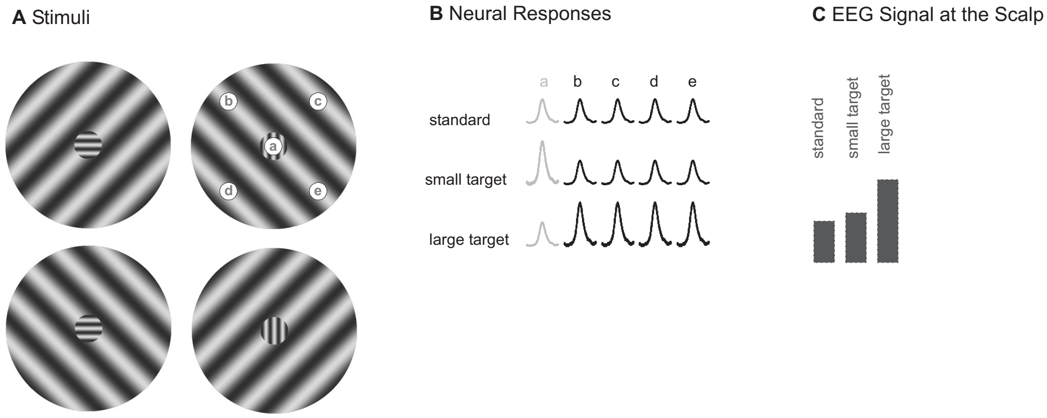


Figure 5.1: Schematic depiction of the processes assumed to be involved in the experimental paradigm. (A) Stimuli used in the experiment. In the small–area condition subjects were instructed to detect one out of two possible grating orientations in the small center of the stimulus. In the large–area condition subjects had to detect the orientation of the large surrounding grating. Receptive fields of five hypothetical neural assemblies are labelled a-e. (B) Schematic responses of the neural assemblies to standard stimuli, target stimuli with the target feature presented in the small center, and target stimuli with the target feature presented in the large surround. Responses of the assembly coding the stimulus center are depicted gray. Responses to attended features are enhanced. (C) Average response of assemblies as measured at the scalp. A salient difference between target and standard stimuli is visible for large–area targets while effects are minor for small–area targets.

and Rolls, 1974; Horton and Hoyt, 1991). Therefore, the surrounding part of the stimulus was chosen to be considerably larger than the central part, since for the purpose of the present investigation it was critical that the cortical representation of the large stimulus part actually recruits a larger cortical area than the small part. Targets and standards were defined by the orientation of the grating patterns. Targets were to be detected either in the small or the large subregion of the stimulus. We hypothesized that target effects on evoked gamma–band activity would only be obtained if targets had to be detected in the large stimulus part. In this condition the physical feature (grating orientation) defining the target is distributed over a large portion of the stimulus. We assumed that selective attention to this stimulus feature leads to an enhancement of neural activity in response to the target stimulus. Thus, in the large–area condition the activity of a large neuronal assembly would be enhanced upon presentation of the attended stimulus, resulting in a large difference between targets and standards. In contrast, if targets were to be detected in the small part of the stimulus only a small assembly would be enhanced by target detection and, thus, only a small target effect would be measured on the scalp.

5.2 Materials and Methods

5.2.1 Subjects

16 subjects participated in the study (mean age 23; range 21-35 years, 13 female), all were paid for participation. Subjects gave informed consent prior to the start of the experiment. All subjects had normal or corrected to normal vision and were free of current or past neurological or psychiatric disorders.

5.2.2 Stimuli and Procedure

We presented circular stimuli consisting of two grating patterns: a small one in the center (diameter: 1.5°; 2 cycles/degree; 40% Michelson contrast; luminance: 6 cd/m^2) superimposed on a larger surrounding pattern (diameter: 9°; 0.6 cycles/degree; 40% Michelson contrast; luminance: 6 cd/m^2; see Figure 5.1A). According to the cortical magnification factor provided by Cowey and Rolls (1974) and Horton and Hoyt (1991) the cortical representation of the large stimulus part in the present study was approximately 3-4 times larger than the representation of the small part, although the area of the large part on the screen was more than 30 times larger than the small center. The grating patterns in the small center part could have either vertical or horizontal orientation whereas the gratings in the larger part had an orientation of either 45° or 135°. Stimuli were presented on white background (luminance: 23 cd/m^2) on a TFT monitor placed at a distance of 105 cm in front of the subject. Monitor refresh rate was 75 Hz. The experiment consisted of two blocks. In each block one pattern orientation was defined as target and the other orientation as standard. In the small–area block subjects were instructed to detect targets in the small central part of the stimulus and disregard the grating in the large surrounding part. Accordingly, in the large–area block subjects were instructed to detect targets in the large surrounding stimulus part and disregard the grating in the small center. Targets required a speeded button press with the index finger of one hand and standards required button presses with the other hand. Subjects had to fixate a central fixation cross in both blocks. Each block consisted of 100 target and 400 standard stimuli. Stimuli were presented for 1000 ms followed by a variable inter–stimulus interval ranging from 1200 ms to 2800 ms. Target grating orientations in both blocks, block order, and response hand were counterbalanced across subjects.

5.2.3 Data acquisition

The experiments were conducted in an electrically shielded and sound attenuated room. The stimulation monitor was placed 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). 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. Eye movement activity was monitored with an electrode placed supra–orbitally to the right eye and also referenced to the nose. Electrode impedances were below 10 kΩ. Data were sampled at 500 Hz, analog filtered from 0.01 to 200 Hz, and stored on hard disk for off–line analysis. Averaging epochs lasted from 300 ms before to 800 ms after stimulus onset for ERPs, from -300 ms to 400 ms for early gamma–band responses, and from -300 to 1000 ms for late gamma–band responses. Baselines were computed in the interval from 300 to 100 ms prior stimulus onset 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 or electrode drifts. While data analysis was performed on unfiltered data ERPs are displayed low–pass filtered at 20 Hz.

5.2.4 Data analysis

The statistical analysis of ERPs and gamma–band activity was performed after selected channels were pooled into a region of interest (ROI, see Figures 5.4 and 5.5). Based on inspection of the topographies those electrodes that displayed a distinct signal were chosen for a ROI. Channels Fp1 and Fp2 were not included in the analysis due to a considerable amount of electrode noise and muscle artifacts.

For the analysis of gamma–band activity a Morlet based wavelet transform with a “width” of 12 cycles was employed in order to provide a continuous measure of the amplitude of a frequency component (for details refer to Chapter 2.2 or to Herrmann et al., 2004b). To reveal the evoked fraction of gamma activity, the wavelet transform was performed on the averaged evoked potential. In order to also analyze activity which is not strictly phase–locked to the stimulus, the wavelet transform was performed for each single trial, and the absolute values of the resulting transforms values were averaged. This measure reflects the total activity for a certain frequency range, irrespective of whether it is phase–locked to the stimulus or not. We will refer to this measure as total gamma response in order to make explicit that it comprises both the evoked and induced part of the gamma response (the same measure has been used previously for the estimation of only the induced part; Tallon-Baudry and Bertrand, 1999). The degree of phase–locking was calculated by means of the so–called phase–locking factor. To this end, the phase of the complex wavelet decomposition in each single trial was represented as a point on the unit circle irrespective of amplitude. Averaging these points yields values between 0 for randomly distributed phases and 1 for phases that are perfectly phase–locked to stimulus onset across trials. Together, these three measures can shed light on the question of whether stronger evoked gamma–band responses to targets result from stronger phase resetting of ongoing oscillatory activity or, instead, signal increases for target stimuli. Target effects on evoked gamma–responses that are exclusively based on effects on the phase–locking factor but not on total activity would argue for stronger phase resetting to targets. Alternatively, evoked target effects together with stronger total activity would argue for stronger oscillatory activity in response to targets. It should be noted that an increase in phase–locking per se is not informative about the generating mechanism because either phase resetting or additive power can produce an apparent reordering of phases (cf. Jervis et al., 1983; Shah et al., 2004; Yeung et al., 2004). Single trials analysis (a so–called “erpimage”; Makeig et al., 2004) was used to illustrate the phase–locking process in more detail. The erpimage is a colored rectangular image in which each horizontal line represents a single experimental trial, and the color values indicate the amplitude at each time point. Single trials were first band–pass filtered around the subject's individual peak frequency (see below). Subsequently, a moving average across 10 adjacent single trials was used to highlight trial–to–trial consistency. Furthermore, the single trials were sorted according to the phase of the gamma–band rhythm in the baseline (270 ms before stimulus onset).

Since the exact frequency of the gamma–band response varies considerably between subjects the frequency of gamma activity used for the wavelet analysis was determined individually for every subject. Time–frequency transforms were first computed for every channel. Anterior, central, and posterior channels were subsequently averaged to increase the signal–to–noise ratio. From these averaged time–frequency scalograms individual gamma frequencies were obtained as the maximum response in the frequency range between 30-90 Hz in a time–window from 60 ms to 120 ms (early gamma–band response) and from 400 ms to 800 ms (late gamma–band response), respectively. One subject who did not exhibit evoked activity in the early time window was excluded from the analysis of early gamma–band activity and four subjects who did not exhibit total activity in the late time window were excluded from analysis of late gamma–band activity. Using this definition the individual peak frequencies of early evoked gamma–band responses ranged from 30-66 Hz (mean 41 Hz, SD=10.9 Hz), and frequencies of late total gamma responses ranged from 47-83 Hz (mean 59 Hz, SD=11.1 Hz). For the statistical analyses ERP components were defined as peak amplitudes in the time interval 80 ms to 130 ms (P1), 150 ms to 200 ms (N1), and as mean amplitudes in the time interval from 400 ms to 600 ms (P3). Early gamma–band responses were defined as peak amplitudes of evoked gamma activity, the phase–locking factor, and total gamma activity, respectively, in the time window from 50 ms to 120 ms. Late gamma–band responses were defined as the mean amplitude of total gamma–band activity in the time window from 400 ms to 800 ms. Response time (RT) was analyzed for valid responses not exceeding the mean response time by two standard variations after outliers (responses faster than 100 ms or slower than 900 ms) had been removed. Repeated measures ANOVAs of response times, error rates, ERP, and gamma–band effects were computed for the factors stimulus–type (targets vs. standards) and target–area (large–area block vs. small–area block). Greenhouse–Geisser corrections were used to adjust for violations of the sphericity assumption for repeated measures factors (cf. Dien and Santuzzi, 2004). Uncorrected degrees of freedom and corrected P–values are reported. We predicted that an interaction between bottom–up and top–down influences on early gamma–band activity would manifest in a statistical interaction between stimulus–type and target–area with larger stimulus–type effects in the large–area block.

5.3 Results

Stimulus presentation evoked a P1 (mean peak latency 106 ms; Figure 5.4, top row), followed by an N1 (mean peak latency 170 ms; Figure 5.4, middle row), and a late positive deflection we will refer to as P3 (mean peak latency 470 ms; Figure 5.4, bottom row). The analysis of the individually identified gamma–band responses revealed a prominent early evoked gamma response (mean peak latency 86 ms; Figure 5.2 A and Figure 5.5, top row) that was strongly phase–locked to stimulus onset (Figure 5.2 B and Figure 5.5, 2^{nd} row) and was accompanied only by a small increase in total gamma–band power in this early time window (Figure 5.2 C and Figure 5.5, 3^{rd} row). The phase–locking process is further illustrated in Figure 5.3. Furthermore, we observed a later gamma–band response in the time window 400-800 ms which resulted solely from an increase in total gamma–band power (Figure 5.5, bottom row).

Figure 5.3 exemplifies the phase–locking process of the early gamma–band response in more detail. It displays data from the same subject whos time–frequency data is depicted in Figure 5.2 averaged across all experimental conditions at electrode O1. Single trials were band–pass filtered around the subject's

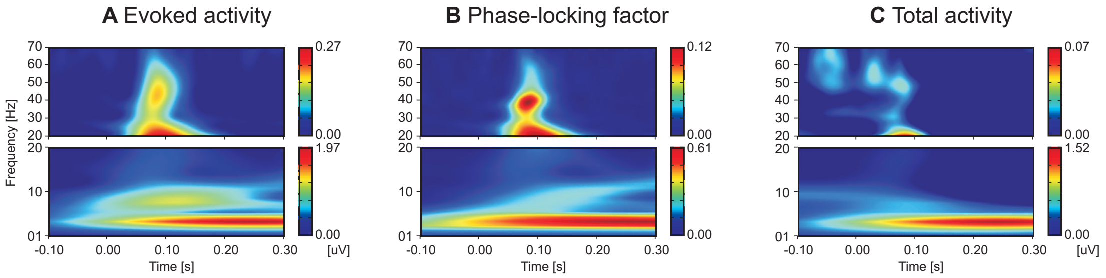


Figure 5.2: Time–frequency plots of a representative subject, averaged across all posterior electrodes and averaged across all experimental conditions. High and low–frequency activity is depicted in separate plots with different amplitudes scales because the low–frequency portion was of considerably higher amplitudes. A distinct signal around 44 Hz is visible in evoked activity (A) and the phase–locking factor (B). In contrast, no equivalent power increase appears in total activity (C).

individual gamma frequency (44 Hz, see Figure 5.2). Single trials were sorted according to the phase of the 44 Hz rhythm in the baseline (270 ms before stimulus onset). The vertical lines indicate a time window corresponding approximately to one wavelength of the 44 Hz rhythm centered around -270 ms and time point of maximal phase–locking (90 ms after stimulus onset). The figure reveals trial–to–trial consistencies around 270 ms before and around 90 ms after stimulus onset. The pattern in the baseline time window is, of course, a product of the phase sorting procedure. Phase sorting the single trials revealed a random distribution of phases in the baseline which appears as diagonal “stripes” in the erpimage. In contrast, phases were markedly consistent across trials at 90 ms after stimulus onset, resulting in almost vertical “stripes” in that time range. This phase–alignment is reflected also in the band–pass filtered ERP, the phase–locking factor, and the evoked gamma activity. Note that amplitudes appear to increase in single trials in these time ranges. This is, however, a result of the moving average which attenuates signals in time ranges that exhibit no consistency across trials. In fact, inspection of total 44 Hz activity revealed only a minor increase of gamma–band power at 90 ms which could not account for the strong increase in evoked phase–locked gamma (see Figure 5.2 C).

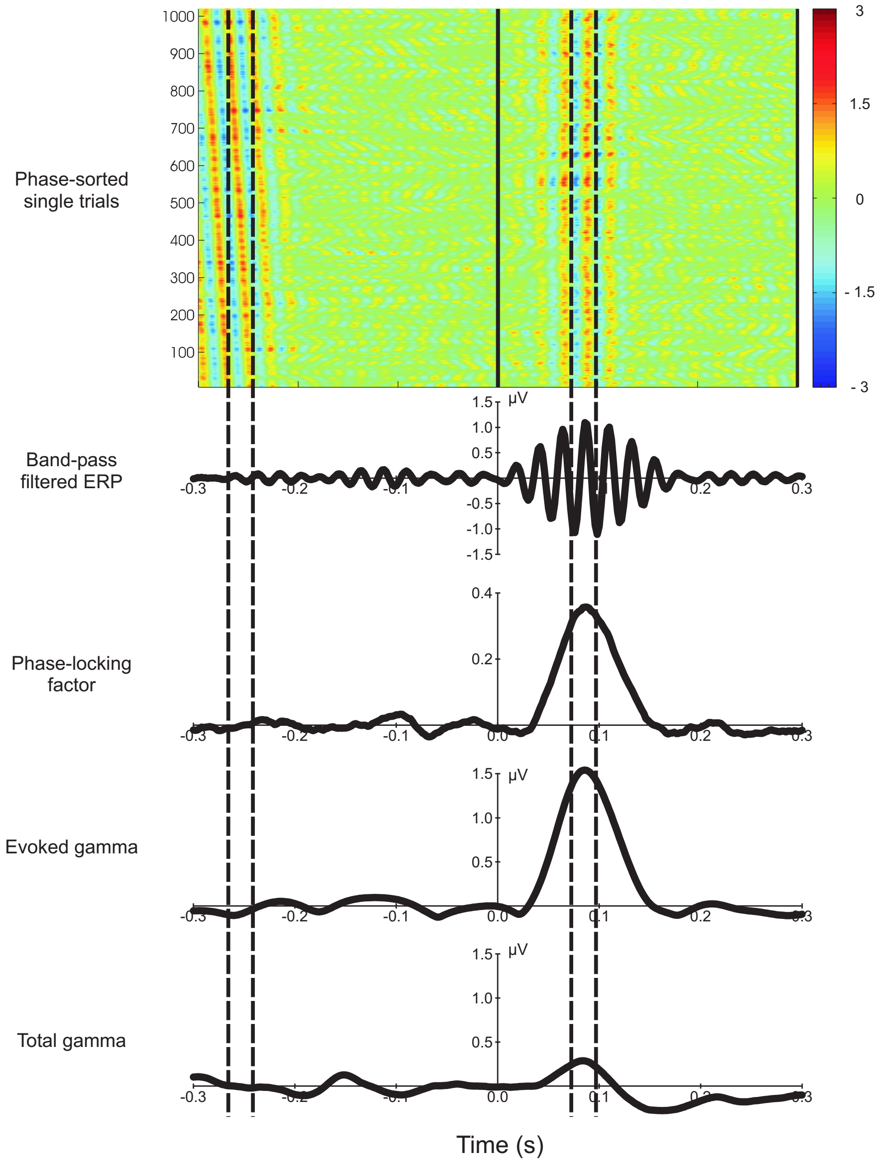


Figure 5.3: Single trial analysis (same subject as in Figure 5.2, electrode O1) reveals strong phase–locking of gamma–band (44 Hz) activity after stimulus onset. The top part depicts color–coded, band–pass filtered single trials from all experimental conditions that were sorted according to the phase of the 44 Hz rhythm in the baseline window. Phases are randomly distributed in the baseline but very consistent across trials around 90 ms post stimulus. This is reflected in the band–pass filtered averaged ERP, phase–locking factor and evoked gamma–band activity. No equivalent increase in total gamma–band power is observed at the same time.

5.3.1 Behavioral data

Subjects reacted more slowly (482 ms vs. 414 ms) in response to target stimuli (main effect of stimulus–type: F(1,15)=161,65, p<.001) and made more errors (77.8 percent correct vs. 94.1 percent correct) compared to standard stimuli (main effect of stimulus–type: F(1,15)=71.03, p<.001). In the large–area block response times were faster (432 ms vs. 465 ms) than in the small–area block (main effect of target–area: F(1,15)=17.62, p=.001) and performance was more accurate (87.3 percent correct vs. 84.5 percent correct) than in the small–area block (main effect of target–area: F(1,15)=7.86, p=.013).

5.3.2 Event–related potentials

P1 amplitudes were most pronounced in electrodes O1 and O2 (Figure 5.4, top row). No significant effects of stimulus–type or target–area were observed for this component.

N1 amplitudes were largest at parietal electrodes (Figure 5.4, middle row). N1 was larger for target than for standard stimuli (main effect of stimulus–type: F(1,15)=40.63, p<.001).

P3 topography was widespread with maxima at CZ and PZ (Figure 5.4, bottom row). P3 amplitudes were larger for targets than for standards (main effect of stimulus–type: F(1,15)=32.30, p<.001) and larger in the small–area than in the large–area block (main effect of target–area: F(1,15)=5.77, p=0.03).

5.3.3 Early gamma–band activity

Early gamma responses were strongest at parietal and occipital electrodes (Figure 5.5, rows 1-3). No main effect of stimulus–type on evoked gamma activity was obtained. Amplitudes of evoked gamma activity were larger in the large–area

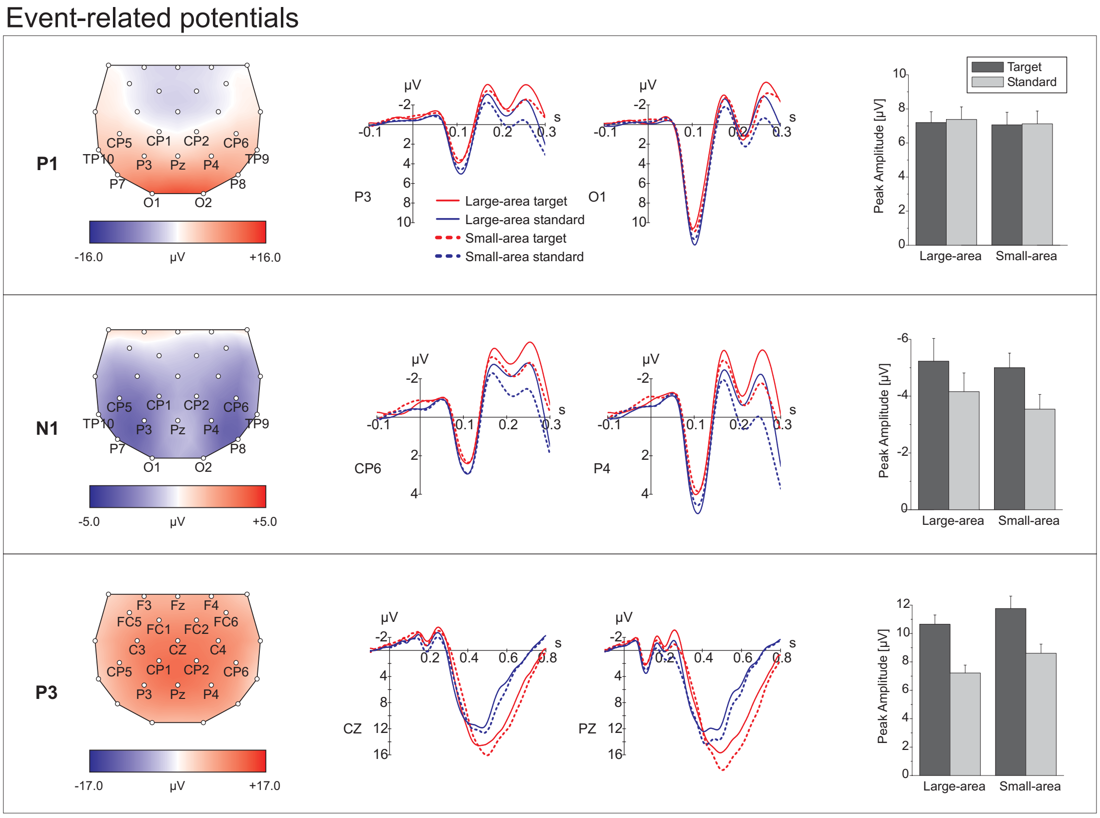


Figure 5.4: Left column: Scalp topographies of P1, N1, and P3 averaged across all conditions. Electrode names are depicted for those channels that were included in the ROIs. Middle column: Time courses of ERPs for selected electrodes. Right column: Amplitudes and standard error for all electrodes within the ROI. Electrodes were chosen for display at which components and effects were most pronounced. Note the different time and amplitude scales for P1, N1, and P3, respectively. All plots represent the average across all subjects.

block than in the small–area block (main effect of target–area: F(1,14)=16.96, p=.001; Figure 5.5, top row). Additionally, target stimuli evoked larger gamma responses than standards in the large–area block, but not in the small–area block (stimulus–type x target–area interaction: F(1,14)=8.26, p=.012). Post–hoc tests revealed significant differences between target and standard stimuli in the large–area block (F(1,14)=11.05, p=.005) but no such differences in the small–area block (F(1,14)<1).

Analysis of the phase–locking factor revealed no differences in phase–locking between stimulus–types but stronger phase–locking in the large–area condition compared to the small–area condition (main effect of target–area: F(1,14)=9.27, p=.009; Figure 5.5, 2^{nd} row).

Early total gamma–band activity was larger on average in response to target stimuli as compared to standards (main effect of stimulus–type: F(1,14)=9.77, p=.007; Figure 5.5, 3^{rd} row), and stronger in the large–area block as compared to the small–area block (main effect of target–area: (F(1,14)=6.31, p=.025). Furthermore, target–standard differences were larger in the large–area condition (stimulus–type x target–area interaction: F(1,14)=6.72, p=.021). Post–hoc tests revealed an increase in total gamma activity in response to target stimuli only in the large–area block (F(1,14)=13.30, p=.003) but not in the small–area block (F(1,14)<1).

5.3.4 Late gamma–band activity

Late total gamma activty had a parieto–occipital topography, similar to early gamma activity (Figure 5.5, bottom row). No effects of stimulus–type or target–area were obtained for total gamma–band activity in the late time window.

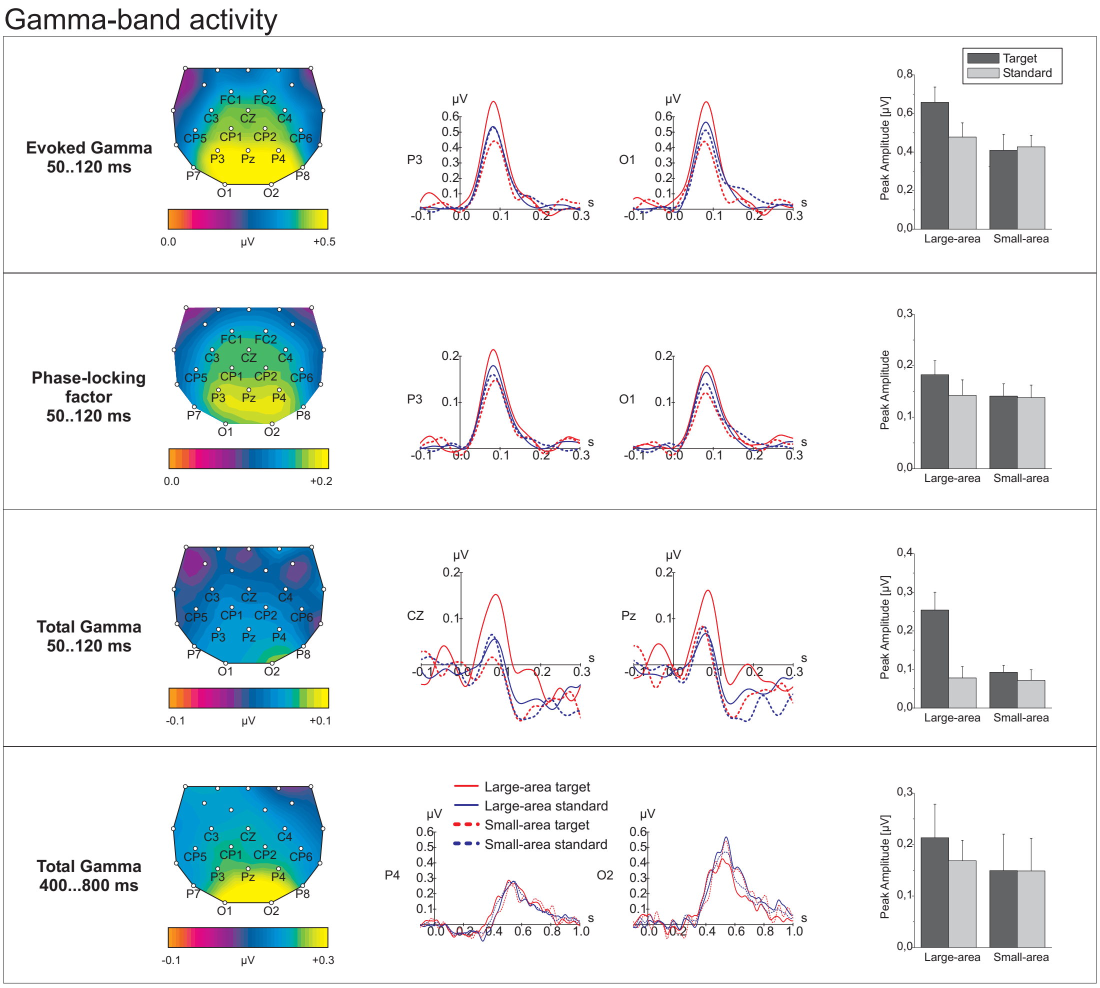


Figure 5.5: Left column: Scalp topographies of early evoked gamma–band activity, phase–locking factor, total gamma–band activity, and of late total gamma–band activity averaged across all conditions. Electrode names are depicted for those channels that were included in the ROIs. Middle column: Time courses for selected electrodes. Right column: Amplitudes and standard error for all electrodes within the ROI. Target effects occurred only in the large–area condition. Electrodes were chosen for display at which components and effects were most pronounced. Note the different time and amplitude scales. Also note that different frequencies were analyzed for early and late gamma–band responses. All plots represent the average across all subjects.

5.4 Discussion

In the present investigation we attempted to resolve two issues: under which conditions is early gamma activity modulated by target detection, and do such modulations rather involve changes in phase distributions or changes in spectral power.

5.4.1 Target detection and the early evoked gamma–band response

Regarding ERPs and behavioral performance we observed a pattern which is considered typical for target detection experiments: larger P3 amplitudes, slower response times, and more errors for infrequent target stimuli (Herrmann and Mecklinger, 2000; Kok, 2001; Linden et al., 1999; Mecklinger and Ullsperger, 1993). P3 amplitudes were larger for targets than for standards irrespective of the size of the targets and, hence, rather reflected the stimulus category. Thus, we could confirm and extend previous reports of “endogenous” and “exogenous” contributions to the P3. Previous ERP studies reported larger P3 amplitudes in response to more intense stimuli in the auditory, visual and somatosensory domain (Covington and Polich, 1996; Nakajima and Imamura, 2000). Polich et al. (1996, p. 61) suggested that “stimulus intensity affects P300 because of the increased attention and arousal that can occur with increased levels of stimulation”. While these results suggest that there exists an “exogenous” aspect of the P3 component, no interaction between stimulus factors and top–down factors has been reported. In a somatosensory target detection paradigm for instance, Nakajima and Imamura (2000) varied the physical intensity of both target and standard stimuli. While P3 amplitudes were larger for targets (a top–down factor) as well as for more intense stimuli in general (a bottom–up factor) no interaction between the two factors was observed.

Most importantly, we were able to demonstrate that early gamma activity is in fact larger for targets than for standard stimuli. However, the pattern of results observed for early gamma–band responses differed from those of the P3 in one important aspect. Target effects on gamma activity were found only for large targets, i.e. when the stimulus feature defining the target was distributed over a large area of the stimulus. This finding is relevant both for theoretical and practical reasons. The interaction of stimulus category and area occupied by the target defining feature suggests that modulations of early gamma–band activity reflect an interaction of bottom–up and top–down processes. At stimulus presentation a stimulus is processed by neural assemblies some of which are feature selective. The strength of activation of these assemblies depends largely on the extent to which the preferred feature is present in the stimulus (bottom–up). Target detection involves the expectation of a stimulus (top–down) defined by specific stimulus features, e.g. orientation. In the present experiment a grating in the large surround of the stimulus activates a larger orientation selective network than the grating in the small center. We argue that top–down influences enhance activity in these feature selective networks. In case of a larger feature distribution (such as in the large–area condition) top–down influences lead to modulation of a larger network. This interaction leads to a larger gamma amplitude measured at the scalp and, thus, to the target effect we observed. Accordingly, in the case of a smaller distribution of the target defining feature (such as in the small–area condition) the difference between targets and standards is less pronounced and, therefore, harder to be detected reliably at the scalp. Thus, our results confirm and extend previous studies that found the evoked gamma–band response to be under the influence of top–down cognitive mechanisms. Such a property may not be commonly associated with early visual processing. Recent models of the primate visual system, however, assume that visual processing relies on the interaction of feed–back and feed–forward connections already at a very early stage (Bullier, 2001; Lamme and Roelfsema, 2000).

These results also bear practical implications for the design of stimuli and experiments destined for the investigation of cognitive effects on early gamma–band activity. In the previous experiment (see Chapter 4) we were able to demonstrate that only strong stimulation will lead to a measurable gamma–band response in scalp EEG. In combination with the present data it seems advisable that experimental conditions which differ in some cognitive parameter (e.g. targets vs. standards) be not different with respect to physical stimulus features which are known to modulate gamma–band activity (e.g. different size, contrast or spatial frequency). The difference that defines the cognitive conditions should be distributed over a large area of the stimulus in order to modulate the activity of a larger neuronal assembly. Furthermore, more salient effects might be achieved employing a salient perceptual difference between conditions (e.g. a difference in line orientation of 90° instead of, say, 10°).

5.4.2 Power increase vs. phase resetting

A second concern of this study was to determine the origin of the target effect on evoked gamma–band activity. The early evoked gamma–band response has so far been mainly described as being accompanied by strong phase–locking to stimulus onset with little or no increase in gamma–band power (see the previous experiment in Chapter 4 and Sannita et al., 2001). Therefore, one might argue that this type of gamma oscillations reflects a phase reorganization of ongoing gamma activity due to sensory stimulation without an increase in signal power (Fell et al., 1997). In contrast, other EEG signals such as ERPs or induced gamma oscillations are believed to be generated by an increase in (oscillatory) activity, although the generation of ERPs is still an issue of ongoing debate (e.g. Makeig et al., 2004; Shah et al., 2004; Yeung et al., 2004). Two alternative (but not necessarily exclusive) mechanisms have been proposed. On the one hand sensory stimulation may induce "phase resetting" of ongoing electroencephalographic (EEG) rhythms in each trial (but no other neural response additional to background activity), and averaging these phase–coherent rhythms produces the ERP. The alternative view proposes that the stimulus elicits an additive, neural–population response in each trial and that averaging these evoked responses produces the ERP. Although early evoked gamma–band responses as such appear to result from the first aforementioned mechanism (see Figure 5.3), it is so far unclear whether task differences in evoked gamma activity are caused by a different degree of phase–locking or a difference in signal power. Most previous studies which investigated phase resetting phenomena focused on data from a single experimental condition. It might be possible, however, that the two proposed mechanisms are involved in different modes of processing. For instance, the previous experiment (cf. Chapter 4) revealed that changes in stimulus properties (bottom–up factors) affected mainly the phase–locking of the early gamma–band response with little effect on total gamma–band power. On the other hand, studies employing auditory oddball and choice reaction tasks (involving top–down processes) found target stimuli to elicit stronger early evoked gamma–band activity than standards (Debener et al., 2003; Yordanova et al., 1997) which was not caused by an increase in phase–locking as in studies manipulating stimulus properties, but instead stemmed from an increase in gamma–band power. In the present study we observed stronger evoked (i.e. phase–locked) gamma activity for large targets. Although we observed strong phase–locking in the gamma–band (cf. Figure 5.3), the degree of phase–locking was not influenced by stimulus–type. In contrast, early total gamma–band activity, an index of signal power, was increased for large targets at the same time. In fact, total gamma–band responses were almost absent in the other conditions. We therefore suggest that the early evoked gamma–band response is a combination of phase–locking across trials due to bottom–up processing of stimulus features plus additional signal power due to top–down processing. Our results thus seem to concur with the notion that event–related brain responses are not completely independent of ongoing activity (Arieli et al., 1996; Makeig et al., 2004). It should be noted, however, that an increase of total gamma–band activity in scalp recorded EEG could, in principle, be generated by two different underlying mechanisms. On the one hand, changes in spectral gamma power could be caused either by more neurons oscillating in the gamma–band range, i.e. by changing firing rates or dendritic current fluctuations from low frequencies to gamma frequencies. Alternatively, stronger synchronization between neural assemblies without a change in the number of assemblies oscillating with that frequency would also lead to more gamma–band power at the scalp.

5.4.3 Conclusion

Our results suggest that early evoked gamma–band activity in scalp recorded EEG is modulated by target detection if enough neural assemblies process the target defining stimulus feature. Furthermore, we propose that sensory stimulation as a bottom–up process results in a phase–locking of evoked gamma–band activity while target detection as a top–down influence increases the power of gamma–band activity within the same neural assemblies that are activated by stimulation.

Chapter 6

Experiment 3: Top–down modulations of gamma–band activity

The experimental results presented in this chapter have been published in the journal BMC Neuroscience (Herrmann et al., 2004a).

6.1 Introduction

Human and animal brain activity frequently exhibits oscillations in the gamma frequency range (approx. 30-80 Hz; Kaiser and Lutzenberger, 2005; Engel et al., 2001; Sannita et al., 2001). This activity can be either phase–locked to stimulation (evoked activity) or not (induced activity; Başar-Eroglu et al., 1996). Both types of oscillations have been shown to be correlates of numerous cognitive functions. Among the first functions to be associated with gamma activity was visual feature binding, coherent visual objects inducing more gamma oscillations than others (Gray et al., 1989; Tallon-Baudry and Bertrand, 1999). Gamma activity is also found in the auditory domain (Pantev et al., 1991), and attention was associated with auditory gamma activity, attended tones evoking larger auditory gamma peaks than unattended ones (Tiitinen et al., 1993). In addition, it has been shown that object perception seems to be a crucial factor for the presence of gamma activity (Başar et al., 2000). For example, faces have been reported to induce more gamma activity than rotated faces which were not recognizable (Keil et al., 1999) and elicit stronger synchronization among brain areas within the gamma–band (Rodriguez et al., 1999). In addition, gamma activity can be found when subjects suddenly see a meaningful picture in random–dot patterns (autostereoscopic pictures; Revonsuo et al., 1997). Furthermore, linguistic processes have been associated with gamma activity: words evoke stronger gamma oscillations than do pseudo–words (Pulvermüller et al., 1996), and language–related gamma activity is most prominent over the language dominant left hemisphere (Eulitz et al., 1996).

In a series of previous experiments Herrmann and colleges investigated the contributions of some of these processes to human gamma activity. They employed four different stimuli to directly contrast visual feature binding and attention. Two of the stimuli were Kanizsa figures for which the constituing parts could be bound together while for the remaining two stimuli this was not possible. One out of the four stimuli was defined as a target and had to be detected by the subjects. The experiments revealed that the attended target evoked significantly more gamma oscillations as compared to three the standards (Herrmann et al., 1999). In a further experiment Herrmann and Mecklinger (2001) used stimuli as targets which consisted of features that could not be bound together to coherent objects (a non–Kanizsa square). Nevertheless, this target also evoked the largest gamma activity of all four stimuli. Furthermore, the gamma responses evoked by the three standard stimuli varied in amplitude with the number of features (number of inducer discs and collinearity) which they had in common with the target. This indicated that attention towards a target stimulus is more important for the modulation of gamma activity than the feature binding required to bind together coherent objects. Of course, target detection also requires access to working memory. Every stimulus has to be compared to a template of the target which was previously stored in short–term memory. Therefore, it may be speculated that one mechanism underlying many of the functions that were ascribed to gamma activity is access to memory.

In previous studies it has been demonstrated that access to working memory induces gamma activity. Gamma–band activity is stronger when subjects have to actively maintain visual stimuli in working memory than when no memorization is required (Tallon-Baudry et al., 1998). This finding is corroborated by other studies which have positively correlated gamma activity with learning and memory (Fell et al., 2001; Fries et al., 2003; Gruber et al., 2002). In a recent experiment by Herrmann and Mecklinger (2000) it was explicitely tested whether comparing stimuli to memory templates increases gamma activity. When subjects had to identify targets by discriminating multiple stimulus features via comparison with a template in short–term memory all stimuli evoked significantly more gamma activity than stimuli which could be discriminated by a single feature (their color). Similar results were obtained recently for auditory stimuli in an experiment in which target stimuli were presented that matched a template in working memory together with frequent non–target stimuli and irrelevant novel stimuli that did not match a task related memory representation (Debener et al., 2003). Targets evoked significantly more gamma oscillations than novel stimuli even though both types of stimuli attracted attention and evoked strong P3 components. This lead us to the hypothesis that memory access may be crucial for the top–down modulation of gamma activity. It might be assumed that both access to short–term memory and long–term memory elicits similar effects. Thus, we set out to test whether access to long–term memory modulates human gamma–band responses. We investigated whether simple visual stimuli evoke more gamma activity when subjects already have a memory representation of the presented objects as compared to when they perceive novel visual stimuli which do not match long–term memory.

6.2 Materials and Methods

6.2.1 Subjects

13 subjects (7 female) with a mean age of 25.4 (±4.6) years paticipated in our experiment. All subjects had normal or corrected–to–normal vision and showed no signs of any neurologic or psychiatric disorder. They gave their written informed consent and were paid for their attendance. The experiment was conducted in line with local ethics guidelines.

6.2.2 Stimuli and Procedure

The stimulus material consisted of 210 black–and–white drawings. 105 of these figures were pictures of real objects such as a television screen, an elephant or an envelope. The others were classified as non–objects. In order to produce comparable stimuli for both stimulus groups, the non–objects were created by rearranging components of the object stimuli. This yielded 105 object–non–object pairs, each of which consisted of the same picture parts. Prior to the EEG experiment we performed a pre–experiment with another 10 subjects to select the stimuli and to ensure that each stimulus is consistently perceived as a known object or an unknown non–object. Only those stimulus–pairs were used, for which both figures were judged consistently as objects and non–objects, respectively, by more than 7 subjects. On average this yielded classification rates of 95% and 94% for objects and non–objects, respectively. Objects and non–objects were matched for size and subtended visual angles of 5° to 10°. Sample stimuli are presented in Figure 6.1.

The EEG experiment was divided into one short practice block and 2 experimental blocks, each separated by a short break. The practice block contained 18 figures with 9 figures of each stimulus type. The experimental blocks included the remaining 192 figures (96 objects and 96 non–objects). The temporal sequence

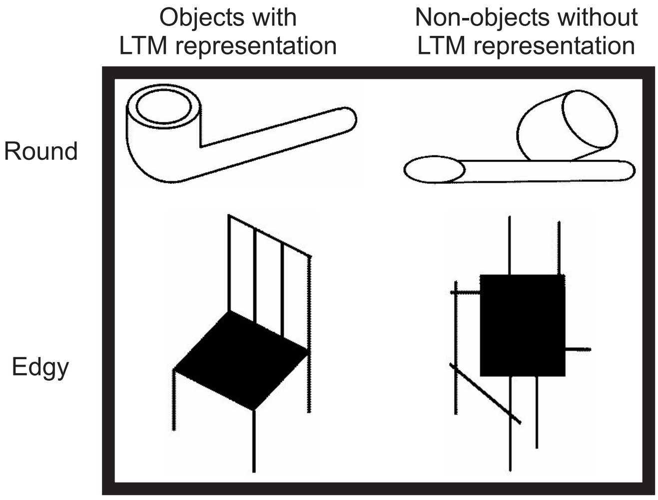


Figure 6.1: Examples of the stimuli used in the experiment: two objects with a long–term memory representation and the corresponding non–objects which are composed of the same parts but have no such memory representation.

of stimuli was pseudo–randomized and equal for each subject. Each figure was shown for 1000 ms, followed by a randomized interstimulus interval of 1300 to 1700 ms in which a black fixation cross was shown. Subjects were instructed to judge whether the stimuli appeared to be either edgy or curvy by pressing one of two buttons (right index finger for edgy, left for curvy objects). Thus, subjects were naive about the purpose of the experiment. This was important, since we did not want subjects to be influenced by the type of stimulus.

6.2.3 Data acquisition

In order to avoid electrical interferences during the measurement, the experiment was performed in a shielded cabin, where no electric devices requiring AC power supply were operated. Visual stimulation was provided by a Sony VPL X600E VGA projector which projected the stimuli into the cabin via a system of mirrors. The projection plane was placed 60 centimeters in front of the subjects. EEG was recorded with 52 Ag–AgCl electrodes mounted in an elastic cap according to the international 10–10 system. All electrodes were referenced to the left mastoid, and the ground electrode was placed at the right mastoid. The vertical electrooculogram (VEOG) was recorded by electrodes placed above and below the right eye, while the horizontal EOG (HEOG) was recorded from positions at the outer canthus of each eye. Electrode impedances were kept below 5 kOhm. Data were sampled at 508.63 Hz and analog filtered from DC to 100 Hz

6.2.4 Data analysis

An automatic artefact rejection was computed which excluded trials from averaging if the standard deviation within a moving 200 ms time interval exeeded 50 μV. Event–related potentials were averaged from -250 to 1000 ms relative to stimulus onset. Before averaging, baseline–activity from -250 to -100 ms was substracted for each electrode. In order to analyze gamma activity the EEG was convolved with Morlet wavelets (see Chapter 2.2). The frequency used for this wavelet analysis was individually adapted via the time–frequency plane of electrode O2: the individual gamma frequency was defined as the highest peak in response to objects in a frequency range of 30 to 80 Hz and in a time range of 50 to 150 ms. Resulting individual frequencies ranged from 31 Hz to 40 Hz. If no clear peak was visible in the gamma–range 40 Hz was chosen for analysis. This had to be done for four subjects. After computation of the wavelet transform baseline activity in the time interval from -250 to -100 ms was subtracted for each frequency. In order to avoid a loss of statistical power electrodes were pooled into regions of interest. We defined a region of interest comprising the following eight electrodes which exhibited strong signals in the gamma–band: PO7, PO3, O1, POZ, OZ, PO4, O2, and PO8. Repeated measures ANOVAs of response times and gamma–band responses in the time–interval between 50 and 80 ms were computed for the factor stimulus–type (objects vs. non–objects). An additional ANOVA was performed on response times and gamma activity comparing responses to curvy and edgy stimuli.

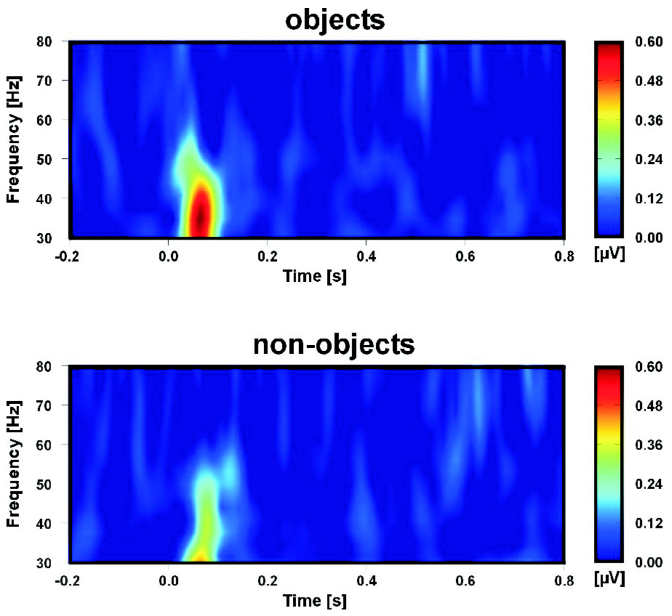


Figure 6.2: Average time–frequency representation of EEG activity at electrode O2 (averaged across all 13 subjects). A clear peak of evoked gamma activity is visible shortly before 100 ms in the frequency range of 30 - 40 Hz. This peak is significantly stronger for objects (top) than non–objects (bottom).

6.3 Results

Responses times were faster (557 ms vs. 591 ms) for edgy as compared to round objects (F(1,12)=10.7, $p<0.05$). This effect possibly resulted from the fact that subjects had to respond to edgy objects with their dominant right hand. No significant differences in responses times were found between objects and non–objects.

The analysis of the individually identified gamma–band responses revealed a prominent early evoked gamma response (cf. Fig. 6.2) with a mean peak latency of 70 ms (Fig. 6.3). This activty was maximal over occipital cortex (cf. Fig. 6.4) indicating that gamma–band reponses originated from extrastriate visual cortex. The statistical analysis revealed that objects evoked larger gamma–band responses than non–objects (F(1,12)=5.171, $p<0.05$). In order to verify that our results were not biased by the four subjects without a clear gamma

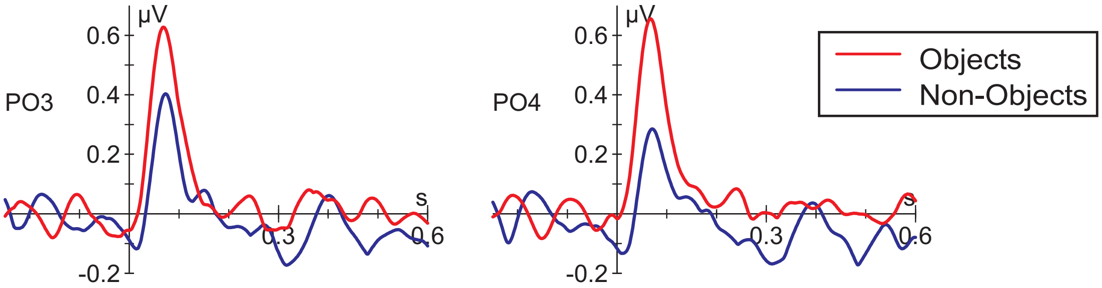


Figure 6.3: The evoked peak of gamma activity shows a clear difference between known objects (red) and non–objects (blue).

peak, we repeated the analysis with the remaining 9 subjects. Effects were almost identical, with objects evoking larger gamma responses than non–objects (F(1,8)=5.59, p<0.05). Gamma activity did not differ between edgy and round stimuli (F(1,12)=0.861, p=0.372). Thus, objects for which subjects already have a representation in long–term memory evoked significantly more gamma activity than did objects which were perceived for the first time.

6.4 Discussion

Our data show that visual stimuli evoke enhanced gamma reponses if they match with contents of long–term memory. The topography of gamma–band activity was maximal over occipital areas indicating that gamma activity was generated in visual cortex. Thus, we assume that feedback loops from memory systems into perceptual systems are responsible for the enhancement of gamma activity in visual areas. These top–down driven influences did not elicit gamma responses themselves as only occipital responses were observed, and the effects resulted from enhancement of a response that was evoked for all stimuli. This is in line with the findings from the previous experiment (see Chapter 5) which suggested that top–down processes modulate gamma responses within the same neuronal assemblies that are relevant for bottom–up perceptual processes.

The notion that memory access modulates human gamma responses may serve

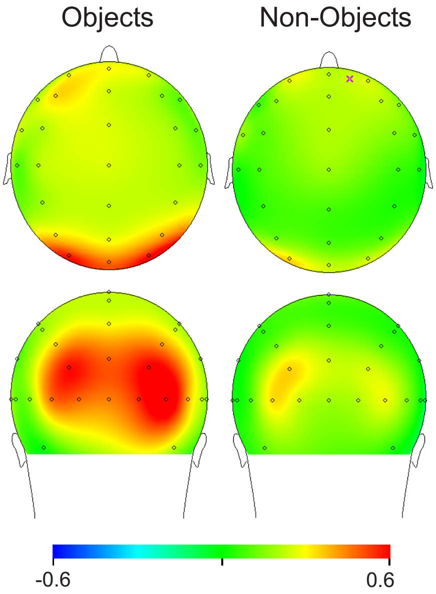


Figure 6.4: The difference between objects and non–objects is also clearly visible in the topographic maps. The bilateral occipital distribution indicates that gamma activity originates from extrastriate visual cortices.

to integrate a large body of literatur on top–down effects on gamma–band activity obtained from apparently divergent paradigms. For instance, words evoke more gamma activity as compared to pseudo–words (Pulvermüller et al., 1996) because there are memory representations of words but not of pseudo–words. Language–specific gamma activity could be lateralized to the left hemisphere (Eulitz et al., 1996) since the mental lexikon resides in the language dominant hemisphere. Attended objects reach short–term memory more easily than unattended ones and thus lead to more gamma oscillations (Tiitinen et al., 1993).

In a target detection paradigm, stimuli have to be compared to a memory template of the target stimulus defined by one or more stimulus features. Upon stimulus presentation all stimulus features of targets match the template stored in short–term memory while a standard stimulus will represent a mismatch for at least one of the features. Thus, auditory as well as visual target stimuli receive more positive feedback from short–term memory than standards and, hence, evoke stronger gamma–band responses (Yordanova et al., 1997; Herrmann et al., 1999; Herrmann and Mecklinger, 2001).

Due to the similar topographical distributions of our evoked response and induced gamma responses (Gruber et al., 2002; Tallon-Baudry et al., 1998), it seems plausible to assume that evoked and induced gamma responses are generated by the same neural systems only varying in their degree of phase–locking and response latency. Under this assumption our explanation might even hold for induced gamma–band responses. It could be argued that objects induce more gamma activity than non–objects (Tallon-Baudry and Bertrand, 1999) because there exist memory representations for objects but not for non–objects. This is not to claim that gamma activity is not related to binding processes. Our main line of argumentation is that a memory comparison must occur prior to the initialization of a binding process in case of a match. The same would hold for faces versus rotated faces (Keil et al., 1999) and meaningful pictures versus random–dot patterns (Revonsuo et al., 1997). However, it is possibly not the aspect of meaningfulness per se that enhances early gamma–band activity. In the experiment by Debener et al. (2003) target tones evoked more gamma activity than novel stimuli. In this experiment targets were simple sine waves while novels were real world (meaningful) sounds. Thus, the effect should have been reversed if meaningfulness as such modulates gamma activity. Also, behavioral relevance is probably not a necessary factor involved in the top–down modulation of gamma activity. In the present study the factor of interest (memory vs. non–memory) was totally irrelevant for the subjects' task. This might indicate that task relevant representations in short–term memory (e.g. of a target stimulus in a target detection task) have stronger impact on gamma–band responses while task irrelevant representations in long–term memory (e.g. of objects such as chairs and pipes) are modulating gamma responses when no such task relevant representations are active as in the present experiment. Of course, also other more unspecific processes which are unrelated to memory access may modulate human gamma activity. It is known, for example, that task–difficulty (Senkowski and Herrmann, 2002) and the speed of manual reaction (Haig et al., 1999) covary with gamma activity. Multiple modulatory mechanisms of gamma responses are conceivable, since multiple oscillatory responses can be found in the human EEG at different frequencies in the gamma range with different topographies and time–courses. Taken together, we propose that gamma activity is modulated by access to short– and long–term memory. When perceived stimuli match with existing representations in memory stronger gamma responses are evoked.

Chapter 7

Summary and General Discussion

This thesis encompasses three experiments that sought to clarify the role of evoked gamma–band activity in human EEG. Although gamma–band activity has been attracting the interest of numerous researchers for several years, our knowledge about the basic functions of this signal appears still incomplete, especially when compared to research on many ERP components. Whereas most ERP components have been located on the exogenous–endogenous dimension (cf. Chapter 1.2, p. 11) the status of gamma–band activity regarding this dimension is still debated. Moreover, the term "ERP component" in the strict sense refers to a theoretical construct that is related to a perceptual or cognitive process. In other words an ERP component is more than just a "bump in the averaged waveform", or as Luck (2004) put it: "Peaks and components are not the same thing. There is nothing special about the point at which the voltage reaches a local maximum or minimum.". Instead, the concept of a component involves a description of the components morphology, topography, neuronal generators and the conditions under which it is elicited, that is a theory about its function (cf. Rugg and Coles, 1995). Compared to this elaborate theoretical formulation of ERP components, research on gamma–band activity in human EEG has often been non–theoretical. In a similar vein (Bertrand and Tallon-Baudry, 2000, p. 212) complained that "different electrophysiological phenomena have been very often gathered under the same term “40–Hz activity” in an undifferentiated manner, and a common framework for interpretation is somehow lacking”. In this thesis my aim was to gather information that allows one to develop such a framework and treat evoked gamma–band activity as more than just a “blob in the averaged time–frequency spectrum”. Besides this theoretical interest, I wanted to determine parameters for optimal experimental design. Research on gamma activity has been contested based on negative results. Some authors reported a failure to find any gamma activity at all in scalp recorded human EEG (Juergens et al., 1999) whereas others argued that the evoked part of gamma activity is not involved in cognitive processes (Karakaş and Başar, 1998). Therefore, the experiments were also aimed at determinig optimal stimulation for the detection of gamma–band responses in general, and optimal task design for the detection of top–down effects. Specifically, I investigated how evoked gamma–band activity is influenced by properties of stimulation, whether top–down processes may also influence this signal and under which conditions such interactions can occur, and finally offer an integrative explanation for the various experimental findings on gamma–band activity and its role in information processing.

7.1 Summary of the experimental results

In the first experiment described in Chapter 4 (p. 36) I investigated how gamma–band activity is dependent on basic properties of stimulation, namely stimulus size, eccentricity and duration. This experiment was published in the journal Clinical Neurophysiology (Busch et al., 2004). The motivation for this experiment was twofold. On the one hand I sought to determine optimal parameters for experimental stimulation. On the other hand the degree to which EEG gamma–band activity is dependent on stimulation properties is largely unknown, and thus, the classification as either exogenous or endogenous has not yet been applied to this sort of signal. If evoked gamma–band activity would turn out to be a rather exogenous component, this would argue for a generation in early visual cortices, which in turn might challenge reports of cognitive effects in the evoked gamma–band. The results revealed that evoked gamma–band activity is very susceptible to properties of stimulation and in some cases even exceeds the sensitivity of early ERPs. The results also suggested that the presentation of a visual stimulus mainly affects the phase of a gamma oscillation rather than its amplitude. As a practical consequence of these results the design of future experiments should adjust stimulus properties such that different experimental conditions do not differ with respect to stimulus properties. Moreover, stimulation can be optimized based on the present results in order to evoke stronger gamma–band signals. It may be speculated that past investigations which failed to find gamma activity (Juergens et al., 1999) failed to optimize their stimulation. The susceptibility to stimulus size and diminuation with stimulus eccentricity suggests that evoked gamma–band responses are generated in a retinotopically organized visual area. Based on the demonstration of a modulation by bottom–up factors evoked gamma activity might be classified as an exogenous EEG component. Although this notion is in line with interpretations of other authors who viewed early evoked gamma–band activity as "sensory in origin" (Karakaş and Başar, 1998) devoid of relevance for cognitive or even perceptual processes, it might contradict several other reports of top–down effects on evoked gamma activity.

In order to investigate a possible interaction of bottom–up and top–down processes in the evoked gamma–band we conducted a second experiment which is reported in Chapter 5 (p. 58) and is currently under review at the journal Neuroimage (Busch et al., 2005). In this experiment it was assumed that early evoked gamma activity is generated in early visual cortex by retinotopically organized, feature selective neuronal assemblies. We conducted a target detection experiment in which the feature that defined the target could be distributed over a large or a small part of the entire stimulus. We found that only targets covering a large area of the entire stimulus evoked stronger gamma–band activity than standards although the over–all stimulus size was identical for all stimuli. This increase in evoked activity resulted from stronger oscillatory power and not exclusively from stronger phase–locking. This stands in contrast to the bottom–up modulations reported in the first experiment which mainly affected the phase–locking of evoked gamma activity. Furthermore, N1 and P3 amplitudes were larger for target stimuli, but irrespective of the distribution of the relevant stimulus feature. These results are consistent with the notion that early gamma–band activity is generated by feature–selective neural assemblies that provide the sensory representation of the stimmulus, the activity of which can be modulated by top–down processes. Thus, in case of a larger feature distribution (such as in the large–area condition) top–down influences lead to modulation of a larger network. Therefore, this interaction of bottom–up and top–down processes in the gamma–band may be only detectable in scalp–recorded EEG if it affects a sufficient number of neural assemblies. In contrast ERP target effects appear to result from signals that are independent of the neuronal assemblies that are coding the stimulus (e.g. in the form of a “selection negativity”, cf. Chapter 1.2.1). This might explain the reported failure to find top–down effects on evoked gamma activity (Karakaş and Başar, 1998). Therefore, these results also bear practical implications. It seems advisable that the experimental design assures that the stimulus property that defines the cognitive conditions is distributed over a large area of the stimulus in order to modulate the activity of a larger neuronal assembly.

In the second experiment top–down processes were investigated in an oddball target detection paradigm. Other reports of top–down influences on gamma activity employed various research strategies, ranging from the presentation of autostereoscopic pictures to linguistic paradigms. Although this disparity of methods and findings may appear to suggest that gamma activity reacts in an unspecific manner to any conceivable experimental mannipulation, we hypothesized that there is a common mechanism at work in all or most of these different experiments. Based on the observation that the very condition that involves the more familiar stimulus usually elicits larger gamma activity we reasoned that matches between stimulus and memory representations might enhance gamma–band responses. This hypothesis was tested in the third experiment (Chapter 6,

p. 81) which was published in the journal BMC Neuroscience (Herrmann et al., 2004a). In this experiment we employed a choice reaction task. Visual stimuli were presented that were either known real–world objects with a memory representation or novel figures never seen before. All stimuli evoked an early gamma response which was maximal over occipital electrodes, and this gamma response was significantly larger for items which matched memory templates. Therefore, we argue that top–down effects on gamma activity result from the feedback from memory into perception systems.

7.2 Early interactions of bottom–up and top–down processes in the gamma–band

The results of the experiments we conducted suggest that early evoked gamma–band responses are generated in feature selective regions of early visual cortex which are influenced by both bottom–up (visual input) and top–down (expectation, memory) signals. It is important to note that these interactions occur at an anatomically and temporally early stage of visual processing. Such an early influence of top–down processes may appear surprising when considering the extant literature on ERP attention effects. It is often stated that the earliest top–down effects that can be observed in the scalp–recorded ERP are effects of spatial attention on the P1 component which has been localized in ventral–lateral and dorsal–lateral extrastriate cortex. Feature and object related attention is supposed to be reflected in ERPs at an even later stage (cf. Rugg and Coles, 1995). Thus, analysis of evoked gamma–band activity offers insights into visual processing that are not readily obtained when analyzing broadband ERPs. Our conclusions are, however, corroborated by intracranial recordings which reported both bottom–up and top–down modulations of gamma activity in human, monkey and cat visual cortex. Visual stimulation elicits gamma–band activity in lateral occipital regions of human visual system (Lachaux et al., 2000; Tallon-Baudry et al., 2004), and monkey areas V1 and V4 (Rols et al., 2001). Moreover, multi–unit activity and local field potentials recorded in primary visual cortex of cats and monkeys revealed that gamma oscillations and synchronization is highly dependent on stimulus features such as orientation and direction of movement (Friedman-Hill et al., 2000; Frien et al., 2000; Siegel and König, 2003). This is in line with our findings of effects of stimulus size and eccentricity (cf. Chapter 4). In addition to these bottom–up driven oscillatory processes top–down inluences (spatial and object selective attention) have been reported to modulate gamma activity in monkey V4 (Bichot et al., 2005; Fries et al., 2001b; Taylor et al., 2005). These top–down effects seem to modulate the neuronal representation of the stimulus itself, rather than being expressed by separate "attention areas" (Taylor et al., 2005). This is consistent with our finding that target effects in the gamma–band are dependent on the size of the neuronal assembly coding the stimulus, rather than being additive to the stimulus evoked response (cf. Chapter 5). Hence, the animal literature suggests that early extrastriate cortex, possibly V4, might be the neuronal substrate of the effects we observed in scalp recorded EEG. Moreover, responses of V4 neurons have been demonstrated to be learning dependent (Rainer et al., 2004; Yang and Maunsell, 2004), which is consistent with our conclusion that evoked gamma responses are modulated by memory representations (cf. Chaper 6). For instance, in the study of Rainer et al. (2004) monkeys were trained to recognize a specific set of natural images degraded by noise. After training, visual responses of V4 neurons were larger for degraded trained images than for degraded untrained images. Interestingly, these effects started with a latency of less than 150 ms and were related to firing rates in the gamma–band which is also consistent with our findings. These authors stressed that learning plays a critical role in facilitating interaction between top–down and bottom–up processing streams and concluded that "vision is an active process involving recurrent interaction of different brain regions rather than a purely feed–forward process" (Rainer et al., 2004, p. 281). Taken together, results from animal and human electrophysiological studies support our claim that gamma–band activity is evoked in early visual cortex and provides an early interface between bottom–up and top–down processes, where one such top–down mechanism might be perceptual memory. A model of such interactions has been formulated in the "match–and–utilization model" put forward by Herrmann et al. (2004c). It assumes that visual input leads to rapid activation of higher visual areas which contain memory representations in form of enhanced synaptic connections between and within visual areas. Input that matches these representation will result in a feedback signal into lower visual areas which in turn will lead to enhanced gamma activity in the cortical network. If there is no memory representation in the form of strengthened synaptic connections, feedback does not occur which leads to weaker gamma responses. The importance of feedback signals in early vision has also been stressed in other recent models of visual processing (Bullier, 2001; Körner et al., 1999; Lamme and Roelfsema, 2000).

7.3 Perspectives for future research

In this project I attempted to increase our knowledge on the mechanisms and the significance of gamma–band activity. The design of future experiments can be guided based on the present results. Experiments 1 and 2 demonstrated that experimental designs that are well suited for the measurement of ERPs can be inappropriate for the investigation of gamma–band responses. First, strong stimulation (central stimuli larger than 4° visual angle) seems necessary to evoke reliable gamma responses. Second, interpretation of cognitive effects on the GBR is difficult if conditions differ systematically with respect to physical stimulus properties such as size or eccentricity. We are currently investigating further visual stimulus properties such as contrast and spatial frequency on their impact on gamma–band responses, and are about to extend these investigations also to the auditory modality. Moreover, the results suggest that the stimulus feature that defines the difference between cognitive conditions should be distributed over a large area of the stimulus in order to modulate the activity of a larger neuronal assembly and, thus, increase the condition effects measured at the scalp.

Furthermore, although I believe that I could resolve several open questions, more question still await answers. In the remainder of this section I would like to highlight problems which I believe are necessary to be adressed in future investigations.

The experiments I described in this thesis were focused on early evoked gamma–band activity. Although the data that were obtained also contained induced gamma responses at longer latencies no effects of stimulus parameters, target detection or memory match were found in the experiments reported in Chapters 4 - 6. This is in contrast to the extensive literature on non–phase–locked gamma oscillations which have been interpreted as a correlate of object processing (Tallon-Baudry and Bertrand, 1999; Kaiser and Lutzenberger, 2005) or of cognitive or behavioral utilization (Herrmann et al., 2004c). When examinig the literature on gamma–band activity in human EEG one might get the impression that in most publications researchers report effects for either evoked or induced activity, but reports of either convergent or divergent effects in both signals are very rare. One reason for this may be that evoked and induced responses are differentially required by different experimental paradigms in a way that is not yet fully understood. A systematic comparison of paradigms might reveal how these two types of gamma responses are differentially required by different cognitive processes involved in different experimental tasks. Moreover, it is still uncertain whether evoked and induced gamma responses share the same neural generators.

The brain areas that generate visual gamma–band responses in human EEG have not yet been convincingly localized. Thefore, source localizations of evoked and induced gamma responses should be performed. These investigations could use paradigms that employ half or quarter field stimulation which have been used succesfully to localize attention related visual ERPs (DiRusso et al., 2002; Martinez et al., 2001). This would also facilitate comparisons with reports of intracranial recordings in humans and animals.

The early evoked gamma response is strongly phase–locked to stimulus onset and some experimental manipulations (especially those involving bottom–up factors) seem to alter the degree of phase–locking. Although phase–locking and phase resetting have received a lot of interest in recent publications, accounts for the possible functions of these phenomena are still scarce. Future investigations should determine whether phase–locking fulfills a certain function or is merely a by–product of perceptual processes.

The mechanisms that are at work in the generation and modulation of early evoked gamma responses are certainly not among the last and highest stages of visual processing. Future studies should investigate the relevance of gamma activity for subsequent perceptual and cognitive processes as well as behavior. Furthermore, we need to understand more about how gamma activity is related to activity of other EEG frequencies and ERPs, which have been shown to be involved in similar perceptual and cognitive processes.

7.4 Conclusion

Functions of gamma–band activity were investigated in three experiments. These experiments revealed that early evoked gamma–band responses show a strong dependency on parameters of stimulation and are probably involved in the sensory representation of the stimulus. At the same time, however, this representation is also subject to top–down influences like expectation in a target detection experiment or matches with representations in visual long–term memory. The data also suggested that bottom–up processes result in a phase–locking of evoked gamma–band activity while top–down influences increase the power of gamma–band activity within the same neural assemblies that are activated by stimulation. The results thus suggest that the evoked gamma–band response is an early interface between bottom–up and top–down processes. Moreover, the results have practical implications for design of future experiments. Also, claims that early evoked gamma activity does not exist in humans (Juergens et al., 1999) or is not related to cognitive processes (Karakaş and Başar, 1998) can be clearly rejected on the basis of the present results. We could thus confirm and extend previous reports from human and animal electrophysiological studies that demonstrated the relevance of gamma activity for perceptual and cognitive processes.

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Zusammenfassung

Oszillatorische Phänomene im menschlichen EEG haben in den letzten Jahren viel Beachtung gefunden. Es konnte gezeigt werden, daß die Analyse von EEG Signalen mit Methoden der Zeit–Frequenz Analyse eine wertvolle Ergänzung der traditionellen ereigniskorrelierten Potentiale (EKP) darstellt (siehe Herrmann et al., 2004b). Insbesondere hochfrequente Oszillationen im Gamma–Band, das ist der Frequenzbereich zwischen 30 und 80 Hz, sind in letzter Zeit vermehrt untersucht worden (Herrmann et al, 2004c; Kaiser und Lutzenberger, 2003; Tallon-Baudry, 2003). Viele Studien konnten belegen, daß Gamma-Band Aktivität im Zusammenhang mit verschiedenen perzeptuellen und kognitiven Prozessen steht. Trotz dieser Popularität der Gamma–Aktivität sind einige wichtige Eigenschaften dieses Phänomens bislang wenig untersucht und infolgedessen unverstanden geblieben. In meiner Arbeit habe ich mich bemüht, einige dieser Wissenslücken zu schließen. Insbesondere habe ich den Versuch unternommen, Parameter für optimale visuelle Stimulation zu finden, um zuverlässige Gamma–Band Signale als Korrelat perzeptueller Prozesse messen zu können, die Umstände zu identifizieren, unter denen diese Prozesse durch höhere Informationsverarbeitung moduliert werden können, und schließlich eine umfassende Erklärung solcher Modulationen zu geben, die eine große Anzahl scheinbar heterogener Forschungsergebnisse integrieren könnte.

Prozesse, welche mit der Verarbeitung von Signalen aus der Umwelt verbunden sind, werden in den kognitiven Neurowissenschaften häufig als “bottom–up” bezeichnet. Hingegen nennt man solche Prozesse, welche aus dem kognitiven System heraus mit der Informationsverarbeitung befaßt sind (etwa Aufmerksamkeit und Gedächtnis), auch “top–down” (siehe Engel et al., 2001). Interessanterweise wurde Gamma–Aktivität in verschiedenen Untersuchungen mit beiden Funktionen in Zusammenhang gebracht (Herrmann et al., 2004c). Es wurde auch kritisch eingewendet, daß tatsächlich sehr verschiedenartige Phänomene in undifferenzierter Weise als Gamma–Aktivität bezeichnet wurden, und daß eine übergreifende Theorie für deren Funktionen bislang aussteht (Bertrand und Tallon-Baudry, 2000). Desweiteren wurde auch ausgehend von Negativbefunden behauptet, Gamma–Aktivität existiere gar nicht im menschlichen EEG (Juergens et al., 1999) oder sie sei ein lediglich sensorisches Phänomen ohne jede Relevanz für perzeptuelle oder kognitive Prozesse (Karakaş und Başar, 1998). In dieser Dissertation habe ich versucht, dieser Kritik zu begegnen.

In einem ersten Experiment wurde untersucht, inwiefern Gamma–Band Aktivität von grundlegenden Parametern visueller Stimulation (Stimulus Größe, Dauer und Exzentrizität) abhängig ist. Die Ergebnisse dieser Arbeit wurden in der Fachzeitschrift Clinical Neurophysiology veröffentlich (Busch et al., 2004) und sind detailliert in Kapitel 4 dargestellt. Die Untersuchung hatte zwei Hauptziele. Zum einen sollten Parameter für optimale Stimulation in zukünftigen Experimenten gefunden werden. Zum anderen sollte der Grad der Beeinflußbarkeit der Gamma–Aktivität durch Stimuluseigenschaften Aufschluß über die Funktion und Herkunft dieses Signals geben. Es zeigte sich, daß frühe evozierte Gamma–Aktivität sehr stark auf Variationen der Stimuluseigenschaften anspricht. Desweiteren wurde beobachtet, daß solche Variationen vor allem die Phase und weniger die Amplitude der Gamma– Aktivität beeinflußten. In zukünftigen Experimenten sollte daher darauf geachtet werden, daß eine möglichst starke Stimulation (große zentrale Stimuli) verwendet wird. Berichte über das Nichtvorhandensein von Gamma– Aktivität im EEG (siehe Juergens et al., 1999) lassen sich daher möglicherweise durch eine ungeeignete Stimulation erklären. Außerdem weisen die Ergebnisse darauf hin, daß Gamma–Aktivität in frühen visuellen Kortexarealen generiert wird. Diese Demonstration der Bedeutung von bottom–up Prozessen für die frühe evozierte Gamma–Band Aktivität steht daher im Einklang mit der Behauptung, dieses Phänomen spiegle rein sensorische und nicht etwa kognitive Prozesse (Karakaş und Başar, 1998) wider. Eine solche Interpretation würde allerdings einer Vielzahl anderer Untersuchungen widersprechen, die auch Einflüsse von Top–down Prozessen fanden.

Ein zweites Experiment wurde unternommen, um mögliche Interaktionen zwischen bottom–up und top–down Prozessen im frühen evozierten Gamma–Band zu untersuchen (siehe Kapitel 5). Die Ergebnisse dieser Untersuchung sind derzeit unter Begutachtung bei der Fachzeitschrift Neuroimage (Busch et al., 2005). Wir gingen von der Annahme aus, daß evozierte Gamma–Aktivität in frühen merkmalsselektiven, retinotop organisierten visuellen Arealen generiert wird. Wir führten ein Zielreiz–Erkennungs–Experiment durch, in dem das Stimulusmerkmal, das den Zielreiz definierte, über einen kleinen oder einen großen Bereich des gesamten Stimulus verteilt sein konnte. Die Ergebnisse zeigten, daß lediglich Zielreize, die großflächig verteilt waren, mehr Gamma–Aktivität als Standard Reize evozierten, obwohl die Gesamtgröße der Stimuli in allen Bedingungen identisch war. Diese vermehrte Aktivität kam nicht durch stärkere Phasenstarrheit zustande wie in Experiment 1, sondern durch eine Zunahme der Amplitude der Gamma–Aktivität. Desweiteren zeigte sich, daß die EKP Komponenten N1 und P3 für Zielreize unabhängig von deren Fläche vergrößert waren. Wir schlußfolgerten daraus, daß frühe evozierte Gamma–Aktivität von jenen merkmalsselektiven neuronalen Verbänden generiert wird, welche die sensorische Repräsentation des Stimulus bereitstellen, und daß deren Aktivität jedoch auch von höheren Prozessen wie der Erwartung eines Zielreizes modulierbar ist. Daher können im Falle einer großflächigeren Verteilung des relevanten Stimulusmerkmals mehr neuronale Verbände moduliert und entsprechend ein stärkerer Effekt im EEG gemessen werden. Bei einer kleineren Verteilung und entsprechned wenigen modulierten neuronalen Verbänden sind die Effekte möglicherweise zu klein, um im EEG noch detektierbar zu sein. Im Gegensatz dazu scheinen die neuronalen Prozesse, welche die EKP Zielreiz–Effekte generierten, unabhängig von der Stimulusrepräsentation zu funktionieren.

Man kann daher mutmaßen, daß das Fehlen von top–down Effekten auf evozierte Gamma–Band–Aktivität in manchen Untersuchungen (z.B. Karakaş und Başar, 1998) auf ungünstige Stimulation zurückzuführen ist.

Im zweiten Experiment wurden top–down Prozesse in einem Zielreiz–Erkennungs–Paradigma untersucht. In anderen Berichten über top–down Modulationen der Gamma–Aktivität wurde eine Vielzahl sehr unterschiedlicher Paradigmen eingesetzt. So wurde etwa gefunden, daß Gesichter zu mehr Gamma–Aktivität führen als Nicht–Gesichter (Keil et al., 1999), Sprachreize zu mehr als nichtsprachliche Reize (Pulvermüller et al., 1996) oder Zielreize zu mehr als Standardreize (Herrmann et al., 1999). Obwohl man mutmaßen könnte, daß Gamma–Aktivität in unspezifischer Weise von jeder denkbaren experimentellen Manipulation moduliert sei, gingen wir davon aus, daß es einen gemeinsamen Faktor in vielen dieser augenscheinlich heterogenen Untersuchungen gibt. Interessanterweise scheint stets diejenige experimentelle Bedingung zu mehr Gamma–Aktivität zu führen, die den Probanden bekannter erscheint. Daher stellten wir die Behauptung auf, daß die Übereinstimmung zwischen einer Stimulus– und einer Gedächtnisrepresentation die entscheidende Voraussetzung für eine top–down Modulation der Gamma–Aktivität darstellt. Diese Hypothese wurde im dritten Experiment untersucht (siehe Kapitel 6), das in der Fachzeitschrift BMC Neuroscience veröffentlicht wurde (Herrmann et al., 2004a). In dieser Untersuchung wurden schematische Stimuli präsentiert, die entweder bekannte Alltagsgegenstände darstellten oder Nonsense–Objekte, die jedoch aus denselben Komponenten bestanden. Die bekannten Stimuli, für welche die Probanden über Repräsentationen im Langzeitgedächtnis verfügten, evozierten mehr Gamma–Aktivität als die unbekannten Stimuli ohne solche Gedächnitniseinträge. Aufgrund dieser Ergebnisse wurde geschlußfolgert, daß top–down Effekte auf Gamma Aktivität durch Feedback Prozesse zwischen Gedächtnis– und Wahrnehmungssystemen zustande kommen.

Zusammenfassend kann gesagt werden, daß die Ergebnisse nahelegen, daß die frühe evozierte Gamma–Aktivität eine frühe Schnittstelle zwischen sensorischen und kognitiven Prozessen darstellt.

Selbstständigkeitserklärung

Hiermit erkläre ich, dass dies mein erster Promotionsversuch ist, dass ich die Dissertation selbstständig verfasst und die benutzen Hilfsmittel und Quellen vollständig angegeben habe.

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>
> Cicero, “Pro Plancio”, 54 v.Chr.

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>
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Eigene Publikationen

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