Neural Synchrony during Perceptual Organization in Schizophrenia

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Abstract

Current theories of schizophrenia suggest that the pathophysiology of the disorder may be the result of a deficit in the coordination of neural activity within and between areas of the brain, which may lead to impairments in basic cognitive functions such as contextual disambiguation and dynamic grouping (Phillips and Silverstein, 2003). This notion has been supported by recent studies showing that patients with schizophrenia are characterized by reduced synchronous, oscillatory activity in the gamma-frequency band during sensory processing (e.g., Spencer et al., 2003; Green et al., 2003; Wynn et al., 2005). However, it is currently unclear to what extent high-frequency gamma-band oscillations ($>$ 60 Hz) contribute to impaired neural synchronization as research has so far focussed on gamma-band oscillations between 30 and 60 Hz. In addition, it is not known whether deficits in high-frequency oscillations are already present at the onset of the disorder and to what extent reductions may be related to the confounding influence of antipsychotic medication. Finally, the neural generators underlying impairments in synchronous oscillatory activity in schizophrenia have not been investigated yet.

To address these questions, we recorded MEG activity during a visual closure task (Mooney faces task) in medicated chronic schizophrenia patients, drug-naïve first-episode schizophrenia patients and healthy controls. MEG data were analysed for spectral power between 25 and 150 Hz, and beamforming techniques were used to localize the sources of oscillatory gamma-band activity. In healthy controls, we observed that the processing of Mooney faces was as-

sociated with sustained high-frequency gamma-band activity (> 60 Hz). A time-resolved analysis of the neural generators underlying perceptual closure revealed a network of distributed sources in occipito-temporal, parietal and frontal regions, which were differentially activated during specific time intervals. In chronic schizophrenia patients, we found a pronounced reduction of high-frequency gamma-band oscillatory activity that was accompanied by an impairment in perceptual organization and involved reduced source power in various brain regions associated with perceptual closure. First-episode patients were also characterized by a deficit in high-frequency gamma-band activity and reductions of source power in multiple areas; these impairments, however, were less pronounced than in chronic patients. Regarding behavioral performance, first-episode patients were not impaired in their ability to detect Mooney faces, but exhibited a loss in specificity of face detection.

In conclusion, our results suggest that schizophrenia is associated with a widespread reduction in high-frequency oscillations that indicate local network abnormalities. These dysfunctions are independent of medication status and already present at illness onset, suggesting a possible progressive deficit during the course of the disorder.

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1 Introduction

Schizophrenia is a severe psychiatric disorder that affects the entire range of human mental activity. Patients with schizophrenia are frequently tormented by intrusive experiences such as hearing voices, and by delusions of persecution. The patient may believe that his thoughts are no longer private or that they are controlled by an external will. In addition, patients with schizophrenia suffer from impairments in basic sensory processing, such that they experience the visual world as fragmented. They also have difficulties expressing emotions and thinking coherently (Andreasen, 2000).

The disorder typically develops in late adolescence and early adulthood causing lifelong disability and impairment in the majority of cases (Carpenter and Buchanan, 1994). Schizophrenia belongs to the most costly public health problems to human society. It has been estimated that the costs for direct treatment and associated disability are about nine billion euros a year in Germany (Clade, 2004). Despite over a hundred years of research into the origins of schizophrenia, the pathophysiological mechanisms are still unknown. As a consequence, current treatments are only partially successful in reducing the symptoms of schizophrenia. At present, there is no biological marker or psychological test that is diagnostic of schizophrenia; thus, schizophrenia is diagnosed based on the presenting clinical syndrome.

Much effort has been devoted to identifying the location of brain disturbances in schizophrenia that may underlie the symptoms and cognitive impairments. However, neuroimaging and histopathologic studies over the last few decades

have revealed that the pathology of schizophrenia may not localize to a particular brain area, but that the disorder is associated with subtle volumetric and molecular alterations in a number of brain regions (Shenton et al., 2001). This led to a new perspective on the disorder, emphasizing the role of impaired connectivity between brain regions. Thus, current theories of schizophrenia and recent empirical data suggest that the disorder may be best conceptualized as a dysconnection syndrome, and that the pathophysiology of schizophrenia may be the result of a deficit in the coordination of neural activity within and between areas of the brain (Andreasen, 1999a; Friston, 1999; Phillips and Silverstein, 2003). It is assumed that a deficit in neural coordination leads to impairments in basic cognitive functions such as contextual disambiguation and dynamic grouping (Phillips and Silverstein, 2003), which may in turn give rise to the impairments in higher cognitive functions and to the clinical symptoms of schizophrenia.

A possible mechanism to account for impaired coordination of neural activity are disturbances in neural synchrony. Transient synchronization of neuronal discharges has been proposed as a possible mechanism to bind distributed sets of neurons into functionally coherent ensembles that represent the neural correlates of a cognitive content or an executive program (Singer, 1999). This hypothesis has received first experimental support from feature binding in vision (Gray et al., 1989). Further evidence has revealed that neural synchrony is also involved in a range of cognitive functions that require the dynamic integration and segregation of distributed neural activity, such as perceptual organization, attention, working memory and awareness (for a review, see Tallon-Baudry, 2009). Gamma-band oscillations (> 25 Hz) have received particular interest in recent years as they establish synchronization with great precision in local cortical networks (Womelsdorf et al., 2007).

In contrast to the large number of studies that investigated the role of neural synchronization in normal brain functioning, less is known whether neural

synchrony may also be relevant for the understanding of neuropsychiatric disorders such as schizophrenia. There is preliminary evidence that schizophrenia is related to impaired neural synchrony (for a recent review, see Uhlhaas and Singer, 2010); yet basic questions concerning the role of neural synchrony as a pathophysiological mechanism in schizophrenia remain as deficits in neural synchrony have mainly been demonstrated in medicated patient populations for example. Furthermore, little is known about the neural generators underlying impaired synchronous gamma-band oscillations in schizophrenia.

This dissertation focuses on the potential role of disturbed neural synchrony as a pathophysiological mechanism in schizophrenia. Specifically, we investigate the hypothesis that deficits in basic cognitive functions such as visual perceptual organization are related to impaired synchronization of high-frequency oscillatory activity in schizophrenia. We aimed to examine whether neural synchrony is impaired already at the onset of the disorder without the confounding influence of medication, and which sources underlie impaired high-frequency oscillatory activity. To this end, neural synchrony was measured with magnetoencephalography (MEG) in medicated chronic schizophrenia patients, unmedicated first-episode schizophrenia patients, and healthy controls. Perceptual organization was examined with a Gestalt perception task to investigate the relation between neural synchrony and visual processing. Furthermore, we collected clinical measures to assess the relation between symptom severity and neural synchrony in schizophrenia patients.

This chapter introduces the main theoretical concepts relevant to this work, beginning with a brief overview of the Gestalt theory of visual perception, and discussing the role of synchronous gamma-band oscillations for cognitive coordination. The focus of this chapter lies on the concept of schizophrenia that will be addressed afterwards, including a description of the clinical features and diagnostic aspects. Major findings regarding perceptual organization and neuronal synchronization in schizophrenia will be reviewed, followed by a dis-

cussion of the underlying neurobiological alterations in schizophrenia. Chapter 1 closes with an overview of the three studies that are presented in this thesis. Chapter 2 outlines general aspects of the methods that are relevant to our studies, including the Gestalt perception task, clinical and cognitive test batteries, and MEG and magnetic resonance imaging (MRI) recordings. Chapter 3 is devoted to the experimental studies carried out in this thesis. I will conclude with a summary of the main findings and a general discussion in Chapter 4.

1.1 Gestalt Theory of Visual Perception

Visual scenes are complex, consisting of many different colors, lines, curves and shapes. A fundamental task of the visual system is to impose structure on this information and organize the visual input into coherent objects: image elements belonging to a single object must be grouped together and segregated from elements belonging to different objects and the background. This is referred to as perceptual organization (Palmer, 1999). The Gestalt psychologists formulated a set of principles specifying the properties of visual features that observers tend to group together (see below).

1.1.1 Origins of Gestalt Theory

The Gestalt theory of perception was developed from about 1912 onwards by Max Wertheimer, Wolfgang Köhler and Kurt Koffka. They addressed the question of how pieces of visual information are structured into the larger units of perceived objects, which they referred to as "Gestalt", meaning "whole form" or "configuration". The Gestalt movement formed partially as a response to the structuralism of Wilhelm Wundt, which represented the predominant psychological theory of perception at that time. The structuralists assumed that perception was based on basic "sensory atoms", which represented indivisible elements of experience that were independent from all other elements of

experience.

In contrast, Gestalt theory was developed as a holistic view of perception that emphasized organized wholes (the Gestalten) as opposed to atomistic sensory elements. Christian von Ehrenfels (1890), an Austrian philosopher, laid the foundation for Gestalt psychology with his famous work "Über Gestaltqualitäten" (On the Qualities of Form), postulating that complex wholes are characterized by emergent properties – the "Gestaltqualitäten" – that are not contained within the individual elements. This idea is reflected by the well-known phrase "the whole is greater than the sum of its parts".

Max Wertheimer was interested in the question of how complex wholes emerge from individual elements. Working on the perception of motion, he noted that rapid sequences of perceptual events, such as rows of flashing lights, create the illusion of motion because our minds seem to "fill in" missing information (Wertheimer, 1912). Wertheimer argued that complex wholes differ from their constituting elements not only because they have new, additional Gestaltqualitäten, as von Ehrenfels had pointed out, but also because the overall structure of the stimulus configuration influences how the individual elements of the configuration are perceived.

1.1.2 Gestalt Principles of Perceptual Organization

The Gestalt psychologists developed a set of principles to explain how various elements in a complex display are perceived as "going together" in one's perceptual experience (Wertheimer, 1923; Koffka, 1935). The classical Gestalt principles include proximity, similarity, common fate, symmetry, continuity, and closure. Later, additional stimulus properties were identified that influence the grouping of individual elements, such as texture (Julesz, 1975), binocular disparity (Nakayama and Silverman, 1986), size (Bergen and Adelson, 1988), and coincidence in time (Alais et al., 1998).

The Gestalt psychologists considered visual grouping as an early step in per-

ception that provided an initial segmentation of a visual scene into its component objects and preceded object recognition. A large number of studies has provided evidence for this view, demonstrating that the grouping processes emphasized by Gestalt psychology operate preattentively (reviewed in Gray, 1999). More recent studies have shown that human vision also uses high-level grouping cues, such as familiarity with the shape of objects (e.g., Peterson and Gibson, 1991; Ullman, 1996; Vecera and Farah, 1997).

An example for the influence of high-level cues on grouping is the well-known Dalmatian dog. If seen for the first time, it is very difficult to reconstruct an object from the black and white blobs in the picture. But if one part of the object, for example the Dalmatian's head, is identified first, prior knowledge of the shapes of dogs' bodies and legs can be used to organize the rest of the image to correspond to these structures. Once the Dalmatian dog has been recognized, it can be easily seen in other presentations of the same picture, illustrating the influence of past experience on perceptual organization, which is especially important if the image is highly ambiguous (Palmer, 1999). Two-tone Mooney images, which were used in the studies presented in this thesis, are another example of ambiguous figures that depend on top-down processes for object recognition (for details, see Chapter 2). Thus, perceptual organization can be viewed as a temporally extended process that includes grouping at both early and later levels of processing.

The research program of the Berlin school of Gestalt psychology is today mainly associated with its contributions to the study of visual perception and problem solving. Less is known about its contribution to the fields of social psychology (Lewin, 1935, 1936), developmental psychology (Koffka, 1924) and abnormal psychology (for a review, see Crochetiere et al., 2001). However, from its beginnings, Gestalt theory was concerned with the application of its insights and theories to psychopathological phenomena. The link between Gestalt theory and psychopathology has recently gained new interest and stim-

ulated a large body of research on perceptual organization in schizophrenia and related disorders (reviewed in Silverstein and Uhlhaas, 2004). This topic will be addressed in more detail in Section 1.3, following a discussion of the neurophysiological mechanisms underlying perceptual grouping in the next section. It is interesting to note that even though the Gestalt psychologists were mainly interested in the relation between the structure of the stimulus and the observer's percept, they also addressed the question of how perceptual grouping is achieved in the brain. They proposed the concept of psycho-physical isomorphism, which holds that one's psychological perceptual experiences are structurally similar to the underlying physiological brain events (Wertheimer, 1912; Köhler, 1947). Wertheimer assumed that dynamic grouping processes might be realized by lateral interactions between sensory inputs processed in parallel. The idea was rejected at that time because it was generally believed that organization in the nervous system was possible only if transmission processes in afferent nerve fibers were strictly separated from each other. Current theories of brain organization correspond with early Gestalt ideas, proposing that cognitive integration is based on dynamic interactions between distributed neuronal populations in the brain (Singer, 1999).

1.2 Perceptual Organization and Neural Synchrony

1.2.1 Theories of Visual Feature Binding

As described in the previous section, perceptual grouping enables the integration of stimulus features into a coherent whole according to Gestalt criteria. Evidence from neuroanatomy and neurophysiology indicates that different feature dimensions such as color, motion, location and object identity are processed in separate brain regions. The coherent perception of even a single

object therefore requires that distributed activity of neurons is coordinated or bound together. The question of how features are bound together in the brain is referred to as the "binding problem" (von der Malsburg, 1981; Singer and Gray, 1995). Over the last few decades, two fundamentally different theories have been proposed to account for the binding problem, known as the "convergent hierarchical coding" and "binding-by-synchrony" theories.

Theory of Convergent Hierarchical Coding

The classical theory of feature integration is the theory of convergent hierarchical coding, which is based on the receptive field paradigm in neuroscience. The receptive field of a neuron corresponds to the area of visual space in which the presence of a stimulus can alter the response of that neuron. Many neurons are tuned to a specific feature in their receptive field. Neurons in the primary visual cortex, for example, increase their firing rate when a light bar with a certain orientation is shown (Hubel and Wiesel, 1962; DeValois et al., 1982), while neurons in area V4 respond to stimuli of a certain color (Zeki, 1973). There is consistent evidence that visual processing proceeds along a hierarchical series of stages, and that the size of the receptive field and the complexity of tuning increase in higher visual areas (Hubel and Wiesel, 1962; Felleman and van Essen, 1991).

The theory of convergent hierarchical coding posits that grouping is mediated by the activity of single neurons in higher visual areas that receive convergent inputs from neurons at lower levels in the hierarchy (Barlow, 1972). In other words, single neurons are supposed to respond to specific feature conjunctions that identify a particular object. Barlow referred to these highly selective neurons as "cardinal cells" (also known as "grandmother cells"). The theory has been supported by a number of studies that demonstrated the existence of highly selective neurons that respond to complex shapes (e.g., Gross et al., 1972; Desimone et al., 1984; Perrett et al., 1987; Fujita et al., 1992; Tanaka,

1996; Kreiman et al., 2002).

The advantage of this binding strategy is that feature integration can be computed rapidly, via a cascade of feedforward connections (Singer et al., 1997; Roelfsema, 2006). However, feature integration is unlikely to be mediated by cardinal cells alone. One reason for this is the so-called "combinatorial problem" (Singer and Gray, 1995; von der Malsburg, 1999), which refers to the fact that the number of combinations to be coded exceeds the number of neurons available. Moreover, the theory cannot account for our ability to perceive new objects. These limitations have been put forward to argue for a complementary processing strategy that allows using the same neurons for the description of many different feature combinations and that enables the representation of new constellations of features (Singer et al., 1997).

Theory of Binding-by-Synchrony

The binding-by-synchrony theory became well-known in the 1980s with theoretical studies on the binding problem by Christoph von der Malsburg (von der Malsburg, 1981; von der Malsburg and Schneider, 1986). Von der Malsburg proposed that feature binding is mediated by a synchronization of the firing of distributed populations of neurons. The binding-by-synchrony theory is based on early ideas by Donald Hebb that sensory and motor patterns should be represented by cooperative firing of neuronal assemblies, not by the activity of individual neurons (Hebb, 1949).

An important question is how the responses of neurons constituting an assembly are labelled so that they will not be confounded with simultaneous responses of other cells. One proposal has been that assemblies are defined by an enhancement of response amplitude. However, if multiple objects are present in a visual scene at the same time, there will be multiple overlapping populations of cells with enhanced activity. This problem, known as the "superposition problem", has been first described by Milner (1974) and von der

Malsburg (1981). They proposed that the superposition problem could be overcome if assemblies were defined by the selective synchronization of the firing of distributed neuronal activities. According to the binding-by-synchrony theory, synchronization is dynamically modulated, so that individual feature-encoding neurons can participate at different times in the representation of different figures; different objects will be represented by different combinations of neurons. As a consequence, the number of neurons required for the representation of different figures is reduced, and new objects can be represented as new patterns of activity across existing neurons (Singer, 1994).

The first experimental evidence for the binding-by-synchrony theory was provided in the late 1980s by Eckhorn et al. (1988) and Gray et al. (1989), demonstrating that coherent visual stimuli increase the synchronization of oscillatory firing in the gamma-frequency range of neurons in the visual cortex of the cat. In the classical study by Gray et al. (1989), multi-unit activity was recorded for a pair of neurons with non-overlapping receptive fields in the primary visual cortex of an anesthetized cat. The authors examined the temporal correlation of the timing of firing of the neurons using cross-correlation analysis when (1) two light bars moved across the two receptive fields in opposite directions, (2) two light bars moved across the receptive fields in the same direction, and (3) one long light bar moved across the receptive fields. In all conditions, the two neurons fired in an oscillatory pattern at around 40 Hz. The critical observation was that gamma-band activity ($35 - 50$ Hz) in the two receptive fields was synchronized only in response to a single stimulus (continuous light bar) moving simultaneously across both fields. Synchronization was reduced or absent when these fields were stimulated independently by two light bars moving in the same direction or the same two bars moving in opposite directions. These findings suggested the validity of the binding-by-synchrony theory for the first time and triggered a large number of studies on the role of synchronous gamma-band oscillations for visual processing.

Further studies by Singer's group in the 1990s confirmed the link between synchronous gamma-band activity and visual feature binding in anesthetized cats (e.g., Engel et al., 1990, 1991a,b,c; Gray et al., 1990). A number of studies in awake cats (e.g., Gray and Di Prisco, 1997; von Stein et al., 2000) and macaque monkeys (e.g., Eckhorn et al., 1993; Frien et al., 1994; Kreiter and Singer, 1996; Frien and Eckhorn, 2000; Friedman-Hill et al., 2000; Maldonado et al., 2000) reported synchronous stimulus-specific gamma-band activity during visual processing, suggesting that gamma-band oscillations serve a functional role in visual perception and that they are not an artifact of anesthesia. More recent studies in awake cats and macaque monkeys have provided evidence that gamma-band oscillations are also related to more general cognitive functions besides visual perception, such as selective attention (Fries et al., 2001; Womelsdorf and Fries, 2006; Womelsdorf et al., 2007; Fries et al., 2008b).

Despite the evidence in support of the binding-by-synchrony theory, the role of gamma-band oscillations in feature binding remains controversial on theoretical and empirical grounds. Regarding theoretical aspects, it has been argued that modulations of oscillatory activity and synchrony might merely be an epiphenomenon of neuronal activity and not have a causal role in cognitive function as the evidence is mainly correlative (Shadlen and Movshon, 1999). However, recent studies have provided critical evidence for a functional role of synchronous oscillations in cortical networks (Fries, 2009, discussed below), and there are numerous studies showing a close relationship between changes in synchronous oscillations and alterations in cognition and behavior (reviewed in Tallon-Baudry, 2009), making it rather unlikely that synchronous oscillations are only an epiphenomenon in neural networks. Nonetheless, direct evidence for the functional role of synchronous oscillations has yet to be provided.

Furthermore, it has been questioned that cortical neurons have the biophysical mechanisms needed for precise coincidence detection at a millisecond time scale (Shadlen and Movshon, 1999, however, see König et al. 1996). Further

controversial points are related to the questions of how binding is actually computed, i.e. what algorithms are used in neural networks to solve the binding problem, and how binding signals are read out without using "cardinal cells" (Shadlen and Movshon, 1999). Ghose and Maunsell (1999) and Riesenhuber and Poggio (1999) address yet another aspect, questioning that the problem of a combinatorial explosion of possible percepts really exists – the authors argue that conventional hierarchical processing relying on neurons with highly specialized response properties may be sufficient for visual performance. Thus, further research is needed to clarify these issues.

With regard to empirical evidence, a number of studies in monkeys failed to find a relation between perceptual grouping and neural synchronization in the gamma-frequency range (Tovee and Rolls, 1992; Young et al., 1992; de Oliveira et al., 1997; Lamme and Spekreijse, 1998; Thiele and Stoner, 2003; Dong et al., 2008; Palanca and DeAngelis, 2005; Roelfsema et al., 2004; Lima et al., 2009). It has been proposed, however, that some of the negative findings may be due to not taking into account that binding functions are realized at different scales, such that early processing stages can support only local grouping operations, whereas global grouping probably takes place in higher cortical areas (reviewed in Uhlhaas et al., 2009a). For example, in a recent study on surface segmentation of plaid stimuli in monkey primary visual cortex (V1), Lima et al. (2009) observed enhanced gamma-band activity in response to single components (gratings), but not in response to the superposition of a second component, suggesting that synchronous gamma oscillations in monkey V1 are relatively local, and that context assessment probably requires processing in higher visual areas with larger receptive fields.

It has also been argued that due to the transitory nature of synchronization, some episodes of synchronous firing may not have been detected with conventional cross-correlation techniques in the studies cited above (Uhlhaas et al., 2009a). However, these reasons may probably not account fully for the negative

findings, and important questions concerning the relevance of the binding-by-synchrony theory for perceptual grouping remain currently unresolved. Nonetheless, the theory has generated widespread interest in the role of neural oscillations in cortical networks and gave rise to a large body of studies investigating the relationship of gamma-band oscillatory activity and cognitive function in humans. In the sections that follow, measures of gamma-band activity and studies using non-invasive magnetoencephalography (MEG) and electroencephalography (EEG) recordings in humans will be reviewed, and the role of synchronous oscillations in cortical networks will be addressed.

1.2.2 Gamma-Band Oscillations and Visual Binding

Measures of Gamma-Band Activity

Neural oscillations occur at different temporal scales, ranging from slow oscillations in the delta- (up to 4 Hz), theta- ($4 - 7$ Hz) and alpha- ($8 - 12$ Hz) frequency bands to fast oscillations in the beta- ($12 - 25$ Hz) and gamma- ($25 - 200$ Hz) frequency bands. Within this spectrum, gamma-band oscillations have received particular attention because their relation to higher brain function is most evident. The temporal resolution of gamma-band oscillations is in the range of tens of milliseconds and thus corresponds to the time scale at which human cognitive processes such as perceptual organization are supposed to occur.

EEG and MEG Recordings. Gamma-band activity can be observed at the various levels of analysis, using single-unit recordings (microscale), recordings of local groups of neurons such as local field potentials and multi-unit activity (mesoscale), and extracortical recordings of the electro- or magnetoencephalogram (macroscale). Most electrophysiological data in humans are obtained at the scalp level by the use of non-invasive EEG or MEG recordings. EEG has been widely used for research and clinical purposes. In contrast, MEG is a

relatively novel method based on complex and relatively expensive technology. The MEG method uses SQUID (superconducting quantum interference device) magnetometers, which are sensitive detectors of magnetic flux (for an extensive review of MEG theory and instrumentation, refer to Hämäläinen et al., 1993).

Both EEG and MEG measure neural activity with excellent temporal resolution at a millisecond timescale. The main generators of MEG and EEG signals are postsynaptic currents at synchronously activated pyramidal cortical neurons. Whereas EEG measures mainly extracellular postsynaptic return currents, MEG signals reflect mostly dendritic postsynaptic currents. Furthermore, MEG is selectively sensitive to activation of fissural cortex where currents flow tangentially to the skull. In contrast, EEG is sensitive to radial and deep sources in addition to tangential currents (Hari et al., 2000).

There is an important advantage of MEG over EEG in that the magnetic field can be measured undisturbed by tissue inhomogeneities: whereas the electric scalp potential is smeared by different electric conductivity patterns of the head, the MEG benefits from the transparency of the skull and the scalp to magnetic fields (Hari and Salmelin, 1997). This results in an improved spatial resolution of MEG recordings, and, thereby, improved detectability of low-amplitude high-frequency oscillations. Furthermore, the improved spatial resolution allows localizing the neural generators underlying gamma-band activity.

Power and Synchrony. Gamma-band activity is typically analyzed for either gamma power or phase synchrony. Gamma power refers to the squared magnitude of gamma-band activity, either in a single neuron or across a population of neurons. The classical technique for analyzing the time-dependent power of different frequencies in a signal (temporal-spectral decomposition) is the short-time Fourier analysis (Percival and Walden, 1993). This technique has recently been complemented by multitaper analysis (Mitra and Pesaran,

1999) and wavelet-based techniques (Bertrand et al. 1999), which are better adapted for the spectral decomposition of non-stationary time series.

Synchrony refers to the functional coupling between pairs of neurons or between populations of neurons. In single-cell studies, gamma synchrony refers to the extent to which gamma activity is in phase between pairs of neurons as measured by a cross-correlogram. In EEG and MEG recordings, however, the distinction between gamma power and gamma synchrony is less clear because these methods measure aggregated electrical activity in the first place (Singer, 1993). EEG and MEG signals can only be observed outside the head if weak synaptic currents are summed across a large number of neurons; scalp signals therefore necessarily reflect synchronized neural activity. A power increase in a given frequency band at an electrode or MEG sensor is thus considered as a measure of local oscillatory synchrony, probably generated through local, within-area neural interactions.

Long-range synchronization, which is thought to arise from between-area recurrent feedback loops, has traditionally been studied using the coherence measure (Bressler et al., 1993). However, as the coherence measure confounds the effects of amplitude and phase in the interrelations between two signals, new phase synchronization measures have been developed that estimate phase relations regardless of the amplitude of the signals (Lachaux et al., 1999). There is evidence that the frequency of synchronous oscillations is inversely related to the extent of functional integration: gamma-band oscillations are mainly involved in local synchronization of neural activity, whereas large-scale integration of different brain areas is mediated by oscillatory activity in lower frequency ranges (von Stein and Sarnthein, 2000).

Evoked and Induced Oscillations. Task-related oscillations have been divided into "evoked" and "induced" oscillations, which are supposed to reflect different aspects of information processing in cortical networks (Tallon-Baudry and Bertrand, 1999). Evoked oscillatory activity typically occurs within a la-

tency window of 50 to 150 ms and has been related to early stimulus-encoding processes. Evoked oscillations are strictly phase-locked to the onset of the stimulus and can be identified by averaging the responses of several trials before spectral decomposition. In contrast, induced oscillations typically occur in a window of 150 to 400 ms and vary in latency from trial to trial; thus, they are not strictly phase-locked to stimulus onset and can therefore be only detected using single-trial spectral decomposition and subsequent averaging. Induced oscillations reflect the internal dynamics of cortical networks and serve a context processing and integration role (Tallon-Baudry and Bertrand, 1999).

Gamma-Band Oscillations and Cognitive Function

Gamma Oscillations and Perceptual Integration. A large body of EEG studies (e.g., Lutzenberger et al., 1995; Müller et al., 1996; Tallon-Baudry et al., 1996, 1997; Revonsuo et al., 1997; Keil et al., 1999; Rodriguez et al., 1999; Klemm et al., 2000; Gruber and Müller, 2005; Martinovic et al., 2008) and MEG studies (e.g., Kaiser et al., 2004; Vidal et al., 2006; Gruber et al., 2008) in humans has demonstrated that oscillatory activity in the gamma-band is correlated with the perception of coherent objects.

Tallon-Baudry et al. (1996) for example examined phase-locked and non-phase-locked EEG gamma-band activity while subjects counted distractor stimuli presented amongst illusory and real triangles and a non-triangle shape. They found that non-phase-locked gamma-band power ($200 - 300$ ms, $30 - 40$ Hz) was enhanced in response to the real and illusory triangles, but not in response to the non-coherent stimulus. In contrast, the early phase-locked gamma peak ($70 - 120$ ms, 40 Hz) did not vary with the stimulus-type. These findings supported the notion that induced gamma-band activity is associated with the binding of stimulus features into a coherent percept.

Several EEG studies used ambiguous face stimuli to examine gamma-band activity in relation to Gestalt perception. Keil et al. (1999) presented subjects

with a rotating face stimulus that could be perceived as either sad or happy in expression, depending on its orientation. Gamma-band spectral power was enhanced over occipital electrode sites when both the happy or sad expressions were in the typical vertical orientation, compared with a horizontal orientation that did not allow an easy recognition of the facial expression. Rodriguez et al. (1999) examined long-range synchronization across EEG electrodes during the perception of upright and inverted Mooney face stimuli. The authors observed enhanced gamma phase synchrony between occipito-temporal and parietal regions for stimuli that were perceived as coherent.

Kaiser et al. (2004) carried out a MEG study using the Kanisza triangle paradigm as employed in the above EEG study by Tallon-Baudry et al. (1996). They found that induced oscillatory responses at around 70 Hz were increased for illusory triangles compared to non-triangle stimuli, with the strongest activation observed around 240 ms over midline occipital cortex and around 430 ms over lateral occipital areas. Compared to real triangles, illusory triangles were associated with increased spectral power at 90 Hz over posterior parietal cortex between 100 and 450 ms. Thus, EEG and MEG studies provide convergent evidence that synchronous gamma-band oscillatory activity is linked to perceptual integration and object recognition in humans.

High-Frequency Gamma-Band Oscillations. Interestingly, MEG and EEG findings differ both in the duration and the frequency range of gamma-band responses. In human EEG, coherent visual perceptions are typically accompanied by a transient peak of induced gamma-band activity in the lower gamma frequency range between 30 and 60 Hz. In contrast, induced gamma oscillations in the MEG are more sustained and most pronounced at high-gamma frequencies between 60 and 140 Hz (Tallon-Baudry, 2009). One reason for these dissimilarities might be the different sensitivity profiles of MEG and EEG to different source configurations (Tallon-Baudry et al., 1999).

High-frequency gamma-band oscillations (> 60 Hz) have received increasing

interest because recent MEG studies demonstrated high-frequency gamma-band responses during a variety of cognitive tasks in the visual cortex and other cortical areas in humans (e.g., Adjamian et al., 2004; Hoogenboom et al., 2006; Hadjipapas et al., 2007; Siegel et al., 2007; Gross et al., 2007; Fries et al., 2008a; Wyart and Tallon-Baudry, 2008; Guggisberg et al., 2008), suggesting that they might be important for cortical function in general. Furthermore, high-frequency gamma oscillations in humans as observed with MEG are consistent with observations in invasive animal recordings (Colgin et al., 2009; van der Meer and Redish, 2009) and intra-cranial data in human patients (Crone et al., 2001; Lachaux et al., 2005; Brovelli et al., 2005; Tallon-Baudry et al., 2005; Dalal et al., 2009).

The question whether different sub-bands within the gamma-band – e.g. low ($25 - 60$ Hz) vs. high (> 60 Hz) gamma-band ranges – have different functional roles has only recently been addressed. Vidal et al. (2006) reported a dissociation between high-gamma band oscillations ($70 - 120$ Hz) related to perceptual grouping and lower gamma-band oscillations ($44-66$ Hz) associated with attention processes in a delayed matching-to-sample task, suggesting that different bands in the gamma-frequency range serve different roles in cognitive function.

The Role of Gamma-Band Oscillations in Cortical Networks. There is consistent evidence that gamma-band oscillations in humans are correlated with a range of cognitive functions besides perceptual integration, including attention (Fries et al., 2001), working-memory (Tallon-Baudry et al., 1998), and even consciousness (Melloni et al., 2007) (for reviews, see Uhlhaas et al., 2008; Tallon-Baudry, 2009).

Recent studies have suggested that gamma-band oscillations may not be an epiphenomenon of these various cognitive processes but represent a fundamental operation of cortical computation (Fries, 2009). Due to their high temporal resolution, gamma-band oscillations enable a precise synchronization of neu-

ronal discharges, which in turn enhances the impact on their postsynaptic targets (König et al., 1996; Salinas and Sejnowski, 2000, 2001). Thus, gamma-band oscillations allow for an effective summation of postsynaptic potentials that leads to enhanced signal transmission (Fries et al., 2007; Fries, 2009).

Precise timing between the output of presynaptic neurons and the corresponding input onto postsynaptic target neurons is important for synaptic plasticity, and experimental evidence has been provided for the role of gamma-band synchronization in modifying the strength of neuronal connections (Wespatat et al., 2004). Furthermore, it has been proposed that neuronal synchronization should also affect the interaction between rhythmically active groups, which is referred to as the communication-through-coherence hypothesis (Fries, 2005). This hypothesis has been supported by a recent study that demonstrated that the phase relation between two local rhythms determined the interaction strength between those rhythmic activities (Womelsdorf et al., 2007).

1.2.3 Mechanisms of Gamma-Band Oscillations

The mechanisms underlying gamma-band oscillations are not yet fully understood, but theoretical and empirical evidence provides strong support for a primary role of inhibitory interneurons in the generation and synchronization of gamma-band oscillations. The interneuron network model by Roger Traub, Miles Whittington and colleagues (Traub et al., 1999) proposes that synchronous gamma-band activity is due to the entrainment of pyramidal cells by synchronized inhibitory output from GABAergic interneurons.

Inhibitory postsynaptic potentials (IPSPs) generated by a single GABA neuron are sufficient to synchronize the firing of multiple pyramidal target cells: every time a GABA neuron fires, its postsynaptic cells are silenced for a brief period of time; the postsynaptic target cells will then fire spikes in near synchrony once the inhibitory effect subsides. If many GABA neurons fire simultaneously, they can synchronize the activity of large numbers of target cells in the

network (Cobb et al., 1995). The question is by what mechanism interneurons are synchronized in the first place. Whittington et al. (1995) demonstrated that cortical interneurons can synchronize their activity through mutual inhibition when they are activated by metabotropic glutamate receptors. Thus, the model suggests that interneuron-to-interneuron connections may be critical for the primary generation of high-frequency oscillations, with the frequency of the rhythms being determined by the time constant of the inhibition among interneurons (Traub et al., 1997; Hasenstaub et al., 2005).

Different types of interneurons have been defined according to electrophysiological properties, neuropeptide content and synaptic connections (Hof et al., 1993; Freund and Buzsaki, 1996; Gupta et al., 2000). Evidence exists that basket and chandelier cells are crucially involved in gamma-band oscillations (Bartos et al., 2007; Sohal et al., 2009). They represent a subpopulation of interneurons that is characterized by a fast-spiking phenotype, the expression of the calcium-binding protein parvalbumin, and perisomatic synapses on the target cells (Gupta et al., 2000).

Besides the GABAergic system, other neurotransmitter systems have also been implied in synchronous gamma-band oscillations. Cholinergic (Rodriguez et al., 2004) and dopaminergic (Seamans et al., 2001) connections modulate the excitability of interneurons. Cholinergic receptor activation is critical for the induction of cortical rhythms in various in vitro models of oscillations, and for oscillations and response synchronization in vivo during behavioral tasks. Glutamatergic connections appear to control the strength, duration, and long-range synchronization of high-frequency oscillations (Traub et al., 2004; Wang and Buzsaki, 1996). In addition to chemical synaptic transmission, direct electrotonic coupling through gap junctions between inhibitory neurons also contributes to the temporal patterning of population activity and, in particular, to the precise synchronization of oscillatory activity (Draguhn et al., 1998; Fukuda et al., 2006; Nase et al., 2003; Traub et al., 2001).

Long-range synchronization of neural activity is based on distant anatomical connections. Studies combining multi-site recordings with the sectioning of the corpus callosum (Engel et al., 1991a) and with developmental manipulations (Löwel and Singer, 1992; König et al., 1993) provided evidence that reciprocal cortico-cortical connections are the main anatomical substrate of neural synchronization in the high-frequency range. In contrast, thalamo-cortical connections are assumed to be crucially involved in the generation and synchronization of oscillatory activity in the lower frequency bands ($0.5 - 15$ Hz) (Steriade, 2005; Llinas and Steriade, 2006).

1.3 Cognitive and Neural Coordination in Schizophrenia

It has recently been proposed that neural synchrony may also be relevant for the understanding of neuropsychiatric disorders, such as schizophrenia (Uhlhaas and Singer, 2006). The following sections provide an overview of the clinical features of schizophrenia and describe current theories of schizophrenia that view neurocognitive impairments as a core feature of the disorder, resulting from a disturbance of neural coordination.

1.3.1 Clinical Features of Schizophrenia

Symptomatology

Various forms of a schizophrenia-like syndrome had been already described in the early nineteenth century. In 1896, the German psychiatrist Emil Kraepelin introduced the term "dementia praecox" to refer to a single disease entity characterized by hallucinations, delusions, a decrease in attention towards the outside world, lack of curiosity, disorder of thought, lack of insight and judgment, emotional blunting, negativism and stereotypes (Kraepelin, 1919). Kraepelin

believed that the disease had its onset in early adult life, hence "praecox", and generally progressed to a pervasive impairment of cognitive and behavioral function, hence "dementia".

The Swiss psychiatrist Eugen Bleuler coined the term "schizophrenia" – which derives from Greek "schizein" (to split) and "phren" (mind) – to highlight a separation of mental functions in this disorder. Bleuler emphasized the heterogeneity of the clinical syndrome and therefore spoke of the group of "schizophrenias", with the main symptoms being flattened affect, autism (turning away from the external world), impaired association of ideas, and ambivalence (Bleuler, 1950). Bleuler realized that the disorder was not a dementia as some of his patients improved rather than deteriorated and hence proposed to use the term schizophrenia instead of dementia praecox.

Kurt Schneider, a German psychiatrist, attempted to define schizophrenia more precisely, listing the symptoms that differentiate schizophrenia from other conditions. These have become known as first-rank symptoms, including auditory hallucinations, thought interference, delusional perception, and feeling as being under external control (Schneider, 1959). Schneider's criteria have significantly influenced current diagnostic criteria, but the specificity of first-rank symptoms has been questioned (Carpenter et al., 1973; Peralta and Cuesta, 1999).

At present, schizophrenia symptoms are most commonly grouped into the so-called "positive" symptoms, in which normal functions are distorted or exaggerated (psychotic symptoms), and the "negative" symptoms, in which normal functions are reduced or not present (Andreasen and Olsen, 1982; Crow, 1980). Positive symptoms include hallucinations, delusions, formal thought disorder and bizarre behaviours. Different types of hallucinations occur in schizophrenia, with auditory hallucinations being most common (Ndetei and Vadher, 1984); they often manifest themselves as voices commenting on the patient's behaviour in a derogatory manner or voices discussing the patient in the third

person.

Delusions represent false unshakeable beliefs and often include persecutory delusions (e.g. the belief that one is followed by the CIA), grandiose delusions (e.g. the belief that one is Jesus Christ), and delusions of control (e.g. the belief that others can interfere with one's thoughts). Formal thought disorder often manifests as incoherent speech, characterized by loose associations, frequent derailment of thought and the creation of new private words (neologisms). Negative symptoms include blunted affect (a reduced ability to express emotions), anhedonia (a lack of pleasure), avolition (a reduced ability to initiate and pursue goal-directed activity), and alogia (a decrease in the fluency of ideas and language). The presence and severity of psychotic symptoms tend to be episodic over time, whereas negative symptoms are more pervasive and strongly associated with poor psychosocial functioning (Eaton et al., 1995; Tamminga et al., 1998).

Diagnostic Criteria

At present, there is no objective biological or psychological marker that is sensitive or specific enough for a diagnostic assessment of schizophrenia. Schizophrenia is diagnosed based on the presenting clinical syndrome, with psychotic symptoms being emphasized as the most characteristic feature. The 4th Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, American Psychiatric Association, 1994) and the 10th International Classification of Diseases (ICD-10, World Health Organization, 1994) are currently used to diagnose schizophrenia. Both systems define schizophrenia in a similar way. The major differences are the DSM-IV requirements of social or occupational dysfunction (not included in the ICD-10) and a six-month duration of illness (versus one month in the ICD-10), resulting in a somewhat narrower definition of the disorder in DSM-IV. The diagnostic criteria according to DSM-IV are listed in the Appendix.

Schizophrenia has been classically divided into hebephrenic, catatonic and paranoid subtypes, depending on the symptoms dominating the clinical picture. Hebephrenia was used to describe profoundly disturbed young patients with marked thought disorder, but the term is rarely used now. However, current classification systems describe a disorganized subtype characterized by disorganized speech and behaviour and inappropriate affect. The paranoid subtype refers to patients whose mental state is dominated by delusions and hallucinations. The catatonic subtype is characterized by pronounced psychomotor abnormalities which may present as excessive motor activity (catatonic excitement) or as an extreme loss of motor activity (catatonic stupor).

The reliability of diagnoses between the DSM and ICD systems is high (Peralta and Cuesta, 2003). However, establishing the validity of these criteria and the boundaries of the disorder remains an ongoing area of investigation. It is currently debated whether schizophrenia is a categorical or continuous construct and how it is related to other diagnostic categories of affective and non-affective psychotic disorder (Esterberg and Compton, 2009; van Os and Kapur, 2009). Recent research in the general population indicates that the experiences associated with schizophrenia such as delusional thinking and auditory hallucinations are observed in an attenuated form in $5-8$ % of healthy people (van Os et al., 2009), supporting the view that schizophrenia and related disorders may be best conceptualized as a dimensional construct.

Epidemiology

A recent review of epidemiological data indicates that the lifetime prevalence and incidence of schizophrenia are $0.3-0.66$ % and $10.2-22$ per $100\,000$ person-years, respectively (McGrath et al., 2008). Contrary to previous views that rates are similar across different countries and cultures (Jablensky et al., 1992; Jablensky, 1997), new data and systematic reviews suggest that the incidence and prevalence of schizophrenia show prominent variation between

locations (Saha et al., 2006; McGrath et al., 2008). There is evidence that compared with native-born individuals, migrants have an increased prevalence and incidence of schizophrenia (Cantor-Graae and Selten, 2005).

The illness tends to develop between the ages of 16 and 30 years, and mostly persists throughout the patient's lifetime. In rare cases, symptoms emerge before the age of 12 (childhood-onset schizophrenia). Recent data indicate that males are more likely to develop schizophrenia than females (1.4 : 1) (McGrath and Susser, 2009); however, estimates for men and women seem to depend on the diagnostic definition of schizophrenia that is used (van Os and Kapur, 2009). Diagnostic definitions that are biased towards negative symptoms and long duration of illness – both associated with poor outcome – produce higher incidence rates for men than for women (Roy et al., 2001), whereas those including more affective symptoms and brief presentations – associated with better outcome – show similar rates in men and women (Castle et al., 1993; Beauchamp and Gagnon, 2004). These data suggest that the symptomatic expression of schizophrenia is more severe in men than in women, which is supported by the finding that women tend to have a later onset than men (Castle et al., 1993; Murray and van Os, 1998), and a more benign course of illness, including fewer hospital admissions and better social functioning (Angermeyer et al., 1990).

Etiology

The cause of schizophrenia is unknown but evidence suggests that genetic factors, early environmental influences and social factors contribute to the etiology of schizophrenia. Studies in relatives have shown that the risk of developing schizophrenia is proportional to the degree of genetic relatedness to an affected individual (Gottesman, 1991). There is a tenfold increase in risk associated with the presence of an affected first-degree family member, and the lifetime risk among children both of whose parents have schizophrenia is

nearly 50 % (McGuffin et al., 1995).

Twin studies have consistently shown higher concordance rates (i.e. both twins schizophrenic) in monozygotic than dizygotic twins and suggest that the heritability of liability is about 80 % (Cardno et al., 1999; Sullivan et al., 2003). Thus, the genetic contribution is currently regarded as the most important of the known etiological factors. The fact that monozygotic twins, sharing the same genes, can have different outcomes for schizophrenia indicates that it is not schizophrenia per se which is inherited but rather a susceptibility to the disorder.

The genetic transmission seems to be complex, not following simple Mendelian single-gene inheritance patterns (Gottesman and Shields, 1967; McGue and Gottesman, 1989). Current genetic models assume that multiple susceptibility genes are implicated in schizophrenia, each of small effect, which interact with epigenetic processes and environmental factors (Harrison and Owen, 2003). Recent findings suggest that a small proportion of schizophrenia incidence might be explained by rare structural variations, i.e. copy number variants occasioned by small duplications, deletions, or inversion (Walsh et al., 2008; Kirov et al., 2009).

Genome-wide scans have yielded rather inconsistent results regarding susceptibility loci in schizophrenia in the past, which has been attributed to a lack of power to detect the weak linkages as expected in a complex genetic disorder such as schizophrenia. More recent studies, however, have provided evidence for strong linkages in several regions, with the best-supported regions being 6p24-22, 1q21-22 and 13q32-34 (Owen et al., 2004). New genome-wide studies have replicated results across multiple samples for schizophrenia and also bipolar disorder, showing in addition that large numbers of genes contribute to both disorders (O'Donovan et al., 2008; Moskovina et al., 2009).

In a recent review of the current status of genetic studies in schizophrenia, Harrison and Weinberger (2005) identified seven plausible risk genes for schizophre-

nia based upon linkage and association studies. These candidate genes include the following: Catechol-O-methyltransferase (COMT; Goldberg et al., 2003), which encodes a key dopamine catabolic enzyme and therefore plays an important role in dopaminergic neurotransmission (Männistö and Kaakkola, 1999); Dysbindin (Blake et al., 1998), thought to be involved in postsynaptic density functions, which include trafficking and tethering of receptors and signal transduction proteins (Husi et al., 2000; Inoue and Okabe, 2003); Neuregulin (Falls, 2003), which is involved in various aspects of neuronal and glial functions, ranging from development (e.g. neuronal migration, axon guidance, synaptogenesis, glial differentiation, and myelination) to neurotransmission and synaptic plasticity (e.g. recruitment of nicotinic, GABA, and NMDA receptors, and long-term potentiation) (Falls, 2003); Regulator of G-protein Signaling 4 (RGS4; Williams et al., 2004), which is involved in neuronal differentiation (Grillet et al., 2003) and modulates G protein-mediated signalling via dopamine, metabotropic glutamate, and muscarinic receptors (Ross and Wilkie, 2000); Disrupted in Schizophrenia 1 (DISC1; Cannon et al., 2005), which is assumed to influence hippocampal structure and function (Austin et al., 2003, 2004); and finally metabotropic glutamate receptor 3 (GRM3; Egan et al., 2004) and G-72 (Chumakov et al., 2002), which are involved in glutamate neurotransmission. Taken together, these findings suggest that the genes may contribute to the pathogenesis of schizophrenia via an influence upon neural development, synaptic plasticity and neurotransmission, which is consistent with anatomical and neurochemical findings that will be reviewed below.

In addition to genetic factors, environmental and social factors that contribute to a risk for schizophrenia and operate throughout the life course have been identified. There is evidence that adverse pre- and perinatal events are associated with increased risk for schizophrenia, including hypoxia, maternal infection, maternal stress, malnutrition, and smoking during pregnancy (Susser

and Lin, 1992; Takei et al., 1996; Cannon et al., 2002; Khashan et al., 2008). Furthermore, it has been suggested that children growing up in urban areas are more likely to develop schizophrenia than those in rural areas (Krabbendam and van Os, 2005). As mentioned above, some immigrant ethnic groups have a higher risk of developing schizophrenia, particularly if they live in an area with few people of the same migrant group (Cantor-Graae and Selten, 2005). Finally, cannabis use has been associated with increased risk for psychotic disorder and symptoms (Moore et al., 2007).

1.3.2 Perceptual Organization in Schizophrenia

Cognitive Deficits as Core Features of Schizophrenia

In addition to the symptoms emphasized by current classification systems, schizophrenia is accompanied by a broad spectrum of cognitive impairments, including deficits in perception, attention, psychomotor speed, working memory, verbal learning and memory, and executive functions (i.e., the ability to plan, initiate and regulate goal-directed behaviour) (Goldberg et al., 1990; Gold and Harvey, 1993; Blanchard and Neale, 1994; Saykin et al., 1994). There is evidence that cognitive deficits are not merely an epiphenomenon of clinical symptoms, resulting from distracting influences of psychotic symptoms, but that cognitive impairments and psychotic symptoms in fact represent dissociable dimensions of schizophrenia (Elvevag and Goldberg, 2000).

Even though positive symptoms are usually the most striking clinical aspect, it has increasingly been recognized that cognitive deficits might represent the core features of schizophrenia (Green, 1996; Elvevag and Goldberg, 2000; Gold, 2004). This view is supported by the following findings: first, is has been shown that cognitive deficits precede the onset of psychotic symptoms. Several studies have provided evidence that patients with adult-onset schizophrenia display subtle cognitive, attentional and neuromotor abnormalities in early childhood (Cornblatt and Keilp, 1994; Walker et al., 1994; Jones et al., 1995) and during

adolescence (Davidson, 1999). Second, the unaffected relatives of patients with schizophrenia also show similar, although milder, cognitive deficits (Cannon et al., 1994; Kremen et al., 1994; Faraone et al., 1995; Sitskoorn et al., 2004), which indicates that the cognitive deficits are not caused by treatment with antipsychotic medication or the chronic nature of the illness. The findings also underline the notion that cognitive deficits can be largely unrelated to the psychosis itself.

Third, cognitive deficits are relatively stable over time (Harvey et al., 1996; Heaton et al., 1994; Sweeney et al., 1991) and independent of the clinical state, whereas psychotic symptoms vary over time in most patients (Putnam et al., 1996). Nuechterlein and Dawson (1984a) reported that cognitive deficits can be found in actively psychotic subjects and in cases where there is relative remission of psychotic symptoms. Studies with first-episode schizophrenia patients demonstrated that cognitive deficits are pronounced already at the very onset of the illness (Saykin et al., 1994; Bilder et al., 1991; Hoff et al., 1992). Fourth, cognitive deficits are correlated to the functional outcome of schizophrenia patients (Green, 1996; McGurk and Mueser, 2004). For example, patients who have worse cognitive functioning are more likely to be chronically institutionalized (Harvey et al., 1998), have poorer self-care skills (Harvey et al., 1997; Wykes, 1994) and impaired social skills and social functioning (Allen, 1990; Mueser et al., 1995; Penn et al., 1995). Numerous studies have shown that cognitive functioning is the best predictor of community functioning following treatment (Bowie et al., 2006; Green et al., 2004; Lowery et al., 2003; Harvey et al., 1998).

Finally, cognitive deficits can be observed across different subtypes of the illness; thus, even though the presenting symptoms may be very heterogeneous across patients, there seems to be a similar decline in neuropsychological functioning relative to normal controls (Elvevag and Goldberg, 2000). A study with monozygotic twins reported that the affected twin performed consistently

worse on all the given cognitive tasks in a large neuropsychological battery than the unaffected twin, irrespective of the affected twin's diagnosis (paranoid, undifferentiated, schizoaffective) (Goldberg et al., 1990).

In summary, there is evidence that cognitive deficits represent a core feature of the disorder and that they are powerful predictors of functional outcome. Cognitive deficits may therefore be important intermediate phenotypes in studies investigating the mechanisms underlying schizophrenia.

Visual Processing Dysfunctions in Schizophrenia

Cognitive neuroscience research of schizophrenia has traditionally focused on dysfunctions at higher cognitive processing levels such as working memory impairments and executive functions. Perceptual functions, however, are also frequently disturbed in schizophrenia patients, with deficits being particularly prominent in the visual domain. Behavioral studies have demonstrated that patients with schizophrenia have greater visual thresholds (Weiner et al., 1990; Butler et al., 1996; Saccuzzo and Braff, 1986), greater sensitivity to backward masking (Braff et al., 1991; Weiner et al., 1990; Butler et al., 1996; Saccuzzo and Braff, 1986; Slaghuis and Bakker, 1995; Rund, 1993; Green et al., 1999), decreased contrast sensitivity (Keri et al., 2002; Slaghuis, 1998), and impaired motion perception, spatial localization and eye tracking (Levy et al., 1993; Malaspina et al., 1994; Chen et al., 1999a,b,c; Stuve et al., 1997; Li, 2002; Kim et al., 2006; Slaghuis et al., 2007).

Thus, there is consistent evidence for impairments in early visual processing in schizophrenia. The findings above have generally been interpreted as evidence for a primary dysfunction in the magnocellular pathway / dorsal visual stream in schizophrenia patients, which has also been emphasized by recent research (King et al., 2008; Coleman et al., 2009). The magnocellular pathway conducts low-resolution visual information rapidly to cortex and is involved in initial attentional capture and processing of overall stimulus organization

(Merigan and Maunsell, 1993; Vidyasagar, 1999; Steinman et al., 1997). This pathway continues in the cortical dorsal visual processing stream ("where", parieto-occipital) that is involved in motion and space perception, eye movement control, action guidance, and initial attention modulation (Ungerleider and Haxby, 1994).

Further evidence for an impairment in early visual processing that also points to magnocellular pathway / dorsal stream dysfunctions in schizophrenia comes from studies using event-related potentials (ERPs), which provide an objective index of neurophysiological processing at the level of the sensory cortex and are obtained by averaging event-related brain responses. The P1 component of the visual evoked potential, with a peak latency typically varying between 75 and 100 ms, is considered an index of early, relatively automatic visual processing (Murray et al., 2001) that has been related to the dorsal stream (Butler et al., 2001, 2007; Foxe et al., 2001).

A reduction in P1 amplitude has been consistently found in chronic schizophrenia patients during a wide variety of visual tasks (reviewed in Yeap et al., 2008a), and has also been reported in first-episode schizophrenia patients (Yeap et al., 2008b, however see Katsanis et al. (1996)) and in unaffected first-degree relatives of patients with schizophrenia (Yeap et al., 2006). Consistent with these findings, a recent study using fMRI imaging and a simple visual activation paradigm reported reduced activation in the dorsal visual stream in neuroleptic-naïve first-episode patients, but found no differences in the primary visual cortex or the object-specific occipitotemporal pathway (Braus et al., 2002).

In summary, schizophrenia patients exhibit early visual sensory processing deficits that are already present at illness onset. Visual dysfunctions in unaffected relatives of schizophrenia patients suggest that these impairments may be endophenotypic of the illness and not simply a function of the disease state itself. Research has so far emphasized dorsal visual stream dysfunctions in

schizophrenia; however, there are also examples of poor form and shape processing in schizophrenia (reviewed in Butler et al., 2008) that imply integration deficits in the ventral visual processing stream related to object recognition (Ungerleider and Haxby, 1994). In this thesis, we focussed on the neurophysiological mechanisms underlying visual integration in schizophrenia during Gestalt perception. The following sections will review phenomenological and empirical evidence related to Gestalt perception in schizophrenia patients.

Gestalt Perception in Schizophrenia

Gestalt Perception – Phenomenological Accounts. Early phenomenological accounts of schizophrenia in the 1950s and 1960s had already pointed out the importance of perceptual deficits, suggesting that disturbances in visual integration are in fact among the most prominent symptoms of schizophrenia (Arieti, 1955, 1962; Chapman, 1966; Conrad, 1958; Matussek, 1987; McGhie and Chapman, 1961). The following reports by patients illustrate that visual perception is often fragmented in schizophrenia.

> "She remembered that she could not look at the whole door. She could only see the knob or some corner of the door. The wall was fragmented into parts." (Arieti, 1962, p. 85)

> "I may look at the garden, but I don't see it as I normally do. I can only concentrate on detail. For instance, I can lose myself in looking at a bird on a branch, but then I don't see anything else." (Matussek, 1987, p. 92)

> "Everything I see is split up. It's like a photograph that's torn in bits and put together again. If somebody moves or speaks, everything I see disappears quickly and I have to put it together." (Chapman, 1966)

Based on these observations, early psychiatrists conceptualized schizophrenia from a Gestalt psychological perspective, suggesting that perceptual deficits in schizophrenia are primary and may underlie the emergence of clinical symptoms such as delusions (Conrad, 1958; Matussek, 1987). Conrad (1958) described different phases in the formation of a schizophrenic psychosis, beginning with the "trema", in which the ability to form a Gestalt disintegrates: patients are still able to identify elements but they loose the ability to recognize the essential Gestalt to give the elements a proper meaning. In the next phase – the "apophanous phase" – the schizophrenic patient begins to attach new meaning to the fragmentary perceptions of the world around him, which then results in delusional beliefs. Thus, according to Conrad, delusions are not abnormal in themselves, but reflect a normal response to a degradation of the perceptual world.

Gestalt Perception – Empirical Evidence. In addition to patients' descriptions of their experience of the visual world, experimental studies provided further evidence for a dysfunction in perceptual organization in schizophrenia. Classical studies by Cox and Leventhal (1978) and Place and Gilmore (1980) are typically credited as the first empirical demonstrations of a perceptual organization deficit in schizophrenia.

There is an earlier investigation that had already suggested that schizophrenia is characterized by an impairment in global compared to local processing (Snyder et al., 1961). Snyder (1961) examined the phenomenon of perceptual closure and asked schizophrenia patients to reproduce line drawings with gaps. Comparison subjects automatically filled in the gaps because of the operation of perceptual closure, drawing more complete pictures of objects than had been requested. In contrast, the patients did not fill in the gaps; thus, paradoxically, due to a deficit in visual closure processes, patients drew pictures that better approximated the fragmented originals than did the comparison subjects.

Cox and Leventhal (1978) examined preattentive visual processing in para-

noid and non-paranoid schizophrenia patients, and in a psychiatric control group using different visual grouping tasks. They found that non-paranoid schizophrenia patients had an impaired behavioral performance in all tasks compared to the paranoid patients and controls, suggesting a deficit in preattentive perceptual grouping in non-paranoid schizophrenia patients.

The study by Place and Gilmore (1980) provided critical evidence for a dysfunction in perceptual organization in schizophrenia. In this study, schizophrenia patients and healthy controls were required to report the number of lines in tachistoscopically presented arrays containing zero to six lines. In the first experiment, the lines appeared either alone or with noise elements (circles); in the second experiment, the stimulus arrays did not contain any noise elements, but the organization of the arrays was manipulated by varying the proximity and the similarity of the line elements.

The results of the first experiment showed that when the lines were presented alone, both groups had a comparable performance. Their report accuracy decreased with increases in the number of lines. In the noise condition, the performance dropped only for the schizophrenia patients. In the second experiment, controls performed better than schizophrenia patients when the lines were arranged in a way that allowed for quick grouping. Their performance deteriorated as the organization of the arrays became more heterogeneous. In contrast, the schizophrenics were not affected by the organization of the lines; in fact, patients performed better than controls in a condition where lines of differing orientations were randomly intermixed, and their average performance was also better than that of controls.

The results of the two experiments were interpreted as evidence that a perceptual dysfunction in schizophrenia may result from a failure to organize information at an early stage of processing. The authors pointed out that the impairments did not result from a generalized cognitive deficit because patients performed relatively better than healthy controls in conditions when percep-

tual grouping would normally interfere with responses to individual elements.

Since then, numerous studies using different tasks have shown that perceptual organization is impaired in chronic schizophrenia patients (e.g., Rabinowicz et al., 1996; Silverstein et al., 1996, 1998; Doniger et al., 2001; Silverstein et al., 2000; Uhlhaas et al., 2005, 2006b; Kurylo et al., 2007; Silverstein et al., 2009). Simple Gestalt tasks involving the perception of basic shapes with non-fragmented contours are not impaired in schizophrenia, however (e.g., Chey and Holzman, 1997; Rief, 1991). Thus, schizophrenia patients show clear impairments in combining non-contiguous elements (e.g. dot or line patterns) into perceptual wholes, but only when strong grouping cues are absent. This has led to the hypothesis that impairments in top-down processing might be an important factor in deficits in perceptual organization in schizophrenia (Silverstein et al., 1996, 2006b).

Deficits in perceptual organization have also been observed in unmedicated first-episode patients (Frith et al., 1983; Rabinowicz et al., 1996) as well as in non-clinical schizotypal students (Uhlhaas et al., 2004), suggesting that the deficits are present at the onset of the disorder and not due to the effects of antipsychotic medication. However, a recent study provided contradicting evidence, reporting no impairments in first-episode patients for a task with known sensitivity to perceptual organization deficits in chronic schizophrenia patients (Silverstein et al., 2006a). The first-episode group demonstrated even more sensitivity to stimulus organization compared to healthy controls, although this difference was not significant. The authors suggested that perceptual organization is not impaired and may even be enhanced early in the illness, with dysfunctions beginning with increased chronicity.

This conclusion is supported by a study that found increased perceptual organization in a prodromal schizophrenia group compared to a control group, but reduced functioning in a chronic schizophrenia group (Parnas et al., 2001). Taking these findings together, it is still unclear whether perceptual organiza-

tion is impaired at an early stage of schizophrenia.

Perceptual Organization Deficit Hypothesis. Early theories of perceptual dysfunctions in schizophrenia patients focused on attention deficits that represent a significant cognitive feature of schizophrenia (Bleuler, 1950; Maher and Maher, 1979; Nuechterlein and Dawson, 1984a). McGhie (1970) proposed that schizophrenia patients possess an inefficient perceptual filter, resulting in an inability to focus on relevant stimuli and filter out irrelevant ones. As a consequence, schizophrenia patients would show an impaired performance in detection tasks where target elements must be distinguished from noise elements. Cash et al. (1972) formulated a related concept, proposing that schizophrenia patients use an inefficient overprocessing strategy for information processing. However, the studies by Cox and Leventhal (1978) and Place and Gilmore (1980) raised the possibility that a primary deficit in perceptual organization may underlie the well-replicated attention deficit in schizophrenia. In particular, Place and Gilmore's findings that schizophrenia patients performed better than controls under certain stimulus conditions could not be explained by overprocessing or deficient filter theories. Place and Gilmore proposed instead that schizophrenia is characterized by a very early deficit in information processing that leads to deficits at higher processing stages. They suggested that schizophrenia patients deal differently with visual input because they do not organize elements in a visual display into coherent object representations. The results supported the view that a perceptual deficit might be central to schizophrenia.

In 1986, Carr and Wale presented a model in which disturbances in the organization of perceptual, linguistic, and motor activity in schizophrenia were all viewed as caused by a breakdown in preattentive Gestalt processes (Carr and Wale, 1986). They proposed that certain psychopathological phenomena in schizophrenia, such as negative symptoms, hallucinations and delusions, could be seen as compensatory operations of a disordered information processing

system.

Current cognitive theories of schizophrenia are based on these earlier accounts and view Gestalt theory as an important framework from which to understand the disorder (Phillips and Silverstein, 2003; Uhlhaas and Silverstein, 2005). They suggest that the impairment in perceptual organization and other cognitive impairments in schizophrenia can be accounted for by a deficit in a single underlying mechanism, specifically the ability to establish coherent organization among contextually related stimuli (Andreasen, 1999b; Cohen and Servan-Schreiber, 1992; Phillips and Silverstein, 2003). Such models are related to recent neuroscientific theories that consider the coordination of neural activity within and between different regions of the brain as being crucial for coherent cognitive and motor activity (Phillips and Singer, 1997). Accordingly, impaired synchronization of neural responses has been proposed as a possible pathophysiological mechanism underlying the pathophysiology and the associated cognitive deficits of schizophrenia (Uhlhaas and Singer, 2006).

1.3.3 Neural Synchrony in Schizophrenia

There is growing evidence from EEG and MEG studies that schizophrenia is related to impaired neural synchrony (Uhlhaas and Singer, 2006, 2010). This section provides an overview of the findings in chronic and first-episode schizophrenia patients, focussing on neural synchrony during sensory processing.

Steady-State Response. Several studies reported reductions in the power of steady-state responses to repetitive auditory (Kwon et al., 1999; Brenner et al., 2003; Light et al., 2006; Vierling-Claassen et al., 2008; Krishnan et al., 2009; Spencer et al., 2009) or visual stimulation (Krishnan et al., 2005) in chronic schizophrenia patients. Steady-state auditory evoked potentials were most consistently reduced to frequencies in the gamma-frequency range (around 40

Hz). Kwon et al. (1999) for example observed that gamma-band responses to auditory click trains presented at 40 Hz were decreased and delayed in chronic schizophrenia patients, whereas responses to click trains at 20 and 30 Hz were intact, suggesting a specific deficit in the generation and/or maintenance of high-frequency oscillations. Similar results were reported by Light et al. (2006), demonstrating reductions in both evoked power and phase synchronization in response to 30 and 40 Hz stimulation but normal responsivity to 20 Hz stimulation. Brenner et al. (2003) and Krishnan et al. (2009) examined a broader frequency range and found that stimuli at lower frequency bands were also associated with deficits of steady-state responses in chronic patients, in addition to deficits in the gamma-frequency range. Krishnan et al. (2005) reported reduced signal power in a visual steady-state paradigm at beta and gamma frequencies in chronic patients, but not at alpha frequencies.

Together, these studies suggest that chronic schizophrenia patients may be characterized by an inability to generate or maintain oscillations in neural networks, which may contribute to deficits in auditory and visual processing. Recent studies demonstrated impaired steady-state responses also in first-degree relatives (Hong et al., 2004), in adolescent patients with a psychotic disorder (Wilson et al., 2008) and in drug-free first-episode patients with schizophrenia (Spencer et al., 2008), suggesting that the deficits are not an artifact of long-term effects of medication or illness chronicity.

Evoked Response. A number of studies provided evidence for a reduction of evoked stimulus-locked oscillatory activity in the high-frequency range during visual and auditory processing. Wynn et al. (2005) employed a visual backward-masking task to examine gamma-band activity in 32 chronic schizophrenia patients and 15 healthy controls. They found that patients had significantly reduced evoked gamma-band responses to masked stimuli between 50 and 200 ms, going along with a poorer performance during the masking task. Moreover, the distribution of activation differed from that in normal

controls, such that patients failed to show a lateralization of activity to the right hemisphere.

Gallinat et al. (2004) investigated gamma-band responses in an auditory oddball paradigm in 15 unmedicated schizophrenic patients and 15 healthy controls. Ten patients were drug-naïve and experienced their first psychotic episode, whereas the other patients had been drug-free for more than four weeks. The authors observed a reduction of evoked gamma-band responses only in a late latency range ($220 - 350$ ms) over frontal electrodes, whereas the early auditory evoked response ($20 - 100$ ms) was relatively intact. Consistent with the latter finding, a recent study by Spencer et al. (2008) reported that early auditory-evoked gamma oscillations were not affected in chronic schizophrenia patients, suggesting relatively preserved processing for simple tone stimuli at early stages in the auditory cortex. The same study provided evidence that early visual-evoked gamma oscillations were reduced in chronic schizophrenia patients, which is in line with earlier studies by this group that reported reduced evoked activity for the early gamma-band response in chronic schizophrenia patients in a visual binding task using illusory square stimuli (Spencer et al., 2003, 2004).

In contrast to the findings by Gallinat et al. (2004) and Spencer et al. (2008), three studies reported a reduction of the early auditory evoked response around 50 ms in the beta- and gamma-frequency ranges in chronic schizophrenia patients (Johannesen et al., 2008; Hirano et al., 2008; Roach and Mathalon, 2008), suggesting dysfunctions in the initial neural registration of auditory stimuli.

Induced Response. In addition, there is evidence for a reduction of induced, non-stimulus locked oscillations in the gamma-frequency band during sensory processing. Green et al. (2003) used a backward masking task and observed enhanced induced gamma-band activity between 200 and 400 ms following target presentation in controls but not in chronic schizophrenia patients. Haig et al. (2000) observed abnormal induced gamma-band activity in an auditory

oddball task in chronic patients. For targets, schizophrenia patients showed a significant decrease in gamma-band activity in the left hemisphere and frontal sites and an increase in right hemisphere and parieto-occipital sites; for non-targets, schizophrenics showed a widespread gamma decrease. The authors proposed that the gamma-band findings in non-targets reflect an abnormality in appropriately processing irrelevant stimuli, which could result in defective processing of the context of relevant target information.

Phase Synchrony. Besides the analyses of spectral power, several studies have examined large-scale synchronization between electrode sites during auditory and visual processing in schizophrenia, indicating that neural synchrony between brain areas may also be impaired (Slewa-Younan et al., 2004; Spencer et al., 2003; Symond et al., 2005; Uhlhaas et al., 2006a; Williams et al., 2009). Uhlhaas et al. (2006a) examined the EEG activity in 19 patients with chronic schizophrenia and 19 healthy controls during a Gestalt perception task. They found that deficits in Gestalt perception in schizophrenia patients were associated with reduced phase synchrony in the beta-band, whereas induced spectral power in the gamma-band ($40 - 70$ Hz) was relatively intact.
Slewa-Younan et al. (2004) and Symond et al. (2005) examined gamma phase synchrony in medicated first-episode patients during an auditory oddball task. In both studies, first-episode patients were characterized by a decreased magnitude and delayed latency of early (-150 to 150 ms) 40 Hz gamma phase synchrony compared to healthy controls, whereas no group differences were observed for late ($200-550$ ms) gamma snychrony. Williams et al. (2009) investigated the relations between 40 Hz gamma-band synchrony, measured with an auditory oddball paradigm, and grey matter volume in medicated schizophrenia patients at first-episode and 2.5 years later. The authors observed that compared to controls, schizophrenia patients, at first contact, showed a disruption to the laterality of early ($0 - 150$ ms) gamma synchrony and a global reduction in late ($350 - 500$ ms) gamma synchrony, accompanied by a loss

of fronto-temporal-parietal grey matter. At follow-up, patients showed an increase of gamma-band synchrony compared to the first measurement, which was related negatively to a further loss of grey matter. The authors interpreted the increase of gamma synchrony as an attempt to adapt to a progressive loss of cortical grey matter.

Gamma-Band Activity and Clinical Symptoms. Several studies have reported correlations between abnormal gamma-band responses and the severity of clinical symptoms. Baldeweg et al. (1998) found that intense somatic hallucinations were associated with excessively high gamma power. Gordon et al. (2001) observed that reality distortion was associated with increased gamma activity, whereas psychomotor poverty was related to reduced gamma-band activity. In line with these findings, Lee et al. (2003) reported that enhanced phase synchrony in response to targets in an oddball paradigm correlated positively with increased positive symptoms, whereas negative symptoms were associated with a decrease in gamma-band activity in a sample of chronic patients with schizophrenia. Bucci et al. (2007) reported that induced gamma power and coherence were relatively preserved in patients with primarily negative symptoms. Finally, Spencer et al. (2003) observed a relationship between the frequency of phase locking in the beta-frequency range and the severity of core symptoms of schizophrenia such that lower frequencies of the evoked oscillations were associated with more severe symptomatology.

In summary, a number of studies has shown that impairments in perceptual processes in schizophrenia patients are related to abnormal local and long-range synchronization of neural responses. Abnormal neural synchrony has also been related to deficits in higher cognitive functions in chronic schizophrenia patients, such as working memory (Basar-Eroglu et al., 2007; Haenschel et al., 2009) and executive function (Cho et al., 2006). In line with EEG and MEG studies, fMRI studies have also provided evidence for dysfunctions in large-scale coordination in schizophrenia, reporting a reduction in functional

connectivity during a variety of tasks (Honey et al., 2005; Meyer-Lindenberg et al., 2005; Schlosser et al., 2003).
The next section outlines possible mechanisms of abnormal connectivity and impaired neural synchronization in schizophrenia.

1.3.4 Neurobiology of Schizophrenia

Evidence from a large body of brain imaging, histopathologic, genetic and pharmacologic studies suggests that both altered brain structure and abnormalities in several neurotransmitter systems may contribute to the impairments in neural coordination and brain function in schizophrenia.

Neuroanatomical Abnormalities

Macroscopic Structural Findings. Brain imaging studies using structural MRI in adult schizophrenia patients have consistently documented enlarged lateral ventricles and smaller gray matter volumes in a variety of brain regions, including the prefrontal cortex, the temporal cortex, the hippocampus, the amygdala, and the thalamus (for reviews, see Lawrie and Abukmeil, 1998; Harrison, 1999b; Shenton et al., 2001; Ross et al., 2006). Results of studies with first-episode patients are quite similar to those reported for chronic patients (Degreef et al., 1992; Lim et al., 1996; Gur et al., 1998b; Whitworth et al., 1998; Zipursky et al., 1998), suggesting that brain structural abnormalities in schizophrenia are not a consequence of medical treatment or the chronicity of the illness. Moreover, adolescents at high risk for schizophrenia show enlarged ventricles (Cannon et al., 1993) and smaller medial temporal lobes (Lawrie et al., 1999; Pantelis et al., 2003), indicating that the brain pathology precedes the onset of symptoms.
Structural alterations have also been found in the white matter of schizophrenia patients. Diffusion tensor imaging (DTI) is a relatively new MRI technique that is based on the directional distribution of water diffusion coefficients and

allows investigating the structural integrity of white matter fiber tracts in vivo. Decreased diffusion anisotropy has been found in schizophrenia in prefrontal, temporal and parietal lobes (for reviews, see Kanaan et al., 2005; Kubicki et al., 2007), indicating that the coherence or density of fiber bundles in these brain regions is decreased in schizophrenia patients. A recent DTI study reported that altered white matter integrity in the uncinate fasciculus is already present at the early stage of illness in recent-onset schizophrenia patients (Kawashima et al., 2009).

Microscopic Histopathologic Findings. Microscopic post-mortem investigations have revealed subtle abnormalities of neuronal cytoarchitecture that may underlie the alterations observed in macroscopic structural MRI and DTI studies. It has been suggested that reductions in gray matter probably result from a reduction in the volume of cortical neuropil, i.e. decreases in the volume of dendritic and axonal processes, based on findings that the total number of neurons in the cortex of schizophrenia patients is not altered (Pakkenberg, 1993), whereas neuronal density appears to be increased (Selemon et al., 1995, 1998; Selemon and Goldman-Rakic, 1999).

The reduced neuropil hypothesis is supported by findings of decreased presynaptic and dendritic markers, which indicate a reduction in the length and density of dendritic spines and in the number of synaptic contacts (Harrison, 1999b; Arnold et al., 2005). In addition, several studies have reported a reduction in neuronal size in various brain regions (e.g., Arnold et al., 1995; Zaidel et al., 1997; Pierri et al., 2001).

These findings are consistent with results of magnetic resonance spectroscopy (MRS) studies in schizophrenia (Harrison, 1999b), which have shown reductions in signal for the neuronal marker NAA (N-acetyl-aspartate) (Bertolino et al., 1996; Deicken et al., 1997, 1998). Interestingly, the lowered NAA signal is also seen in unmedicated (Bertolino et al., 1998) and first-episode (Renshaw et al., 1995) schizophrenia patients, suggesting that the cytoarchitectural ab-

normalities seen in post-mortem studies may also be present at the early stage of the illness (Harrison, 1999b).

Concerning microscopic alterations of white matter, recent neuropathological studies in schizophrenia have reported abnormalities in oligodendroglial cells that provide myelination to axons in the central nervous system (Davis et al., 2003; Uranova et al., 2001, 2004, 2007). Furthermore, it has been suggested that cortical neuronal migration is disturbed in schizophrenia because there is evidence for an abnormally high frequency of aberrant neurons in the white matter underlying prefrontal cortex (Akbarian et al., 1996), temporal and parahippocampal regions (Arnold et al., 2005). Evidence from in-vivo phosphorus MRS studies of drug-naïve schizophrenic patients suggests that destructive white matter changes may be already present at disease onset (Pettegrew et al., 1991; Fukuzako et al., 1999).

In summary, schizophrenia patients are characterized by grey and white matter abnormalities, which may contribute to dysfunctions in local and long-range connectivity in schizophrenia. There is consistent evidence that alterations in brain structure are already present at the onset of the disorder. It is less clear, however, whether these structural abnormalities are progressive or remain static over the course of the illness. Results from longitudinal studies, which examine changes in structural brain morphometry over time, are equivocal: a number of studies provided evidence of worsening of the structural abnormalities during the course of the illness (DeLisi et al., 1997; Nair et al., 1997; Gur et al., 1998a; DeLisi et al., 2004; Gogtay et al., 2004; Pantelis et al., 2003; Cahn et al., 2006; DeLisi, 2008; Williams et al., 2009) while others reported no progression over time (DeLisi et al., 1992; Jaskiw et al., 1994; Vita et al., 1997).

Thus, it seems that more recent studies indicate that brain changes in schizophrenia may be progressive, but the significance of these findings is not yet clear: progressive brain changes may indicate neurodegenerative processes,

but they might also reflect ongoing developmental changes (discussed below) or occur secondary to treatment with antipsychotic medication.

Neurochemical Abnormalities

Dopamine. Hypotheses regarding the pathophysiology of schizophrenia were originally derived from pharmacology. The classical dopamine hypothesis, proposed by Arvid Carlsson in the 1960s, maintains that excessive dopamine transmission underlies schizophrenic symptoms (Carlsson and Lindqvist, 1963). This idea originated from the finding that antipsychotic drugs exert their effects primarily by blocking dopamine D2 receptors (Seeman and Lee, 1975; Creese et al., 1976; Snyder, 1981; Seeman, 2002). Further support came from the observation that dopaminergic agents, such as amphetamines, can cause schizophrenia-like psychosis in normal individuals and worsen psychotic symptoms in schizophrenia patients (Connell, 1958). Recent studies using single photon emission computed tomography provided more direct support for the hypothesis of a dysregulation of dopamine function in schizophrenia, showing an exaggerated striatal dopamine transmission following acute amphetamine challenge in untreated patients with schizophrenia (Laruelle et al., 1996; Abi-Dargham et al., 1998) and in first-episode patients never previously exposed to antipsychotic drugs (Laruelle and Abi-Dargham, 1999).

While Carlsson's original theory implied a general hyperdopaminergic state, the modern view is that schizophrenia may involve both an excess of mesolimbic dopamine in the striatum (subcortical hyperdopaminergia), related to psychotic symptoms, and a deficit in prefrontal dopamine neurotransmission (cortical hypodopaminergia), related to negative symptoms and cognitive deficits (Davis et al., 1991). Which deficit is primary remains controversial; a prevalent hypothesis is that alterations in the subcortical dopaminergic systems may be secondary to a primary hypofunction of the prefrontal cortex (Weinberger, 1987; Davis et al., 1991), which is supported by a study showing increased stri-

atal dopamine levels in rodents with prefrontal cortex lesions (Jaskiw et al., 1990). A recent study by Kellendonk et al. (2006) provides evidence that the opposite causal relationship is also possible; the authors found that D2 receptor overexpression in the striatum of D2 transgenic mice affects activation in the prefrontal cortex and leads to cognitive impairments.

Glutamate. Schizophrenia likely involves other neurotransmitter systems besides dopamine since antipsychotic drugs that block D2 receptors improve only some of the symptoms. An alternate explanation for the etiology of schizophrenia is the glutamate dysfunction hypothesis, which posits that schizophrenia results from an alteration in glutamatergic transmission due to a hypofunction of N-methyl-D-aspartate (NMDA) receptors (Javitt and Zukin, 1991; Olney and Farber, 1995). The glutamate hypothesis is supported by the observation that noncompetitive antagonists of NMDA receptors such as phencyclidine (PCP) and ketamine produce schizophrenia symptoms, including both positive and negative symptoms (Luby et al., 1959; Krystal et al., 1994; Malhotra et al., 1996; Allen and Young, 1978; Abi-Saab et al., 1998; Lahti et al., 2001). The glutamate hypothesis is not inconsistent with an important role of dopamine in the pathogenesis of schizophrenia because there is evidence for interactions between dopamine receptors and NMDA receptors in the hippocampus (Lisman and Otmakhova, 2001) and between glutamatergic afferents and subcortical dopaminergic nuclei (Lisman and Grace, 2005). Neuroreceptor imaging studies demonstrated that treatment with NMDA antagonists produces schizophrenia-like dopaminergic dysregulation in rodents (Miller and Abercrombie, 1996) and humans (Kegeles et al., 2000), supporting the view that dopamine dysregulation in schizophrenia may be secondary to an alteration in glutamatergic transmission (Grace, 1991; Olney and Farber, 1995).

GABA. As described above, the GABAergic interneuron network may have a primary role in the generation of synchronous gamma-band activity. There is

strong evidence for a potential role for GABA in the pathogenesis of schizophrenia, which derives mostly from neuropathologic studies that were pioneered by Francine Benes (Benes et al., 1991) and confirmed in a series of studies by David Lewis and others. The findings summarized in the following are reviewed extensively in Benes and Berretta (2001) and Lewis et al. (2005). One of the most consistent findings in post-mortem studies in schizophrenia is a reduced concentration of glutamic acid decarboxylase (GAD67) – an enzyme that synthesizes GABA – in the parvalbumin-containing subpopulation of inhibitory GABA neurons in the prefrontal cortex (Akbarian et al., 1995; Volk et al., 2000; Knable et al., 2002).

The reduction in GABA synthesis is accompanied by an upregulation of post-synaptic $GABA_A$ receptors in the same brain areas (Volk et al., 2002) and by a decrease in presynaptic GAT1 (Volk et al., 2001), a protein responsible for reuptake of released GABA into nerve terminals. These alterations are likely to be compensatory responses to a more primary deficit in GAD67 mRNA expression. It seems, however, that these pre- and post-synaptic compensatory responses are not adequate to overcome the effects of decreased GABA synthesis in schizophrenia, resulting in impaired perisomatic inhibition of pyramidal cells by parvalbumin-expressing GABA neurons, which in turn may contribute to the reported deficits in gamma-frequency synchronized neuronal activity in schizophrenia (Lewis et al., 2005).

Cholinergic System and Serotonin. In addition, disturbances in the cholinergic system have been associated with schizophrenia, based on evidence for alterations in muscarinic and nicotinic receptor availability or expression in post-mortem studies (Crook et al., 2001; Deng and Huang, 2005; Freedman et al., 1995; Guan et al., 1999), as well as the fact that nicotine is heavily abused by patients with schizophrenia (Olincy et al., 1997), which has sometimes been explained as an attempt at self-medication. Indeed, acute nicotine administration has been shown to improve various cognitive functions in

schizophrenia patients (e.g., Adler et al., 1998; Avila et al., 2004; Harris et al., 2004; Myers et al., 2004; Baldeweg et al., 2006).

Finally, the serotonin (5-Hydroxytryptamine, 5-HT) system is thought to be involved in schizophrenia because the hallucinogen LSD (lysergic acid diethylamide) is a 5-HT antagonist. There is evidence for 5-HT1A and 5-HT2A receptor alterations in schizophrenia (Harrison, 1999a; Burnet et al., 1996), and it is assumed that a high affinity for the 5-HT2A receptor may explain the different therapeutic and side-effect profiles of novel antipsychotics (Meltzer, 1996).

Thus, various neurotransmitter systems appear to be affected in schizophrenia, which likely contributes to the impairments in functional connectivity. However, there is still no clear picture which of these alterations are primary in the pathophysiology of schizophrenia.

Neurodevelopmental Model of Schizophrenia

The etiology and pathophysiology of schizophrenia are not yet clear, but the data reviewed in the above sections have been interpreted as evidence that schizophrenia is a neurodevelopmental disorder in origin. The neurodevelopmental hypothesis maintains that schizophrenia results from an early (pre-, perinatal) disturbance of the development of the brain, with a long latency until the appearance of clinical signs and symptoms (Murray and Lewis, 1987; Weinberger, 1987). The hypothesis is supported by several lines of evidence, such as the neuropathologic findings described above, the evidence for adverse events during the pre- and perinatal periods (reviewed in Lewis and Levitt, 2002), reports of behavioral and cognitive abnormalities in children that develop schizophrenia in adulthood (Jones, 1997), and finally studies showing that experimental neonatal lesions may have delayed effects on relevant behavioral and neurochemical indices (Lipska and Weinberger, 1993; Lipska et al., 1995).

An earlier hypothesis of the pathogenesis of schizophrenia has been the neurodegeneration model, which is based on findings that there is a progression of decreases in cortical volume in schizophrenia patients (DeLisi et al., 2004; Gogtay et al., 2004). However, there is no evidence for neuronal loss and gliosis in schizophrenia, which are the typical signs of neurodegenerative disorders such as Alzheimer's disease or Parkinson's disease. Bartzokis (2002) points out that the two hypotheses are not necessarily exclusive of each other if one takes into account that developmental processes in the normal brain – such as continuing myelination and expansion of white matter volume, as well as decrease of grey matter – extend into middle age (Bartzokis et al., 2001). In schizophrenia patients, an arrest in the process of myelination and an exaggerated decrease of grey matter volume could result in progressive brain structural deficits in the absence of neurodegeneration (Arango and Kahn, 2008).

The question is why the onset of schizophrenia generally occurs in late adolescence or early adulthood, given that structural brain abnormalities are present since early in life and presumably persistent. It has been proposed that late developmental insults, such as aberrant synaptic pruning during adolescence, may be critical for the onset of schizophrenic symptoms (Feinberg, 1982). According to the "Two-hit" model proposed by Keshavan and Hogarty (1999), early developmental insults may lead to dysfunctions of specific neural networks that would account for premorbid signs and symptoms observed in individuals that later develop schizophrenia. At adolescence, excessive elimination of synapses and loss of plasticity may account for the emergence of symptoms (Keshavan, 1999; Keshavan and Hogarty, 1999). A recent study by Uhlhaas et al. (2009b) supports the view that adolescence may be a critical period regarding brain developmental processes. The authors examined neural synchrony in children and adolescents ranging in age from 6 to 21 years, and observed that neural synchronization patterns showed marked changes during adolescence, which suggests a reorganization of cortical networks during this

period. Based on this finding, Uhlhaas et al. (2010) suggest that in schizophrenia, cortical circuits may be unable to support the neural coding regime that emerges during late adolescence, which in turn leads to a breakdown of coordinated neural activity and the emergence of psychosis and cognitive dysfunctions.

Comprehensive models of schizophrenia take into account that both genetic susceptibility, leading to an altered brain development, and environmental events play a role in this disorder. The vulnerability-stress-model of schizophrenic episodes (Nuechterlein and Dawson, 1984b) highlights the role of environmental stressors for the onset of psychotic episodes in vulnerable individuals, and emphasizes that the combination of genetic and environmental factors needs to pass a critical threshold for clinical symptoms to occur. This model also provides a useful heuristic in guiding treatment for the management of schizophrenia: important treatments include medication to reduce biological vulnerability, minimization of substance misuse and environmental stress, enhancement of patients' coping skills, and improved social support (Mueser and McGurk, 2004).

1.4 Synopsis and Overview of Studies

Current theories of schizophrenia propose that cognitive deficits such as impaired perceptual organization represent a core feature of the disorder, and that the pathophysiology of schizophrenia may be the result of a deficit in the coordination of neural activity within and between areas of the brain (Andreasen, 1999a; Friston, 1999; Phillips and Silverstein, 2003). Consistent with these notions, recent studies have provided empirical evidence that schizophrenia is associated with reduced evoked (e.g., Spencer et al., 2003; Wynn et al., 2005) and induced (e.g., Haig et al., 2000; Green et al., 2003) oscillatory activity, as well as with impaired long-range synchronization (e.g., Uhlhaas et al., 2006a) during sensory processing.

However, most of the studies focused on a narrow frequency range ($30 - 60$ Hz). The contribution of high-frequency gamma-band (> 60 Hz) oscillations towards the pathophysiology of schizophrenia is largely unknown. One recent study provided preliminary evidence that impairments in working-memory may be associated with a deficit in high gamma-band activity in early-onset schizophrenia patients (Haenschel et al., 2009).

Furthermore, the majority of studies has been conducted with chronic medicated schizophrenia patients. It is therefore unclear to what extent the observed deficits in neural synchrony are present at the onset of the disorder, and secondly, to what extent the deficits in neural synchrony are present without the confounding influence of neuroleptic medication. There is only one study in unmedicated patients that reported a reduction of the evoked gamma-band response during an auditory oddball paradigm (Gallinat et al., 2004).

As reviewed above, three other studies found a reduction of gamma phase synchrony in medicated first-episode patients, also using an auditory oddball task. Thus, neural synchrony during visual processing has not yet been investigated in first-episode patients, and it remains unknown whether induced, i.e. self-generated, task-related oscillations are impaired at the onset of the disorder.

Regarding induced oscillations during sensory processing in chronic patients, mixed results have been reported, with two studies showing a reduction of induced oscillations in the gamma-frequency band (Green et al., 2003; Haig et al., 2000) during visual and auditory processing, whereas a recent study by Uhlhaas et al. (2006a) observed that induced spectral power ($40 - 70$ Hz) was relatively intact during a Gestalt perception task in chronic patients. Whether induced task-related oscillations during visual processing are impaired in chronic schizophrenia patients remains therefore unclear.

Another important question that has not yet been addressed is related to the sources underlying synchronous oscillatory activity: it is currently unknown

which neural generators underlie the impairments in neural synchrony associated with impaired visual integration in schizophrenia patients. To address this question, it is important to have a thorough understanding of the neural network underlying synchronous oscillations during perceptual organization in healthy subjects, which has not been characterized in detail until now.

Finally, concerning behavioral data on visual integration in schizophrenia, there is consistent evidence for a deficit in perceptual organization in chronic schizophrenia patients (reviewed in Uhlhaas and Silverstein, 2005); it remains unclear, however, whether this deficit is present at the onset of the disorder as mixed results have been reported (e.g., Frith et al., 1983; Silverstein et al., 2006a).

This thesis comprises three studies that addressed these questions: The purpose of the first study (Section 3.1) was to examine the spatio-temporal dynamics of cortical source activity underlying perceptual closure processing in healthy controls. So far, perceptual closure has only been studied with event-related potentials (ERPs), revealing a closure-related ERP component around 250 ms (Doniger et al., 2000). Generators of this component were located in the lateral occipital complex (Sehatpour et al., 2006). In contrast, the role of high-frequency gamma-band oscillatory activity and its neural generators in visual closure tasks have not been examined yet. To explore the functional network underlying perceptual closure processes, we recorded the MEG activity in 15 healthy subjects during a Gestalt perception task (Mooney faces task) and performed source analysis with a beamforming technique over a sequence of successive short time windows to localize high-frequency gamma-band activity. In order to validate the sources obtained with beamforming, we carried out an additional fMRI experiment with 19 subjects using the same visual closure task as in the MEG experiment.

In the second study (Section 3.2), we examined the hypothesis that deficits in perceptual organization in schizophrenia are related to impaired temporal

coordination of neural activity. Specifically, we addressed the question to what extent high-frequency gamma-band activity (> 60 Hz) is impaired in chronic schizophrenia patients, and investigated the sources of impaired gamma-band activity. To this end, we recorded MEG data from 16 medicated patients with chronic schizophrenia and 16 matched healthy controls during the same Gestalt perception task as employed in our first study. MEG data were analysed in a broad frequency band ($25 - 150$ Hz) for evoked and induced spectral power, and a beamforming technique was used to identify the sources of oscillatory activity.

The third study (Section 3.3) aimed to examine to what extent dysfunctional neural synchronization is present at the onset of schizophrenia and without the confounding influence of medication. Here, we recorded MEG data from 19 first-episode neuroleptic-naïve patients with schizophrenia and 20 matched healthy controls during the visual closure task. Again, we analysed the MEG data in a frequency range from 25 to 150 Hz for evoked and induced spectral power and performed source analysis with beamforming.

2 General Methods

2.1 Participants

For the studies reported in this thesis, we examined the following participant groups: a sample of chronic patients with schizophrenia ($N = 16$), recruited from the Department of Psychiatry, Johann Wolfgang Goethe - University Frankfurt, a sample of never-medicated, first-episode patients with schizophrenia ($N = 19$), recruited from the Department of Psychiatry, Cologne University, and two groups of healthy controls ($N = 16$ and $N = 20$), age-matched to the samples of chronic and first-episode schizophrenia patients, respectively. Before testing these clinical participants and their matched controls, we performed a study with a separate group of 15 healthy subjects. All healthy control subjects were recruited from Frankfurt local area. A detailed description of the demographic and clinical characteristics of each group will be given in the respective sections in Chapter 3.

Regarding general criteria for recruitment, we included participants aged at least 18 years without neurological or ophthalmologic disorders that might have affected performance. Participants were excluded if they met criteria for alcohol or substance dependence within the last month, or if they had a psychiatric disorder in the past or exhibited clinical symptoms at present. Finally, subjects with metal implants in the body, e.g. cardiac pacemakers, or with non-removable metallic objects on the body were excluded. Metallic objects would contaminate MEG data and they are strongly prohibited in the

fMRI scanner for safety reasons. All subjects had normal or corrected-to-normal (via contact lenses) visual acuity. Prior to the study, participants were informed about the experiments in oral and written form. All subjects provided informed written consent to the study and were paid for participation. All experiments were approved by the ethical committee of the Johann Wolfgang Goethe - University in Frankfurt.

2.2 General Procedure

Each subject participated in several sessions, including an assessment of psychopathology and cognition, an MEG measurement, an anatomical and – in a subset of participants – a functional MRI scan. Each session lasted approximately 1.5 to 2.5 hours. In the first sessions, we collected demographic data of participants and assessed psychopathology and cognitive function. All testing sessions took place in a quiet, well-lit room in the Department for Psychiatry at the Johann Wolfgang Goethe - University Frankfurt. We conducted a brief interview to collect information about the education, history of psychiatric problems, and other demographic data of participants. Furthermore, participants were administered a standard visual acuity examination (Landolt ring), which involved examining acuity monocularly in each eye, and then binocularly. All subjects completed the Edinburgh handedness inventory (Oldfield, 1971) to measure handedness.

Next, the Structured Clinical Interview for DSM-IV (SCID) (Sass and Wittchen, 2003) was conducted to establish diagnosis of schizophrenia in patients and to screen control subjects for clinical symptoms. In a separate session, psychopathology in patients with schizophrenia was assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987).

Cognitive function in all participants was assessed with the Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe et al., 2004). General intelligence was measured with the "Mehrfachwahl-Wortschatz-Intelligenztest" (MWT)

(Lehrl, 2005).

After the clinical and cognitive testings had been carried out, we conducted an MEG measurement at the MEG unit of the Brain Imaging Centre Frankfurt to measure cortical magnetic fields during a Gestalt perception task. Subjects completed $4 - 6$ runs in the MEG. The entire session, including preparation of the subject, took about 1.5 hours. Finally, subjects participated in an MRI measurement at the Brain Imaging Center Frankfurt. We obtained an anatomical brain scan of most of the subjects; with a smaller group of participants, we also conducted fMRI scans using the same Gestalt perception task as in the MEG experiment. The anatomical scan took about 20 minutes including preparation. The entire session including four functional scans took 1.5 hours. The following sections provide more detailed information about the test batteries and the MEG and fMRI measurements.

2.3 Assessment of Psychopathology and Cognitive Function

As described above, each subject underwent extensive clinical and neuropsychological testing before taking part in the MEG and fMRI experiments. All testing materials were used in a German version.

2.3.1 Psychopathology in Schizophrenia

Psychopathology in schizophrenia patients was assessed with the Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987). The PANSS consists of 30 items, each of which corresponds to a symptom that is rated on a seven-point scale. The different symptoms are assessed with a structured interview which takes about 40 minutes. The interviews with chronic schizophrenia patients were conducted by Dr. Peter Uhlhaas from the Max-Planck-Institute for Brain Research in Frankfurt; the interviews with first-episode schizophrenia patients

were conducted at the Clinic for Psychiatry in Cologne.

The PANSS is based on findings that schizophrenia comprises at least two distinct syndromes: the positive syndrome, consisting of productive symptoms, and the negative syndrome, consisting of deficit features. Traditionally, separate scores are computed from the PANSS for the positive syndrome, the negative syndrome, general psychopathology, and a composite index. Our analysis was based on a more recent model by Lindenmayer et al. (1994), grouping the items into the five factors "positive", "negative", "depression", "excitement", and "cognitive". Chronic schizophrenia patients were additionally rated on the item inappropriate affect (Cuesta and Peralta, 1995) to allow for an assessment of the disorganization factor (for details on the five factor model, see Table A.1 in the Appendix).

2.3.2 Assessment of Cognitive Function

Cognitive function in all participants was measured with the Brief Assessment of Cognition in Schizophrenia (BACS, Keefe et al., 2004). The BACS assesses those aspects of cognition that have been found to be consistently impaired in schizophrenia patients and that have been consistently related to outcome in patients with schizophrenia: verbal memory, working memory, motor speed, attention, executive function, and verbal fluency. The BACS takes about 30 minutes to complete in schizophrenia patients. An overview of the tests is given in the Appendix.

2.3.3 Assessment of General Intelligence

The "Mehrfachwahl-Wortschatz-Intelligenztest" (MWT, Lehrl, 2005) assesses the general level of intelligence, specifically the crystallized general intelligence. The test samples general knowledge retrieved from long-term memory, which places only minor demands on the person's current achievement potential. Therefore, the results of the MWT are hardly influenced by psychological

disorders. The MWT contains words put between or next to meaningless assemblies of letters that are similar in sound. The task of the subject is to find and mark the correct word in each row. The MWT consists of 42 rows with five letter groups each, which are arranged according to the level of difficulty. In healthy controls, the MWT takes only a couple of minutes to complete.

2.4 Visual Closure Task

2.4.1 Mooney Faces Stimuli

Background. To examine perceptual organization, we used a Gestalt perception task – the Mooney faces task –, which is based on the Gestalt principle of closure. Mooney faces are degraded pictures of human faces, in which all shades of gray are removed, thereby leaving the shadows rendered in black and the highlights in white. Perception of Mooney faces involves the grouping of the fragmentary parts into coherent images. These two-tone images were first introduced by Mooney and Ferguson (1951), and then used in a later study to examine the ability of children to form a coherent percept of shape on the basis of very little visual detail (Mooney, 1957). Since then, Mooney face stimuli have been employed in a number of studies to gain insights into the mechanisms and neural correlates of visual closure processes and face perception. It has been shown, for example, that Mooney faces are more difficult to recognize as faces than photographs of faces (Latinus and Taylor, 2006) and that they are typically identified only when presented in the upright orientation (e.g., Andrews and Schluppeck, 2004; George et al., 2005).

Early studies by Cavanagh (1991) and Moore and Cavanagh (1998) addressed the question whether the object recovery of two-tone images is based primarily on bottom-up processes, driven by the extraction of essential features of the image, or alternatively whether it is essentially a top-down process, driven by stored image representations. Moore and Cavanagh (1998) found that the in-

terpretation of two-tone images was possible only when the image depicted familiar objects. They suggested that stored image representations are required for the interpretation of two-tone images and that complex familiar objects are processed primarily holistically, without an initial part-based analysis.

Dolan et al. (1997) showed that pre-exposure to original gray-level images facilitated the recognition of Mooney images of faces and objects, supporting the view that the perception of Mooney faces is a conjoint function of sensory input interacting with memory processes. Kemelmacher-Shlizerman et al. (2008) addressed the question from a mathematical perspective using algorithms to extract shape from shading information. Monocular gray-level and color images contain various cues from which a 3D shape can be inferred, including perspective cues, texture distribution, bounding silhouettes, and shading cues. In Mooney images, however, the main low-level information that remains is shading, although even these cues are degraded and extremely ambiguous. The authors found that a unique 3D percept of shape from a Mooney image cannot be retrieved from two-tone shading cues alone, but that algorithms using prior knowledge of faces work well on the impoverished images. Thus, they concluded that the recognition of Mooney images is guided primarily by top-down processes in which prior knowledge plays a crucial role.

Studies using fMRI and EEG have examined the neural correlates of visual closure and face processing in the Mooney faces task. FMRI studies have shown that Mooney faces activate known face-selective regions such as the fusiform face area (FFA, Andrews and Schluppeck, 2004; Kanwisher et al., 1998; McKeeff and Tong, 2007). The above study by Dolan et al. (1997) used fMRI to measure brain activity during perceptual learning of Mooney images and found that learning-facilitated perception of Mooney faces was linked to enhanced activation in the fusiform gyrus and also in memory-related parietal regions such as the precuneus. A recent study provided evidence that 3D structure from shading cues are primarily processed in the caudal inferior

temporal gyrus (Georgieva et al., 2008).

EEG studies have shown that upright Mooney faces elicit the well-known face-specific N170 component, a negative component around 170 ms over temporal electrodes (Latinus and Taylor, 2005, 2006; George et al., 2005), albeit with a smaller amplitude than for photographic faces (Latinus and Taylor, 2006). The usual inversion effect seen with photographic faces (delayed and larger N170) is not seen with Mooney faces, suggesting that Mooney faces are primarily processed holistically and that Mooney faces lack individual facial features that could be processed analytically when the image is turned upside down in order to perceive the face. Rodriguez et al. (1999) examined neural synchrony during the processing of upright and inverted Mooney faces and found that visual closure was correlated with a significant increase in the synchronization of gamma-band activity between parietal-occipital and fronto-temporal regions as measured by phase-locking values.

Stimulus Material for the Present Studies. In the present studies, we used a set of 160 different stimuli, consisting of the 40 original Mooney stimuli presented in an upright manner, mirrored at the vertical axis and in corresponding versions mirrored at the horizontal axis (Fig. 2.1).

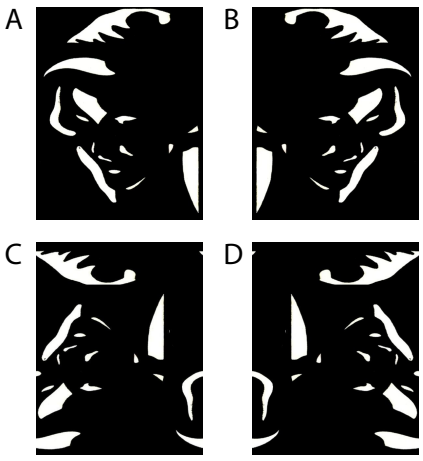

Figure 2.1. Examples of upright (A), upright-mirrored (B), inverted (C) and inverted-mirrored (D) Mooney face stimuli.

The inverted stimuli were additionally scrambled by moving single contiguous white or black foreground patches across the black or white background areas, respectively. This scrambling ensured that no faces were perceived in the inverted stimulus condition. Importantly, upright and inverted-scrambled stimuli were matched with respect to low-level stimulus properties such as luminance and spatial frequencies. Luminance of the white stimulus parts was 1140 cd/m^2 and of the black stimulus parts 30 cd/m^2.

2.4.2 Stimulus Presentation

For the MEG experiments, the stimuli were displayed in the center of a translucent screen at a viewing distance of 53 cm and subtended 19 degrees of visual angle. The background of the screen was set to gray (145 cd/m^2). An LCD projector located outside the magnetically shielded room of the MEG was used to project the stimuli onto the screen via two front-silvered mirrors. Stimulus presentation was controlled using the Presentation software package (version 11, Neurobehavioral Systems, Inc.). For the fMRI section of the study, the stimuli were delivered through MR-compatible liquid crystal display goggles.
The timing of presentations for the MEG experiment was such that each image appeared for 200 ms, followed by a black fixation cross in the center of a grey screen. The duration of the inter-stimulus interval (ITI) varied randomly between 3500 and 4500 ms (Fig. 2.2).
In the first study (Section 3.1), we aimed to examine the differences in brain activity between the face and the non-face condition in healthy controls. Each run therefore contained an equal number of upright and inverted stimuli (45 upright and 45 inverted stimuli) which were presented randomly intermixed. Each participant completed six runs, and the duration of each run was approximately 6.5 minutes. In the clinical studies (Sections 3.2 and 3.3), the procedure was changed a little because patients were not able to accomplish six runs and stay concentrated during the task. Thus, only four runs were con-

ducted with patients and the matched healthy control participants. In order to ensure a sufficient number of trials in the upright face condition for data analysis – despite the reduced number of runs –, we increased the number of upright Mooney stimuli relative to the inverted-scrambled condition such that each run contained 60 upright and 30 inverted stimuli. The duration of each run was 6.5 minutes as in the first experiment. We opted to focus on the face condition in the clinical studies because we were primarily interested in the comparison of brain activity underlying the integration of stimulus elements into a coherent percept between schizophrenia patients and healthy controls.

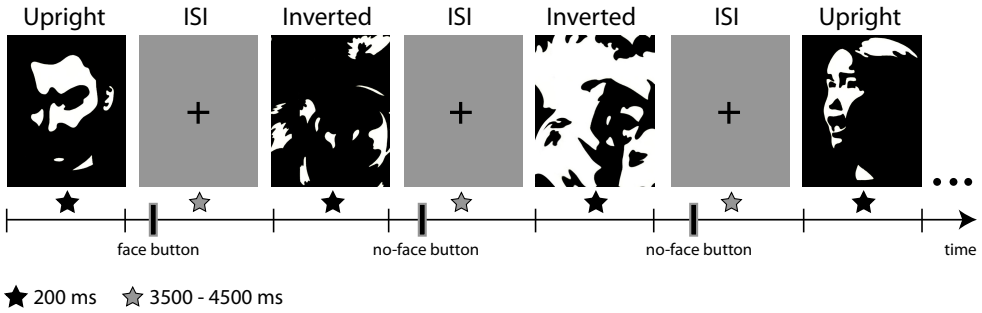

Figure 2.2. Timing of stimulus presentation. Upright and inverted-scrambled stimuli were presented in a random sequence. Each stimulus was presented for 200 ms, and the inter-stimulus interval varied randomly between 3500 and 4500 ms. Subjects indicated whether a face was shown or not after each stimulus via button press.

For the fMRI experiment, we employed a rapid event-related fMRI design, using the same stimuli and timing as in the MEG recordings, except for the following changes: each of the four fMRI runs consisted of 111 trials, being composed of a random number of face, non-face and fixation trials. A two-back randomization procedure ensured that the order of presented stimuli was balanced within runs in each subject. Each trial was 4 s long, consisting of 200 ms stimulus duration and a fixed ITI of 3800 ms, where the fixation cross was presented. The stimulus was either an upright Mooney face, an inverted-scrambled Mooney face, or just the fixation cross. Thus, the duration of the interval between successive Mooney stimuli presentations was at least the length of the fixed ITI (3800 ms), which was followed by a random

number of fixation trials from the interval $1 - 4$. Including these fixation trials provided the jitter between face and non-face presentations necessary for rapid event-related fMRI: the jitter allows the time course of hemodynamic responses to such stimuli to be derived from the temporally overlaid responses by deconvolution techniques. Each run began and ended with an eight second fixation period. The duration of each run was approximately 7.5 min. Subjects performed an anatomical scan and four fMRI runs within one scanning session.

2.4.3 Task

Subjects were required to indicate whether they detected a face or not via button press after each stimulus. They were instructed to respond as quickly and accurately as possible and to keep fixation on the central fixation cross during the ITI. In order to control for motor responses, half of the subjects pressed one button with their right index finger when they detected a face and another with their left index finger when they did not; for the other half of subjects the buttons were reversed.

2.5 MEG and FMRI Recordings

2.5.1 MEG Data Acquisition

Subjects first removed all metallic objects (e.g., jewelry, belt, keys etc.) and changed into MEG-suitable clothes. Prior to the recordings, the task and the measurement procedure were explained, and the participant performed a practice run to become familiar with the stimuli and the response buttons. Subjects were seated in a magnetically shielded room. MEG data were recorded continuously using a 275-channel whole-head system (Omega 2005, VSM MedTech Ltd., BC, Canada) at a rate of 600 Hz in a synthetic third order axial gradiometer configuration (Data Acquisition Software Version 5.4.0, VSM MedTech

Ltd., BC, Canada). Behavioral responses were recorded using a fiberoptic response pad (Lumitouch, Photon Control Inc., Burnaby, BC, Canada) on the stimulus PC and fed through to the MEG acquisition system as an additional channel. Before and after each run, the subject's head position relative to the gradiometer array was measured using coils placed at the subject's nasion, and 1 cm anterior to the tragus of the left and right ear. Runs with a head movement exceeding 5 mm were discarded. Cushions were used to stabilize subjects' heads inside the MEG helmet. Eye movements were recorded with six electrodes placed at the outer canthi of the right and left eye to record horizontal eye movements, below and above the left eye to record vertical eye movements, and on the forehead for ground and reference.

2.5.2 FMRI Data Acquisition

Subjects first removed all metallic objects. We placed vitamin E capsules at the nasion and 1 cm anterior to the tragus of the left and right ear to facilitate coregistration with the MEG recordings. Vitamin E capsules contain fat and can therefore easily be recognized in the anatomical scan. The task and the measurement procedure were explained before placing the subject in the scanner. The subject was made familiar with the response box and the alarm ball for emergency cases. Structural and functional MRI scans were acquired on a 3-T Siemens Allegra scanner (Siemens, Erlangen, Germany) using the standard CP birdcage coil. Functional images were acquired using a T2*-weighted echo planar imaging (EPI) sequence sensitive to blood oxygenation level-dependent (BOLD) contrast (repetition time TR = 1000 ms, echo time TE = 30 ms, and flip angle 60°). 18 axial slices covering occipital, parietal, frontal lobes and the posterior part of the temporal lobe were collected (field of view FOV = 220 mm, in-plane resolution 3.3 mm × 3.3 mm, slice thickness 5 mm, and gap thickness 0.5 mm). These slices did not cover the anterior inferior temporal cortex and the inferior frontal cortex. Each functional run

was preceded by eight volumes that were discarded to allow for magnetization to reach a stable state. A 3D MPRAGE sequence (160 slices, voxel size 1 mm $\times$ 1 mm $\times$ 1 mm, FOV = 256 mm, TR = 2300 mm, and TE = 3.93 ms) was used to obtain high-resolution anatomical images. These anatomical images were used to coregister and display functional data and to create individual headmodels for MEG source reconstruction.

3 Experimental Series

3.1 Neuroelectromagnetic Correlates of Perceptual Closure Processes[1]

3.1.1 Introduction

An important ability of human vision is the recognition of objects even when only incomplete visual information is available. The Gestalt principle of closure refers to the perception of an object which is not completely or immediately represented (Mooney, 1957; Snodgrass and Feenan, 1990). Perceptual closure has often been studied using fragmented pictures of geometric figures and event-related potentials (ERPs) to outline the timing of neural processes underlying closure. Doniger et al. (2000) found a closure-related ERP component that was present over occipito-temporal electrodes between 230 and 400 ms. Source analyses localized the underlying neural generators in the lateral occipital complex (LOC) (Sehatpour et al., 2006), which has been related to object recognition (e.g., Malach et al., 1995; Grill-Spector et al., 1998). As reviewed in Section 1.2, there is a large body of evidence that oscillatory activity in the gamma-frequency range is correlated with the perception of coherent objects (Tallon-Baudry and Bertrand, 1999). Most EEG gamma-band studies have focused on lower gamma-band frequencies (< 60 Hz); however,

[1] This section is based on the manuscript entitled "Neuroelectromagnetic correlates of perceptual closure processes" by C. Grützner, P. J. Uhlhaas, E. Genc, A. Kohler, W. Singer and M. Wibral, which has been submitted for publication in the Journal of Neuroscience.

recent MEG and intracranial EEG studies have shown that oscillations in the high-frequency gamma-band (> 60 Hz) are reliable markers of cortical activity during a variety of cognitive tasks (e.g., Kaiser et al., 2004; Lachaux et al., 2005; Hoogenboom et al., 2006; Vidal et al., 2006; Siegel et al., 2007; Guggisberg et al., 2008).

The present study examined the role of high-frequency gamma-band activity recorded with MEG during perceptual closure, using a visual closure task (Mooney faces task) that consists of two-tone face images (Mooney and Ferguson, 1951). As mentioned in the previous chapter, Mooney faces provide 3D structure from shading cues as the only low-level visual features, which are processed in the caudal inferior temporal gyrus (Georgieva et al., 2008). However, the recognition of Mooney faces cannot be based on shading cues alone, but is guided by top-down processes (Kemelmacher-Shlizerman et al., 2008) such as object familiarity (Dolan et al., 1997; Moore and Cavanagh, 1998) and memory processes (Dolan et al., 1997) represented in posterior parietal cortex (Wagner et al., 2005). In addition, there is evidence that Mooney faces activate face-selective areas such as the fusiform face area (Kanwisher et al., 1998; Andrews and Schluppeck, 2004; McKeeff and Tong, 2007). We therefore expected to find closure-related activation in these brain regions. The spatio-temporal dynamics at the level of cortical sources underlying perceptual closure has not been studied yet; thus, we reconstructed the underlying dynamic network of neural generators with time-resolved beamformer source analysis and additionally performed fMRI to further validate source localization.

3.1.2 Methods

Subjects

Fifteen healthy volunteers (11 females; mean age 25.4 years ± 5.6 SD) participated in the MEG experiment. 19 subjects (8 females; mean age 23.5 years ± 2.6 SD) participated in the fMRI part of our study. All subjects were right-

handed as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971) and had normal or corrected-to-normal visual acuity. All subjects gave written informed consent prior to the experiment. The study was approved by the local ethics committee (Johann Wolfgang Goethe - University, Frankfurt).

Stimuli and Recordings

We used the Mooney task during MEG and fMRI recordings as described in Section 2.4. Subjects completed six runs in the MEG, and four runs in the fMRI scanning session. Details on the MEG and fMRI recordings can be found in Chapter 2.

Data Analysis

MEG Data Analysis. MEG data were analyzed using the open source Matlab toolbox Fieldtrip (version 2008-12-08; http://www.ru.nl/fcdonders/fieldtrip/). For data preprocessing, data epochs were defined from the continuously recorded MEG signals from -1000 ms to 1000 ms with respect to the onset of the visual stimulus. Data epochs were sorted according to the two experimental conditions, the face condition, containing trials with upright stimuli, and the non-face condition, containing trials with inverted-scrambled stimuli. Only data epochs with correct responses were considered for all further analyses, i.e., hits for the face condition and correct rejections for the non-face condition. Data epochs contaminated by eye blinks, muscle activity or jump artifacts in the sensors were discarded using automatic artifact detection and rejection routines from the Fieldtrip toolbox. Data epochs were baseline-corrected by subtracting the mean amplitude during an epoch ranging from -500 to -100 ms before stimulus onset.

We performed three analyses: first, we analyzed event-related magnetic fields (ERFs) to identify a MEG-ERF analogue of the perceptual closure index (Ncl) observed in previous EEG-ERP studies (Doniger et al., 2000). Second, we

analyzed task-related changes in spectral power associated with perceptual closure at the sensor-level. This analysis served to determine the frequencies of interest for later source analysis and to demonstrate closure-related effects at the sensor-level. Third, and most important to the aim of our study, the electrical generators of these spectral components of interest were localized in the brain using a frequency domain beamformer (DICS – dynamic imaging of coherent sources; Gross et al., 2001) as implemented in Fieldtrip on successive short time windows. We used DICS to estimate local source power (formula (5) in Gross et al., 2001), not source coherence estimates, which would be the typical use of this method. Therefore we constrained the analysis to real-valued spatial filters, to reflect instantaneous linear mixing from sources to sensors; this latter constraint is dropped when DICS is used to image source power that is coherent to an external reference (e.g. the electromyogram signal) and coupling with a delay is expected.

Event-Related Fields. ERFs were obtained by averaging the segmented trials in the time range between −500 and 500 ms separately for each subject in each condition. For each subject, the ERF to non-faces was subtracted from the ERF to faces to assess the amplitude and the latency of the event-related activity associated with closure processes. We tested the obtained ERFs for effects of activation versus baseline and differences between conditions in the interval from 200 to 350 ms using randomization testing with a cluster-based threshold correction method (Maris and Oostenveld, 2007) to correct for multiple comparisons. A cluster p-value below 5 % (two-tailed testing) was considered significant. Source analysis for event-related fields was performed with minimum norm estimation (Hämäläinen et al., 1993) for the time interval between 250 and 300 ms. Normalized leadfields and the same headmodel as in the beamforming analysis (see below) were used. The regularization parameter was 5 %. We performed a randomization test with $p < 0.01$ (uncorrected) for statistical testing of minimum norm estimates.

Analysis of Event-Related Spectral Power Changes at the Sensor-Level. Time-frequency representations (TFRs) were computed by means of Morlet wavelets with a width of 5 cycles per wavelet at center frequencies between 25 and 150 Hz, in 1 Hz steps. Time-frequency transformations were computed in a time window of −500 ms pre-stimulus to 500 ms post-stimulus. We tested the obtained time-frequency transformations for effects of activation (50 ms to 350 ms) versus baseline (−350 ms to −50 ms) and for differences between conditions in the interval between 50 ms and 350 ms using the same randomization testing and cluster-based threshold correction method (Maris and Oostenveld, 2007) that was also used for the ERF analysis. Again, a cluster p-value below 5 % (two-tailed testing) was considered significant. In addition, we performed a correction for multiple comparisons using the false discovery rate (FDR, $q < 0.05$; Genovese et al., 2002). A frequency window for the beamformer source analysis of the generators of oscillatory sensor-level signals was chosen by inspecting the time-frequency transformation for significant task-related effects that lasted for at least 200 ms.

Reconstruction of the Sources of Oscillatory Sensor-Level Components. We used a frequency domain beamformer (DICS, Gross et al., 2001) at the frequencies of interest that had been identified at the sensor-level. Beamformers are spatial filters that project sensor activity to specified source locations in the brain using a linearly weighted sum of the sensor signals. Source power from a given location is reconstructed with unit gain while interference from all other source locations is suppressed as much as possible. As beamformer source analysis exhibits a bias for erroneously high power values for the center of the head, source power values have to be normalized appropriately. This is typically achieved by comparing the source power of interest from the task interval to that obtained from a corresponding baseline interval (dual state beamforming; see Huang et al., 2004, and references therein).

We performed DICS beamformer analyses for a sequence of overlapping, short

intervals (duration 200 ms; onsets at every 50 ms from 0 to 450 ms). We decided to perform time-resolved beamforming to examine power differences between conditions because sensor-level analysis of condition-specific spectral power changes had revealed transient effects with a duration on the order of $100 - 200$ ms. The center frequency for DICS was 80 Hz. The cross-spectral density matrices were computed using the multi-taper method (Percival and Walden, 1993) with four Slepian tapers (Slepian, 1978), which lead to a spectral smoothing of 20 Hz. To compensate for the short duration of the data windows, we used a regularization of $\lambda = 5$ % (Brookes et al., 2008). The baseline interval for comparison in dual state beamforming was chosen from -350 ms to -150 ms before stimulus onset.

To investigate differences in source power between faces and non-faces, we computed DICS filters for combined data epochs ("common filters") consisting of activation (duration 200 ms; onsets at every 50 ms from 0 to 450 ms) and baseline data (-350 to -150 ms) for each analysis interval. Our analysis thus covered a total time interval from 0 to 650 ms. Computing common filters for task and baseline data later enabled a statistical test of the hypothesis that source power is changed by a stimulus. In contrast, when computing separate sets of filters for task and baseline, the hypothesis to be tested is that either source power changes or beamformer filters differ between task and baseline because of a changing number of active sources between task and baseline (Nieuwenhuis et al., 2008). We then projected the sensor data through these common filters for each trial, separately for task and baseline. Next, we computed a within-subject randomization test statistic (pseudo-t) based on these single trial data. We thus obtained a test statistic for activation versus baseline effects for each grid point, each subject and each condition. The values of this test statistic were subjected to a second-level randomization test at the multi-subject level to obtain group-wise effects of differences between conditions; a p-value < 0.01 was considered significant. The main focus of

the beamforming analysis was the time-resolved reconstruction of sources of differential activity, as described above. In addition, we analysed task vs. baseline effects for each condition at 80 Hz between 50 and 350 ms.

The set of potential source locations, i.e. the source grid, was constructed as follows: first, we overlaid a regular three-dimensional dipole grid with an isotropic spacing of 10 mm on the T1 template of the SPM2 toolbox (http://www.fil.ion.ucl.ac.uk/spm), provided by the Montreal Neurological Institute (MNI, Montreal, Canada; http://www.bic.mni.mcgill.ca/brainweb). Next, we transformed each individual subject's anatomical MRI onto this template using the linear transformation from SPM2 and recorded each subject's individual transformation matrix. Then we warped the regular dipole grid with the inverse of each individual transformation matrix. Thus, we obtained specific dipole grids for each subject, enabling us to perform beamformer source analysis with individual headmodels. The corresponding forward solution (leadfield) for each subject was computed using its individual dipole grid and a realistic single-shell volume conductor model (Riera and Fuentes, 1998; Nolte, 2003). Importantly, each location of the dipole grid in MNI space had a unique corresponding grid location in each subject. This enabled multi-subject statistics over corresponding anatomical locations in each subject.

FMRI Data Analysis. FMRI data were analyzed using the Brain Voyager QX software package (version 1.10.3, Brain Innovation, Maastricht, The Netherlands). The first four volumes of each event-related run were discarded to preclude T1 saturation effects. Pre-processing of the functional data included motion correction, linear trend removal to remove baseline drifts, temporal high-pass filtering at 0.01 Hz to remove slow fluctuations in the BOLD signal time course, and slice scan-time correction. Spatial smoothing was performed with a Gaussian filter with a 6 mm kernel for the group analysis. For each subject the functional and structural 3D datasets were normalized to Talairach space (Talairach and Tournoux, 1988). The BOLD signal time courses for the

different experimental conditions were estimated using a deconvolution analysis (Burock et al., 1998; Glover, 1999). Twenty predictors were defined for each condition to cover the temporal extent of a typical hemodynamic response. For statistical analysis, a multi-subject fixed-effects general linear model was computed on the three peak time points of the BOLD signal. Linear contrasts of faces minus non-faces were computed to identify closure-related activity. Coordinates for activated clusters were tabulated and converted to MNI space (Collins, 1994) for comparison with MEG source locations by means of the WFU pick-atlas (Maldjian et al., 2003) and the Jülich histological atlas (Eickhoff et al., 2007) provided by FSL (http://www.fmrib.ox.ac.uk/fsl).

3.1.3 Results

Performance

We analyzed the percentage of correct responses as well as reaction times in correct trials for the face and the non-face conditions. Paired t-tests were computed to test the behavioral data for significance. The performance accuracy did not differ significantly between the face and the non-face condition (faces correct: mean = 81.13 %, SD = 5.84; non-faces correct: 82.47 % ± 14.32 SD; $t(14) = -0.28$; $p = 0.78$). Reaction times were significantly longer in the non-face condition (faces RT: 723.81 ms ± 131.6 SD; non-faces RT: 801.07 ms ± 144.19 SD; $t(14) = -3.39$; $p = 0.004$).

Event-Related Fields

To assess closure-related activity, we computed the difference between ERFs in the face and in the non-face conditions between 200 and 350 ms after stimulus onset. Differences were most pronounced between 250 and 300 ms (Fig. 3.1 E, middle row). These differences were observed bilaterally at sensors over lateral occipital and temporal cortex. Potential sources of these differences were localized in temporal (middle and superior temporal gyrus), parietal (precuneus,

inferior parietal lobule) and occipital brain areas (Fig. 3.1 E, bottom row).

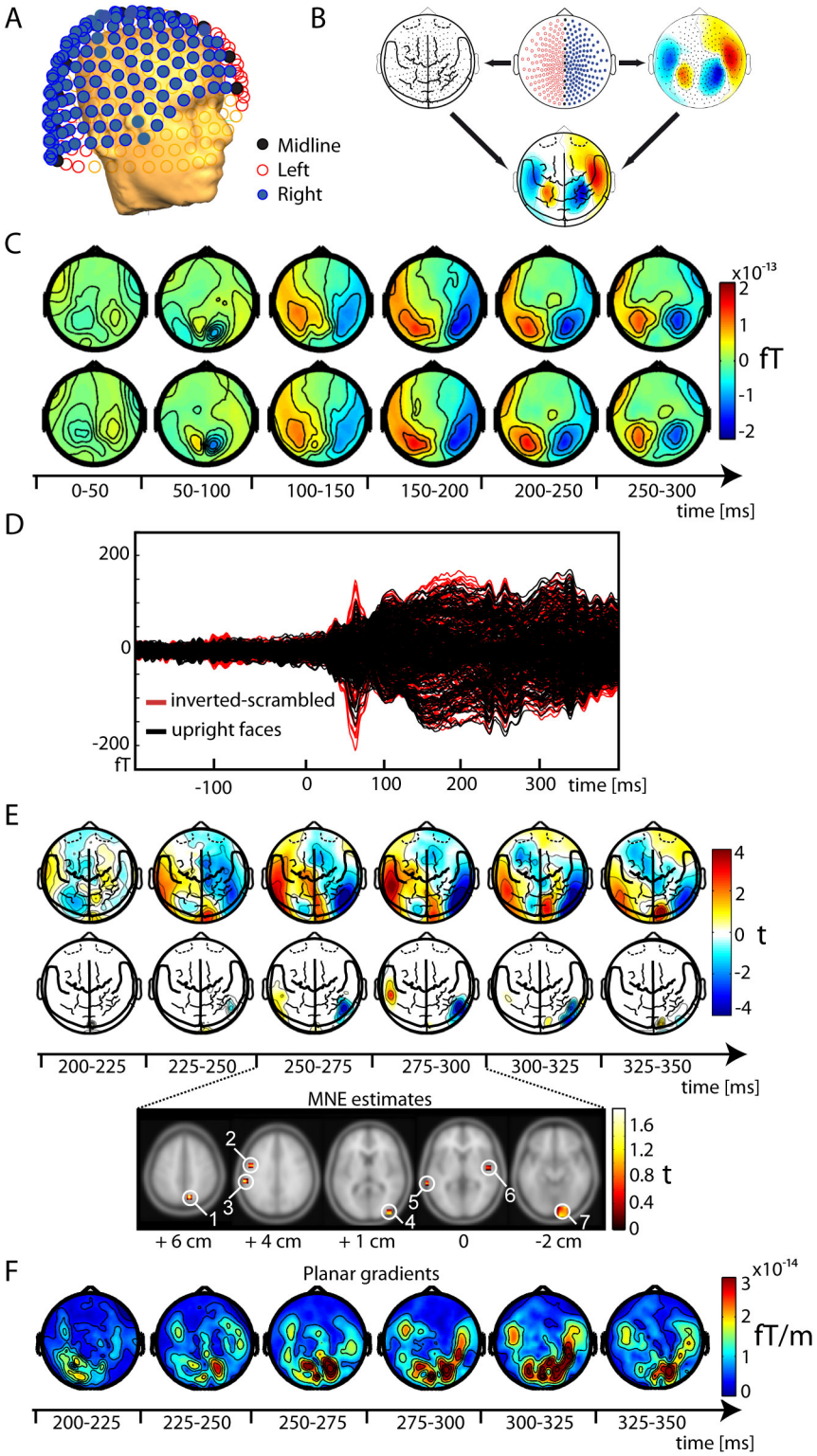

Figure 3.1. Event-related fields.

Figure 3.1. Event-related fields. (A) 3D-arrangement of the 275 MEG sensors around the subject's head. (B) Plotting conventions for 2D sensor-level topographies. Upper row, center: all sensors are plotted inside a schematic top view of the head (colors refer to the 3D plot in (A)). Coregistration between a reconstructed 2D topography of the major anatomical landmarks of the brain (upper row, left) (Kaiser et al., 2002) and the sensor positions (upper row, right). Bottom row: Interpolated sensor-level topographies coregistered with the major anatomical landmarks via sensor positions. This display type is used for the remainder of this study. (C) Raw, baseline-corrected event-related field topographies for the face (upper row) and the non-face (bottom row) conditions. (D) Corresponding event-related fields traces for all sensors; red: non-face condition, black: face condition. (E) Significant differences between event-related magnetic fields in the face minus the non-face condition. Upper row: Sensor-level topographies of t-values over time. Middle row: Sensor-level topographies masked by a statistical significance mask ($p < 0.05$ corrected). Bottom row: Statistical differences between the face and non-face conditions for MNE source amplitude estimates ($p < 0.01$, uncorrected) for signals averaged from 250 to 300 ms. White circles indicate significant clusters; cluster 1: precuneus (Talairach coordinates: 10, −66, 49); cluster 2: precentral gyrus (−48, 3, 28); cluster 3: inferior parietal lobule (−59, −29, 33); cluster 4: middle occipital gyrus (−42, −87, 14); cluster 5: middle temporal gyrus (−67, −39, 2); cluster 6: superior temporal gyrus (54, −10, −1); cluster 7: lingual gyrus (16, −94, −5). (F) Absolute of the planar gradient of raw field differences between face and non-face conditions.

Event-related Spectral Power Changes on Sensor-Level

Time-frequency spectral power was analyzed in a broad frequency band ($25 - 150$ Hz), including both the low-frequency ($25 - 60$ Hz) and the high-frequency ($60 - 150$ Hz) gamma bands. For the presentation of upright Mooney stimuli, we found increases in event-related spectral power in a cluster of parieto-occipital sensors (Fig. 3.2 A, top panel). These effects were present both in the lower and higher gamma band. Time- and frequency-resolved analysis revealed transient broadband effects at latencies around 50 and 250 ms post-stimulus onset, most likely related to stimulus-locked activity in response to onset and offset (at 200 ms) of the visual stimulus. In addition, we found sustained significant increases in event-related spectral power in a more confined frequency band from 60 to 100 Hz in the interval from approximately 100 to 300 ms (Fig. 3.2 A, bottom panel, left). Significant decreases in event-related spectral power were found at a cluster of frontal and central sensors (Fig. 3.2 A, top panel). This cluster was dominated by power changes in the

lower gamma-frequency range at latencies starting around 150 ms and lasting till the end of the analysis interval (Fig. 3.2 A, bottom panel, right). Event-related changes in spectral power for inverted Mooney stimuli (Fig. 3.2 B) were similar in time and frequency to those found for upright Mooney stimuli.

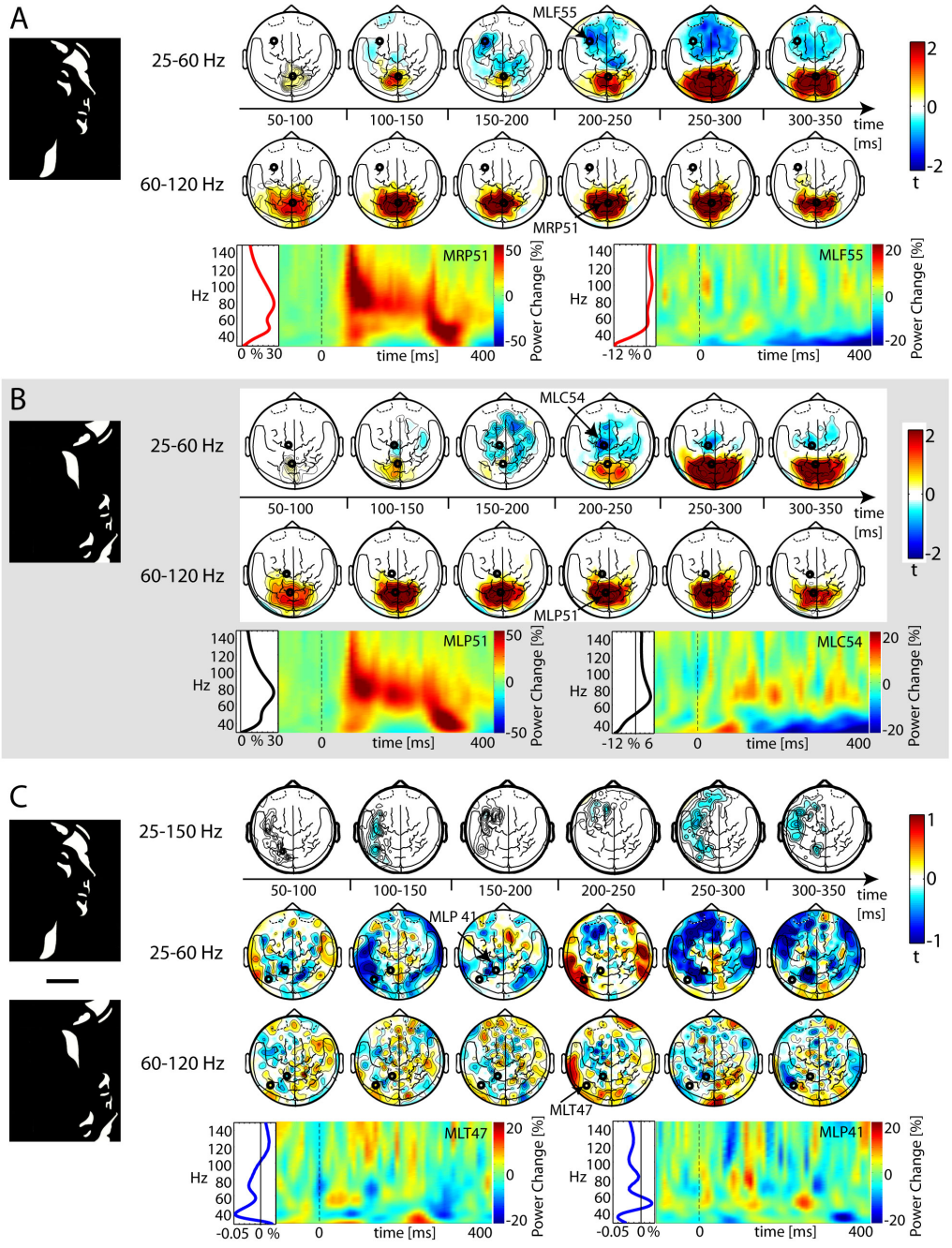

Figure 3.2. Time-frequency transformations and statistical analysis of power changes in response to upright and inverted Mooney faces.

Figure 3.2. Statistical analysis of power changes in response to upright Mooney faces (A), inverted Mooney faces (B), and for the difference between upright and inverted stimuli (C). All data represent grand averages across all subjects. The upper part of each panel shows the temporal evolution of the topography of the statistical analysis; below, each panel contains power spectra and time-frequency representations (TFRs) for specific sensors. Topographies: (A, B) Significant differences between the respective Mooney stimulus condition and the 0.5 s pre-stimulus baseline, separately for the lower ($25 - 60$ Hz) and the higher ($60 - 120$ Hz) gamma-band. The effect is masked by the spatiotemporal pattern of the two significant clusters that resulted from the nonparametric cluster-based test. Red denotes the positive cluster (higher activation during stimulus presentation compared to baseline) and blue denotes the negative cluster (less activation during stimulus presentation compared to baseline). (C) Significant differences between the face and the non-face condition. Top row: power differences masked by the significant cluster that resulted from the nonparametric cluster-based statistical testing. Blue denotes higher activation for the non-face condition compared to the face condition. The middle and the bottom row of panel (C) show the same topography as the top row, but masked by the significance map derived from false-discovery rate (FDR, $q < 0.05$) statistical testing, tested together but plotted separately for the lower (middle row) and higher (bottom row) gamma-band. Power spectra and TFRs: power spectra and TFRs are shown for the sensors with the most pronounced positive and negative effects. These sensors are marked by black circles in the topographic plots. In panels (A) and (B), the effect is expressed as percent change of the power in the post-stimulus window compared to baseline. In (C), channel MLT 47 represents the channel with the strongest positive effect of the difference between the face and the non-face condition (face > non-face), whereas channel MLP 41 is the channel with the strongest negative effect of the difference between the face and the non-face condition (face < non-face). The power spectra are shown as a function of frequency ($25 - 150$ Hz), averaged for the time window between 0 and 400 ms. The TFRs are plotted for the frequency range between 25 and 150 Hz, and the time interval between -100 to 400 ms. The dashed lines indicate stimulus onset.

For faces compared to non-faces, we found a significantly stronger decrease in event-related power at fronto-central sensors at latencies from 200 to 350 ms (Fig. 3.2 C, top panel, upper row). This effect was dominated by power changes in the lower gamma frequency range. In other words, both conditions induced task-related power decreases at these sensors, latencies and frequencies; the decrease was significantly stronger in the face condition. This effect was the only effect reaching significance at the level of a cluster-based threshold. When using FDR ($q < 0.05$) to correct for multiple comparisons, a more diverse picture emerged (Fig. 3.2 C, middle and bottom rows). While we found a complex pattern of significant changes over sensors, latencies and frequencies, its main features can be described as follows: between 200 and 250 ms, i.e. in

the interval where the perceptual closure index was found in EEG studies, there was significantly higher event-related spectral power in the lower and higher gamma-frequency band at temporal-occipital sensors for the face compared to the non-face condition. In the time intervals from 100 to 150 ms and from 250 ms to the end of the analysis interval, we found a significantly stronger power decrease for the face compared to the non-face condition at frontal and temporal sensors.

Beamformer Source Analysis

The source analysis for the face and the non-face conditions as compared to baseline revealed very similar patterns (Fig. 3.3). In both conditions, source power was strongly enhanced in parietal regions such as the precuneus and the supramarginal gyrus. Furthermore, we found clusters of enhanced source power in the inferior frontal gyrus (IFG), the precentral gyrus, and the superior temporal gyrus (STG) in both conditions. The non-face condition showed additional activations in the middle occipital gyrus and the anterior cingulate.

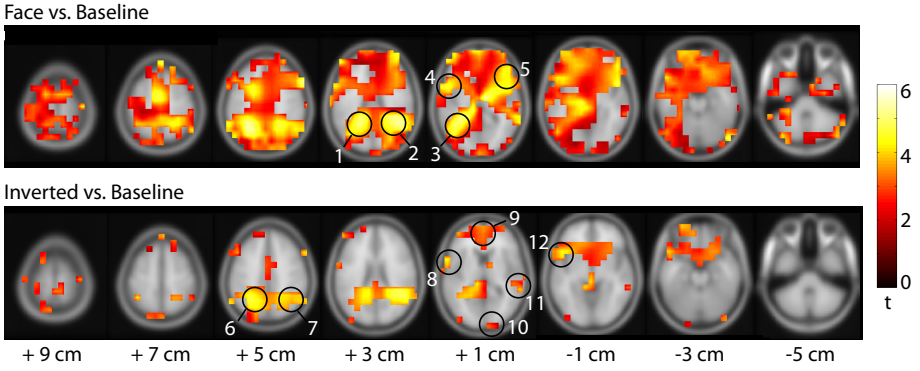

Figure 3.3. Source power at 80 Hz for the face and the non-face condition (t-values masked by $p < 0.05$, corrected). In both conditions, we found enhanced source power for the task compared to baseline, mainly in parietal and frontal areas. 1: inferior parietal lobule/precuneus (−22, −60, 40); 2: supramarginal gyrus/precuneus (50, −54, 30); 3: superior temporal gyrus (STG) (−40, −54, 10); 4: precentral gyrus (−52, 8, 12); 5: inferior frontal gyrus (IFG) (48, 36, 10); 6: precuneus (−16, −58, 32); 7: supramarginal gyrus (48, −54, 30); 8: precentral gyrus (−58, 2, 17); 9: anterior cingulate (8, 54, 2); 10: middle occipital gyrus (18, −98, 10); 11: STG (64, −34, 12); 12: IFG (−42, 20, 2).

As mentioned above, the main focus of this study was the time-resolved re-

construction of sources of differential activity. To this end, source power was estimated for a sequence of short, overlapping intervals in the high-frequency gamma-band (60 – 100 Hz). Fig. 3.4 shows the differences in reconstructed source power between faces and non-faces, and Table 3.1 lists the corresponding anatomical locations as coordinates in MNI space.

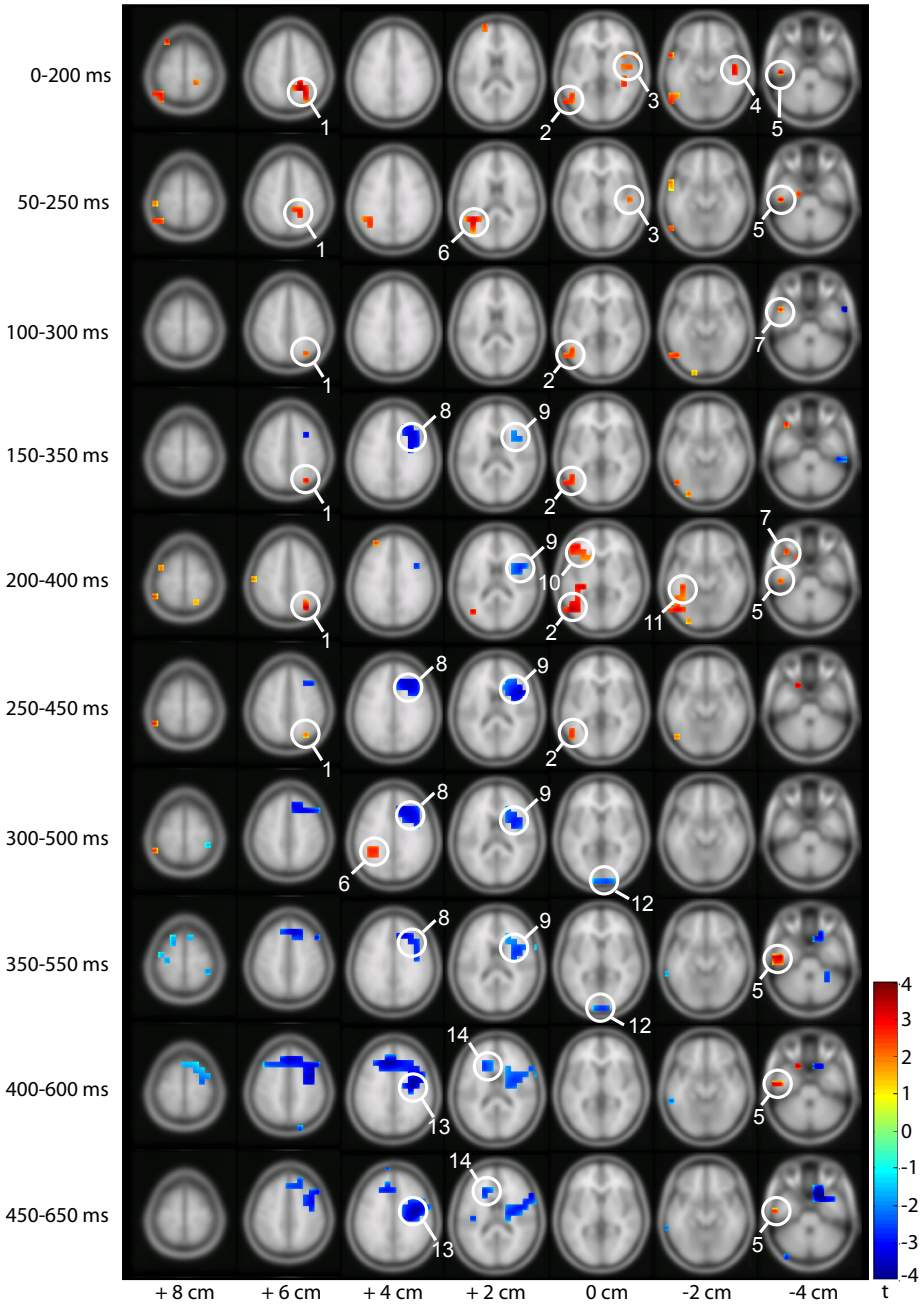

Figure 3.4. Differences in source power at 80 Hz between the face and the non-face condition.

Figure 3.4. Differences in source power at 80 Hz between the face and the non-face condition (t-values masked by $p < 0.01$, uncorrected). Time intervals are plotted from top to bottom, consecutive brain slices are plotted from left to right for each time interval (slice distance 20 mm) in neurological convention. Each cluster is marked on one slice per time interval, with the circles representing the center of each cluster ($1 - 14$). Red clusters represent stronger source power for faces; blue clusters represent stronger source power for non-faces (t-values masked by $p < 0.01$, not corrected). 1: superior parietal lobe (SPL); 2: caudal inferior temporal gyrus (cITG); 3: superior temporal gyrus (STG); 4: right anterior inferotemporal cortex (aIT); 5: left aIT; 6: angular/supramarginal gyrus; 7: orbitofrontal cortex (OFC); 8: middle frontal gyrus (MiFG); 9: right inferior frontal gyrus (IFG); 10: left IFG; 11: fusiform face area (FFA); 12: primary visual cortex; 13: premotor cortex; 14: cingulate gyrus. The coordinates for all clusters are given in Table 3.1.

In the first time intervals (onset times from 0 to 150 ms), source power was predominantly stronger in the face condition compared to the non-face condition (red clusters, numbers $1 - 7$, 10 and 11). Enhanced source power for faces was observed in parietal regions, more specifically in the right superior parietal lobule (SPL)/precuneus and the left angular/supramarginal gyrus. Furthermore, occipital-temporal cortex showed enhanced activation for the face condition in the left LOC/cITG. Finally, regions in the temporal lobe including the right superior temporal gyrus (STG), and left and right anterior inferotemporal cortex (aIT) were more strongly activated for faces compared to non-faces.

In the time interval between 150 and 350 ms, there were two clusters in the right frontal cortex – one in the middle frontal gyrus (MiFG) and the other one in inferior frontal gyrus (IFG) – with stronger activation for the non-face compared to the face condition (blue clusters 8, 9).

During the time interval where the perceptual closure index was found in EEG studies ($200 - 400$ ms, "closure interval"; Doniger et al., 2000), we observed enhanced activity for faces compared to non-faces in the left cITG; this cluster also extended to the fusiform gyrus (fusiform face area, FFA). Furthermore, there was enhanced activity for faces in the left inferior frontal gyrus (IFG) and also in the left aIT. FFA and left IFG were activated more strongly for faces specifically during the closure interval, whereas the aIT showed enhanced activation for faces during almost all time windows. As in the preceding time

interval, the right IFG showed stronger activation for non-faces compared to faces.

During later time intervals (onset times from 250 to 450 ms), the activation pattern shifted from primarily enhanced activation for faces to primarily enhanced activation for non-faces. The main clusters showing enhanced source power for non-faces were located in the right frontal cortex, more specifically in the MiFG, in the IFG and also in the premotor cortex. Additional clusters with stronger activation for non-faces were found in primary visual areas between $300 - 500$ ms and $350 - 550$ ms and in the anterior cingulate gyrus between $400 - 600$ ms and $450 - 650$ ms.

Table 3.1. MNI coordinates and anatomic locations for the sources of high-gamma activity (face condition – non-face condition)

	MEG			FMRI			
Cluster	x	y	z	x	y	z	Anatomic Location
1	27	−60	51	33	−62	52	superior parietal lobule/precuneus
2	−50	−69	−4	−49	−69	−10	caudal ITG/LOC
3	50	−13	−5	53	−14	−4	superior temporal gyrus
4	54	−16	−20	–	–	–	anterior inferotemporal cortex
5	−52	−16	−30	–	–	–	anterior inferotemporal cortex
6	−40	−53	33	−40	−57	34	angular/supramarginal gyrus
7	−36	21	−31	–	–	–	orbitofrontal cortex
8	37	22	37	34	30	42	middle frontal gyrus
9	40	19	17	–	–	–	inferior frontal gyrus
10	−44	36	0	–	–	–	inferior frontal gyrus
11	−40	−46	−10	−41	−49	−15	fusiform gyrus
12	2	−100	−2	−6	−98	4	primary visual cortex
13	44	2	39	−39	−24	48	premotor cortex
14	−13	29	24	−9	27	27	cingulate gyrus

FMRI Data

In order to obtain an independent measure of the brain regions that were differentially activated for the face and non-face condition, we repeated the same experiment with fMRI. Overall, there was a very close correspondence between the MEG source locations and regions showing differential activation in fMRI (Fig. 3.5, Table 3.1). In the fMRI data, however, we found bilateral activa-

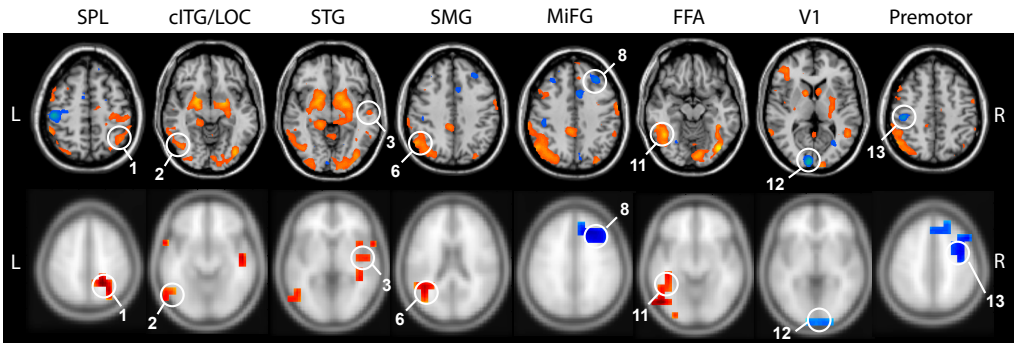

Figure 3.5. Differential activation maps for faces minus non-faces, overlaid on the structural image of one subject at a statistical threshold of $q < 0.05$ (FDR, corrected). Orange voxels showed greater activation for faces than non-faces, whereas blue voxels showed greater activation for non-faces than faces. Clusters corresponding to fMRI (top row) and MEG (bottom row) source locations are marked with white circles; the numbers refer to the clusters in Table 3.1 and in Fig. 3.4. The clusters 4 (right aIT), 5 (left aIT), 7 (OFC), 9 (right IFG) and 10 (left IFG) are missing because these areas were not covered during the functional MRI scans.

tion for most areas (except for the MiFG and the premotor cortex), whereas the MEG source reconstructions showed mostly clusters lateralized to only one hemisphere. This might be due to differences in analysis techniques because MEG beamformer filters tend to misplace or suppress correlated sources (Huang et al., 2004; Hillebrand et al., 2005), which in combination with thresholding might mask certain sources. The cluster in the premotor cortex was located in the right hemisphere in the MEG data, but in the left hemisphere in the fMRI data. We did not cover the IFG and the temporal pole in the fMRI experiment, meaning that it was a priori not possible to find fMRI activations in these regions. Therefore, we cannot draw any conclusions about a correspondence between MEG and fMRI activations regarding these areas (clusters 4, 5, 7).

3.1.4 Discussion

In the present study, we examined the spatio-temporal dynamics underlying perceptual closure using MEG recordings, time-resolved beamforming and cross-validation of source localization by fMRI. Our data provide evidence

that distributed neural generators in occipito-temporal, parietal and frontal areas are involved in high-frequency gamma-band activity ($60-100$ Hz) in the processing of Mooney images.

Upright and inverted Mooney stimuli elicited sustained spectral amplitude increases in the high-frequency gamma band ($60-100$ Hz) that were present for the entire stimulus duration, suggesting that the network relevant to our task operated predominantly in the high-gamma frequency range. Human EEG studies have shown that coherent object representations are associated with increases in gamma-band activity (for reviews see Tallon-Baudry and Bertrand, 1999; Keil et al., 2001), but effects in these studies were mainly in the lower gamma-band (< 60 Hz). Compatible with our findings, however, recent MEG and intracranial EEG studies demonstrated gamma-band responses between 60 and 200 Hz during a variety of cognitive tasks (e.g., Crone et al., 2001; Kaiser et al., 2004; Brovelli et al., 2005; Lachaux et al., 2005; Hoogenboom et al., 2006; Siegel et al., 2007; Guggisberg et al., 2008), suggesting that oscillations in the high-gamma frequency range (> 60 Hz) might be important to cortical function in general.

The comparison between upright and inverted Mooney stimuli at the sensor-level revealed a complex pattern, with differences rapidly changing over frequencies, sensors and time. Even though closure-specific effects showed a strong variation over time and were found over many different channels, there was a pronounced enhancement of gamma-band activity for faces in a time window between 200 and 300 ms at occipito-temporal sensors. This finding agrees with a previous EEG study on neural synchronization during the perception of Mooney faces, showing that spectral power in the gamma-band differentiated between the perception and the non-perception of a face around 230 ms (Rodriguez et al., 1999). The time range and the topography of closure-related oscillatory activity in the present study also correspond well with the timing of the perceptual closure index found in EEG studies (Doniger et al., 2000;

Sehatpour et al., 2006) and to the ERFs in the present study. The complex pattern of differences between upright and inverted Mooney stimuli suggests that the network underlying perceptual closure comprises a large number of different sources that are difficult to interpret at the sensor-level.

The analysis of the sources underlying perceptual closure revealed a network of distributed sources in occipito-temporal, parietal and frontal regions, which were differentially activated during specific time intervals. In early time ranges ($0-200$ ms), activity was predominantly enhanced for faces, mainly in parietal and occipito-temporal areas. The activation in occipito-temporal areas was located in cITG, and in the aIT. Georgieva et al. (2008) demonstrated that cITG is activated when a 3D object is reconstructed from shading cues. Our finding of stronger activation in cITG for Mooney face stimuli supports our initial hypothesis that the extraction of 3D shape cues provided by shading (Kemelmacher-Shlizerman et al., 2008) is indeed essential for the perception of Mooney faces.

Furthermore, we found enhanced source power for faces in the aIT, which has been related to face processing (Kriegeskorte et al., 2007; Tsao et al., 2008). The aIT cluster in our data was located more posterior compared to the activation observed by Kriegeskorte and colleagues; this discrepancy could be due to inaccuracies in MEG beamforming or fMRI localization near the petruous bone. Kriegeskorte and colleagues proposed that FFA detects faces and engages aIT for identification. In the current data, however, the aIT cluster was activated throughout almost all time intervals, and even before activation of the FFA, suggesting that it either plays a more general role in face processing or that information about individual faces is used very early and throughout the processing of Mooney faces to aid the detection of faces.

Enhanced activation for faces in parietal areas was located in the SPL / precuneus in the right hemisphere and in the angular / supramarginal gyrus in the left hemisphere. Activation in posterior parietal cortex has been implicated in

memory processes, especially in matching sensory input to long-term memory (e.g. in old versus new decision tasks; Wagner et al., 2005). The medial parietal cortex (precuneus) has been related to memory-related imagery; it has been proposed that the precuneus reflects the "mind's eye" during reconstruction of object (or face) representations from fragmentary evidence (Fletcher et al., 1995; Dolan et al., 1997). Our findings support the view that memory-related processes play a critical role for the perception of Mooney faces. We suggest that during the early stages of Mooney face processing, shape-processing areas in cITG interact with parietal areas related to retrieval of face templates from memory. Further studies assessing effective connectivity will be necessary to substantiate this hypothesis.

During the closure interval ($200 - 400$ ms), the activation in cITG extended medially to the fusiform gyrus if a face was perceived. The fusiform gyrus is well known to be involved in face processing (e.g., Kanwisher et al., 1997). Thus, at the time of closure, the interaction between shape-processing areas (cITG) and category-specific areas (fusiform gyrus) seems to be required for object identification. An additional cluster in the left IFG showed enhanced activation for faces specifically in the closure interval, suggesting that the IFG is involved in perceptual closure processes. This interpretation is in line with a recent study that investigated perceptual recognition processes with fMRI and found that activation of the IFG was related to the moment of recognition (Ploran et al., 2007).

Interestingly, in time windows succeeding the closure interval (window centers at 350 ms and later), activation was predominantly enhanced for inverted stimuli, mainly in frontal regions located in the IFG, MiFG, and premotor cortex. It has been shown that the frontal lobe is activated during cognitively demanding tasks (Duncan and Owen, 2000). This stronger frontal activation for inverted stimuli may represent increased cognitive demand, assuming that subjects try to detect a face in each picture. Additionally, we observed stronger

activity in the premotor cortex for inverted compared to upright stimuli in this later time interval. This finding could be related to the fact that subjects had significantly longer reaction times in the inverted condition. Primary visual cortex also showed stronger activation for inverted compared to upright stimuli in the later task phases, which could reflect the re-access of early visual memory traces in order to use low-level cues for the reconstruction of a face. The stronger activation could also reflect increased attention.

The localization of closure-related brain areas in the present study is consistent with numerous studies on object recognition that demonstrated a widespread distribution of sources in inferior temporal, parietal and frontal regions (Dolan et al., 1997; Lachaux et al., 2005; Gruber et al., 2008; Martinovic et al., 2008). Our findings suggest that high-frequency gamma oscillations as recorded by MEG allow a reliable reconstruction of perceptual closure processes with high spatio-temporal resolution. However, source locations obtained from MEG beamforming alone should not be taken to represent the true locations with zero error. This is because beamforming is limited by the ill-posed inverse problem (e.g., de Peralta Menendez and Andino, 1998) and will also fail in the presence of sources that are highly correlated over the time-frequency window of interest (e.g. van Veen et al., 1997), leading to missing or mislocalized sources. This limitation applies even when statistical tests are performed because source locations may be systematically biased.

Here, we tried to alleviate this problem by independently estimating sources of differential activity from fMRI data using the same visual closure task. This approach was motivated by the correlation between high-frequency oscillatory activity and BOLD fMRI signals (Logothetis et al., 2001; Brookes et al., 2005; Niessing et al., 2005). For those source locations that were covered by fMRI we found a close match between source locations obtained from beamforming and fMRI (Table 3.1). Interestingly, sources did not only match in location but also with respect to the sign of the differences between the two conditions.

Therefore, we are confident that the reported MEG source locations are close to the actual neural generators for the sources covered by fMRI. It is unclear at present why some bilateral fMRI sources were only unilaterally reported in MEG. Possible reasons include statistical thresholding and extinction or mislocalization of source power due to inter-source correlation. Hence, statements on the lateralization of the processes of interest are not warranted by the current dataset.

Conclusion

The present study examined the mechanisms of visual closure processing at an unprecedented level of spatial and temporal detail combining fMRI and a time-resolved MEG beamforming approach. The reconstruction of the neural generators of high-frequency gamma-band activity revealed closure-related activity in a distributed network of sources in occipital-temporal, parietal and frontal brain areas. In early task phases ($0-200$ ms), there was a coactivation of cITG – a region related to processing of 3D structure from shading cues – and regions in PPC that have been related to activation of long-term memory templates. At the time of perceptual closure ($200-400$ ms), the activation in cITG extended to the fusiform gyrus if a face was perceived, suggesting that the perceptual closure index is related to activation in inferior temporal cortex areas specialized for the perceived object. Thus, the present study suggests that perceptual closure is based on an early interaction of object recognition and memory-related areas.

3.2 High-Frequency Gamma Oscillations during Perceptual Organization in Chronic Schizophrenia Patients[2]

3.2.1 Introduction

Current theories of the pathophysiology of schizophrenia have focused on abnormal temporal coordination of neural activity in cortical circuits as a core impairment of the disorder (Andreasen, 1999a; Friston, 1999; Phillips and Silverstein, 2003). Oscillations in the gamma-band range (> 25 Hz) are of particular interest as they establish synchronization with great precision in local cortical networks (Gray et al., 1989; Womelsdorf et al., 2007). Research has so far particularly focussed on the contribution of oscillations in the $30 - 60$ Hz frequency range as an explanation for the cognitive deficits in schizophrenia (Cho et al., 2006; Haig et al., 2000; Kwon et al., 1999; Spencer et al., 2003, 2008; Uhlhaas et al., 2006a). As reviewed in Section 1.2, there is increasing evidence that high-frequency gamma-band activity (> 60 Hz) may be important for cortical computations – in addition to the lower gamma-band range. However, it is currently unclear to what extent high-frequency gamma-band activity is disturbed in schizophrenia. Furthermore, little is known about the neural generators that underlie the impairments in neural synchrony in schizophrenia.

To address these issues, we examined oscillatory activity in the $25 - 150$ Hz frequency range with MEG in a sample of medicated patients with chronic schizophrenia and a group of healthy control participants. As in our previous study, Mooney faces were presented to test perceptual organization. In addition to the analyses of oscillatory activity over MEG sensors, we employed a

[2]This part contains adapted sections of the manuscript entitled "Deficits in High-Frequency (> 60 Hz) Gamma Oscillations during Perceptual Organization in Chronic Schizophrenia" by C. Grützner, M. Wibral, W. Singer, K. Maurer, and P. J. Uhlhaas, which is being prepared for publication.

beamforming approach to identify the cortical generators of oscillatory activity in both patients and controls. We expected that chronic schizophrenia patients were impaired in their ability to detect Mooney faces, reflecting dysfunctional perceptual organization. Furthermore, we expected that this behavioral impairment would be accompanied by reduced neural synchrony as indexed by reduced evoked and induced spectral power in both the lower and the high-frequency gamma-band. Based on the results of our first study (Fig. 3.4), we hypothesized that source power would be reduced in parietal areas and in the inferior temporal cortex in chronic patients compared to controls.

3.2.2 Methods

Participants

Sixteen medicated patients with chronic schizophrenia were recruited from in- and out-patient units from the Frankfurt University Psychiatry Department. Sixteen healthy controls were recruited from the local community and screened for psychopathology with the German version of Structured Clinical Interview for DSM-IV-R Non-Patient Edition (SCID, Sass and Wittchen, 2003). Written informed consent was obtained from all participants following a description of the study procedures. DSM-IV diagnosis of schizophrenia was established with the SCID, by thorough chart review and in consultation with the treating psychiatrists. Patients and controls were excluded if they had any neurological or ophthalmologic disorders or if they met criteria for alcohol or substance dependence within the last month. Current psychopathology was assessed with the Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987). The symptoms were grouped into the factors “positive”, “negative”, “depression”, “excitement”, “cognitive”, and “disorganization” (Lindenmayer et al., 1994; Cuesta and Peralta, 1995).

Demographic information for patients and controls is given in Table 3.2. Patients with schizophrenia and healthy controls were of similar age and educa-

tion. No differences between groups were found for premorbid verbal IQ and handedness. Cognitive function in patients and controls was measured with the Brief Assessment of Cognition in Schizophrenia (BACS, Keefe et al., 2004). Compared to healthy controls, schizophrenia patients had lower scores on all scales of the BACS (verbal memory, digit sequencing, motor speed, verbal fluency and symbol coding) except for the tower of London test (Table 3.2).

Table 3.2. Demographic, cognitive and clinical characteristics of healthy controls and chronic schizophrenia patients

		Controls ($N = 16$)		Patients ($N = 16$)		Statistics	
		Mean	SD	Mean	SD	χ^2-/t-value	p-value
Gender (m/f)		8/8		11/5		$\chi^2(1) = 0.52$	0.47
Age (years)		34.19	10.56	38.25	9.38	$t(30) = -1.15$	0.26
Education (years)		15.33	3.11	14.43	2.95	$t(27) = 0.80$	0.43
Handedness		69.22	31.45	71.80	25.35	$t(29) = -0.25$	0.80
MWT		30.67	2.85	28.47	3.16	$t(28) = 2.00$	0.06
BACS	Verbal memory	52.00	7.51	36.13	13.22	$t(28) = 4.04$	0.0004
	Digit sequencing	25.13	3.96	20.13	4.12	$t(28) = 3.39$	0.0021
	Motor speed	88.80	9.28	75.73	11.44	$t(28) = 3.43$	0.0019
	Verbal fluency	58.67	14.05	40.47	9.93	$t(28) = 4.10$	0.0003
	Symbol coding	57.21	10.24	45.93	16.38	$t(27) = 2.20$	0.036
	Tower of London	19.73	2.28	18.33	2.82	$t(28) = 1.49$	0.15
	Total score	298.47	31.58	236.73	41.95	$t(28) = 4.55$	0.0001
PANSS	Negative	–	–	18.13	5.60		
	Excitement	–	–	6.31	1.82		
	Cognitive	–	–	10.25	3.45		
	Positive	–	–	9.25	3.59		
	Depression	–	–	12.75	3.47		
	Disorganisation	–	–	5.69	2.44		

Stimuli and Recordings

The Mooney faces task (Mooney and Ferguson, 1951) was used to study perceptual organization in chronic schizophrenia patients and healthy controls. In the present study, each run in the MEG comprised 60 upright and 30 inverted-scrambled Mooney stimuli. As we were primarily interested in the face condition, the number of upright Mooney stimuli was increased relative

to the inverted-scrambled condition to ensure a sufficient number of upright trials for the MEG beamforming analysis. Patients and controls performed four runs in the MEG. In addition, we obtained an anatomical scan from most of the participants that was used for the source analysis of the MEG data (for details on the task and the recordings, refer to Chapter 2).

Data Analysis

MEG Data Processing. As in the previous study, MEG data were analyzed using the Fieldtrip open source Matlab toolbox. Trials were defined from the continuously recorded MEG from −1000 ms to 1000 ms with respect to the onset of the visual stimulus and classified according to the two experimental conditions, the face condition, containing trials with upright stimuli, and the non-face condition, containing trials with inverted-scrambled stimuli. Only data with correct responses were considered for all further analyses, i.e., hits in the face condition and correct rejections in the non-face condition. Data epochs contaminated by eye blinks, muscle activity or jump artifacts in the SQUIDs were discarded using automatic artifact detection and rejection routines provided by the Fieldtrip software and were baseline-corrected by subtracting the mean amplitude during an epoch ranging from −500 to −100 ms before stimulus onset.

Analysis of Sensor-Level Spectral Power Changes. Time-frequency representations (TFRs) were computed by means of Morlet wavelets with a width of 5 cycles per wavelet at center frequencies between 25 and 150 Hz, in 1 Hz steps. For a statistical analysis of the changes in gamma-band power, we focused on the face condition and carried out three tests: first, we tested changes in gamma-band power within each group and compared the raw power during stimulus presentation (50 to 350 ms post-stimulus) to the raw power during baseline (−350 to −50 ms pre-stimulus) using dependent-samples t-tests. Next, we compared gamma-band power between controls and patients for the

interval between 50 and 350 ms post-stimulus using an independent-samples t-test. This between-group analysis was computed on absolute power difference values, that is, the raw baseline power was subtracted from the raw task power for each subject. All statistical tests were computed for the frequency range of $25 - 140$ Hz and included all channels. We used the false discovery rate (FDR, Genovese et al., 2002) with a criterion of $q < 0.05$ to correct for multiple comparisons. Due to the lower number of trials in the non-face compared to the face condition, we did not compare activation between the two conditions in this experiment. However, we conducted a preliminary analysis on the non-face condition computing the same contrasts as for the face condition (within-group task vs. baseline analyses and between-group comparison of task-related activation). Results for the non-face condition are included in the Appendix.

For a more detailed analysis of the modulation of gamma-band activity in the face condition, we computed timecourses of absolute gamma-band power for patients and controls by averaging over the significant channels of each group. To determine significant channels, the t-values given by the statistical analysis were first multiplied with the significance mask that contains zeros for all non-significant time-frequency-channel samples, and ones for all significant samples; this way we obtained a matrix where all t-values unequal zero were statistically significant. This matrix was then averaged across the time and frequency range used in the statistical analysis (50 to 350 ms and 25 to 140 Hz). To determine the channels showing on average a significant increase ("positive" channels) or decrease ("negative" channels) in power, we set a threshold of $t > 0$ (positive channels) and $t < 0$ (negative channels).

Reconstruction of the Sources of Oscillatory Sensor-Level Components. To localize the sources underlying oscillatory activity, we used a linearly constrained minimum variance (LCMV) beamformer (van Veen et al., 1997). This technique estimates the source power for each voxel in the brain by construct-

ing an adaptive spatial filter that connects each voxel with the MEG sensors. The spatial filter at each cortical location is constructed such that the sensitivity to a source at the target location is maximised, while the total output power of the filter is minimised. We first divided each subject's brain volume into a regular 10 mm dipole grid. For the computation of the forward model, we used a realistic single-shell volume conductor model (Nolte, 2003). The head shape was derived from each individual subject's structural MRI and aligned to the MEG data.

To compute the data covariance matrix, we first filtered the data in the low ($25 - 60$ Hz) and high ($60 - 120$ Hz) gamma-band frequency ranges. For each of the two frequency ranges, the covariance matrix was then computed for all face trials, for both patients and controls, separately for baseline (-350 to -50 ms) and activation epochs (50 to 350 ms). The covariance matrices for baseline and activation epochs were averaged to allow for the computation of common filters. Computing common filters for task and baseline data later enabled a statistical test of the hypothesis that source power is changed by a stimulus. In contrast, when computing separate sets of filters for task and baseline, the hypothesis to be tested is that either source power changes or beamformer filters differ between task and baseline because of a changing number of active sources between task and baseline (Nieuwenhuis et al., 2008). Source power was subsequently estimated for each grid location by projecting the sensor data through the common filters for each trial, separately for task and baseline.

For a statistical analysis of the source power, we normalized individual source reconstructions to MNI space (Montreal Neurological Institute, Montreal, Quebec, Canada) using SPM2 (http://www.fil.ion.ucl.ac.uk/spm). Three statistical tests were carried out, analogous to the sensor-level statistical analyses. First, we compared task and baseline source power within each group, using dependent-samples t-tests. Then, we compared task-related source power between controls and patients, using an independent-samples t-test. Again, the

between-group analysis was based on absolute power difference values for each subject, that is, the raw baseline power was subtracted from the raw task power for each subject. Voxel-wise t-values were corrected with FDR ($q < 0.05$) to control for multiple comparisons.

We excluded four subjects from the source analysis, two controls and two patients, because sensor-level power spectra revealed a 50 Hz contamination in these subjects. While an offset due to sustained 50 Hz contamination does not affect the analysis of the raw (absolute) power differences at the sensor level, it can corrupt the results of beamformer source analysis, as the 50 Hz signal will influence the overall filter computation and therefore have an effect at all frequencies. This may lead to shifted source locations. We therefore decided to exclude datasets with slightly elevated power at 50 Hz from the beamformer source analysis. In addition, three patients had to be excluded from the source analysis because we did not have any anatomical data from these patients. Thus, statistical tests were carried out with 14 control subjects and 11 chronic patients. Finally, in the description of source results and their interpretation, we did not include activations in deep brain structures, such as the thalamus, because it is currently unclear whether MEG-based source reconstruction techniques are suited to study deep brain structures.

3.2.3 Results

Performance

We analysed the percentage of correct responses as well as reaction times for the face and the non-face condition (Table 3.3). Furthermore, we computed the discrimination index A' (Grier, 1971), which is a non-parametric measure of signal detection sensitivity that is based on both hits and false alarms (FA, inverted-scrambled stimuli classified as faces). A' ranges from 0.5 for chance performance (50 % hits and 50 % false alarms) to 1 for perfect signal detection sensitivity (100 % hits with no false alarms). A' was used instead of the

Table 3.3. Performance in healthy controls and chronic patients

	Controls ($N = 16$)		Patients ($N = 16$)		Mean difference	
	Mean	SD	Mean	S.D.	t-value	p-value
Hits (%)	80.59	6.67	74.03	10.78	$t(30) = 2.07$	0.047
Correct rejections (CR) (%)	86.59	11.09	84.87	9.33	$t(30) = 0.48$	0.64
Discrimination index A'	0.91	0.04	0.88	0.03	$t(30) = 2.09$	0.046
Reaction time (hits) (ms)	610.04	78.3	688.19	85.45	$t(30) = -2.70$	0.01
Reaction time (CR) (ms)	754.38	86.40	792.08	112.23	$t(30) = -1.06$	0.30

parametric index d' because A' is more robust against violations of the assumption that the variances of the hypothetical distributions are equal (Donaldson, 1993) and A' does not suffer from the indeterminacy of d' that occurs in the absence of false alarms (Mohr and Linden, 2005).

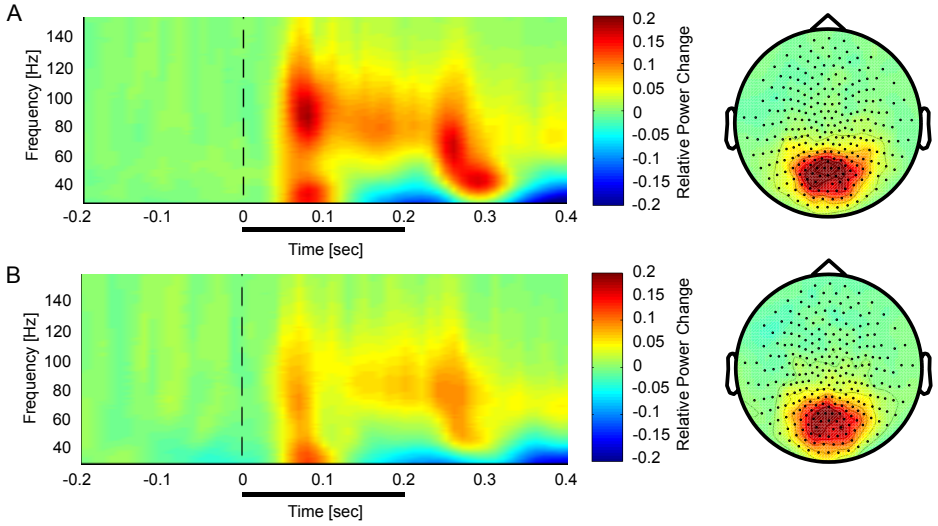

Figure 3.6. Time-frequency representations (TFRs) and topographies of gamma-band spectral power in the face condition for controls (A) and chronic schizophrenia patients (B). The TFRs represent the average across all channels. The dashed vertical line marks stimulus onset. The topographies are averaged across the stimulus interval ($0 - 400$ ms) and between 25 and 150 Hz. The gamma-band signal is expressed as relative power change in the post-stimulus time window compared to baseline. In chronic schizophrenia patients, there is a marked reduction in spectral power, especially in the sustained response in the high-gamma frequency range ($60 - 120$ Hz).

Chronic schizophrenia patients detected significantly fewer faces than controls ($t(30) = 2.07$, $p = 0.047$) and had longer reaction times ($t(30) = -2.07$, $p = 0.01$). No differences were found for behavioural performance in the non-

face condition (correct responses: $t(30) = -1.06$, $p = 0.3$; reaction times: $t(30) = 0.48$, $p = 0.64$). The significant difference between groups in A' ($t(30) = 2.09$, $p = 0.046$) confirmed that controls had a superior discrimination performance compared to patients.

MEG Gamma-Band Power on Sensor-Level

In controls, gamma-band activity was characterised by an increase between 50 and 350 ms after stimulus onset with two prominent gamma-band peaks around 50 ms and 250 ms in the $25 - 140$ Hz frequency range (Fig. 3.6).

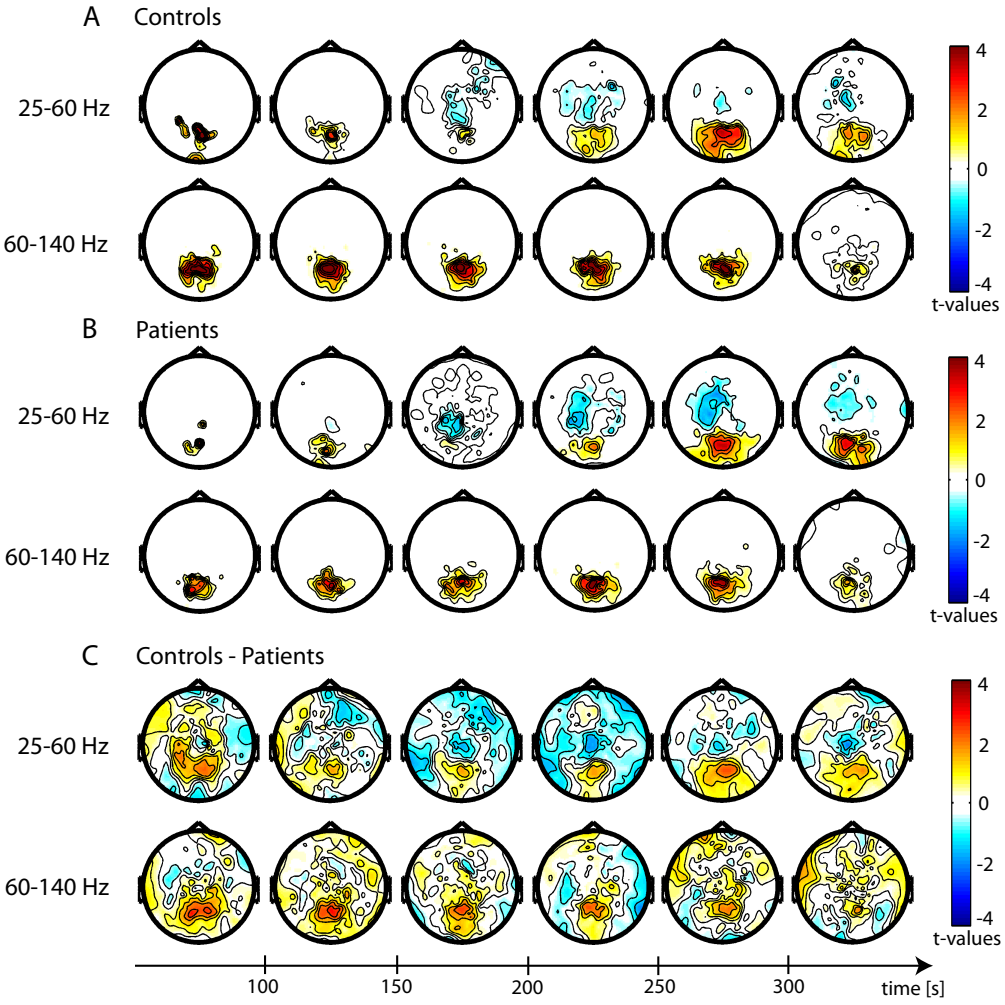

Figure 3.7. Statistical analysis of gamma-band power for controls and chronic schizophrenia patients.

Figure 3.7. Statistical analysis of gamma-band power in response to upright Mooney faces for controls (A), chronic schizophrenia patients (B), and for the difference between controls and patients (C). The topographies in (A) and (B) show significant differences between the face condition and the baseline, separately for the lower ($25 - 60$ Hz) and the higher ($60 - 140$ Hz) gamma-band. The effect is masked by the significance map derived from false-discovery rate (FDR, $q < 0.05$) statistical testing. Red denotes higher activation during stimulus presentation compared to baseline, whereas blue denotes less activation during stimulus presentation compared to baseline. The topographies in (C) show the difference for the face condition between controls and patients. Here, red denotes stronger activation for controls compared to patients, whereas blue represents stronger activation in patients relative to controls.

We observed sustained gamma-band activity between 100 and 300 ms, mainly in the high-frequency range between 60 and 120 Hz. A similar pattern of activity was found in the non-face condition (Fig. A.1 in the Appendix). The statistical analysis revealed a significant increase in low- and high-frequency gamma-band activity over parieto-occipital channels between 50 and 350 ms that was accompanied by a significant reduction in power over fronto-central sensors in the low-frequency gamma-band range between 150 and 300 ms (Fig. 3.7 A). Compared to controls, schizophrenia patients were characterised by significant reductions of task-related low and high-frequency gamma-band activity over parieto-occipital sensors that were present from 50 to 350 ms (Fig. 3.7 C). In addition, there was also significantly stronger activity in schizophrenia patients relative to controls which was mainly found between 25 and 60 Hz over fronto-central channels. The increase can be interpreted as a reduced downregulation of gamma-band power over fronto-central channels in the patient group because task-related gamma-band power in this frequency range was decreased in controls over fronto-central channels (Fig. 3.8 C, blue curves).

Correlation between Gamma-Band Power and Clinical Symptoms

Correlations between clinical symptoms and gamma-band power in the face condition were computed separately with power on positive channels in the high-frequency gamma-band, with power on positive channels in the lower gamma-band, and finally with power on negative channels in the lower gamma-

band. We found a significant negative correlation between high-frequency gamma-band power over positive channels, the disorganisation factor ($r = -0.63$, $p = 0.009$) and the cognitive factor ($r = -0.56$, $p = 0.024$). These factors were also negatively correlated to power in the lower gamma-band (disorganisation: $r = -0.69$, $p = 0.003$; cognitive: $r = -0.62$, $p = 0.01$). Finally, there was a significant negative correlation between the depression dimension and lower gamma-band power ($r = -0.66$, $p = 0.005$).

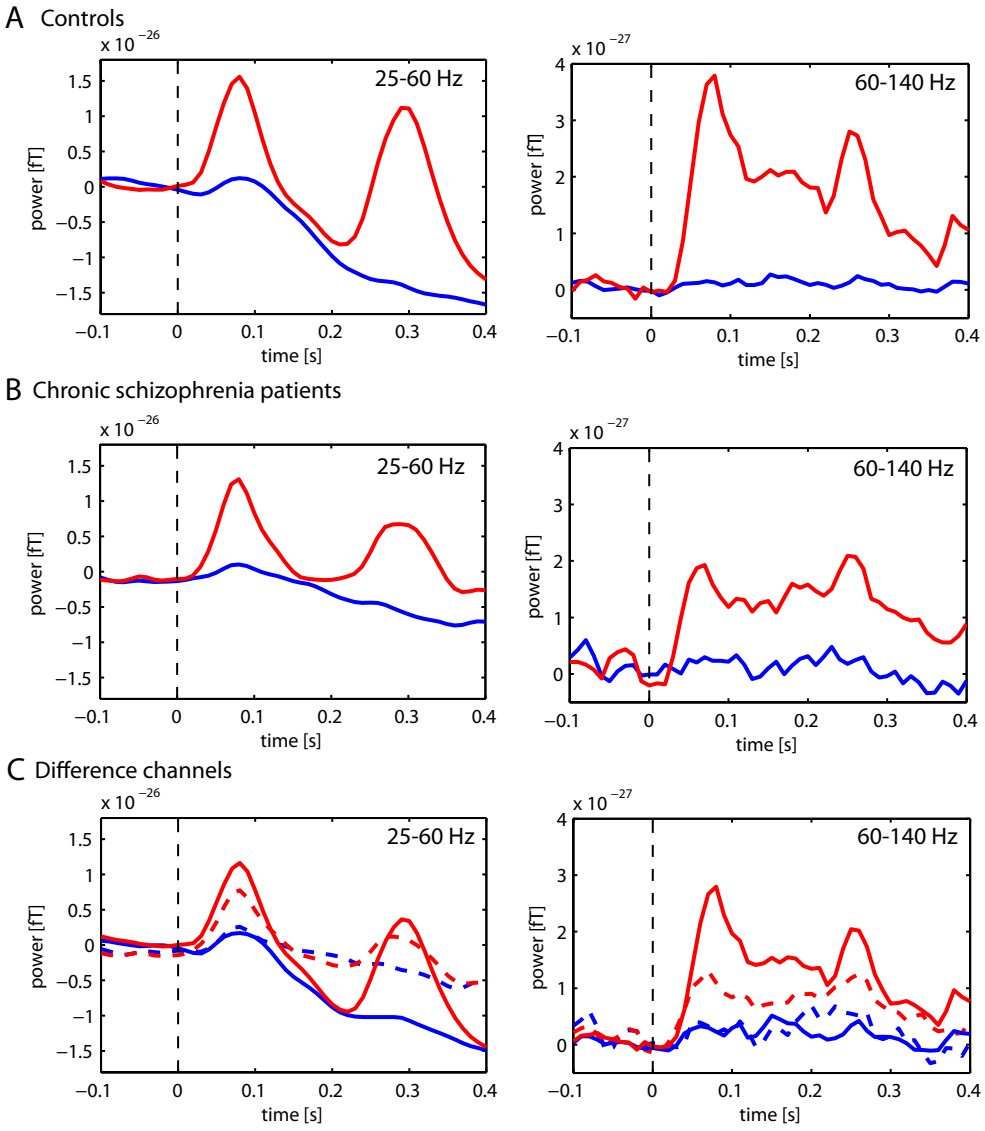

Figure 3.8. Timecourses of gamma-band power in controls and chronic schizophrenia patients.

Figure 3.8. Timecourses of absolute gamma-band power averaged across statistically significant channels. (A) Gamma-band power is shown for controls, averaged across the significant channels from the task versus baseline contrast in controls. The red line represents activity over "positive" channels, i.e., channels that showed significantly increased gamma-band power in response to upright Mooney faces (parieto-occipital channels). The blue line represents activity over "negative" channels, i.e., channels that showed significantly decreased gamma-band power in response to upright Mooney faces (fronto-central channels). The dashed lines indicate stimulus onset. The left and right columns display gamma-band power averaged for the lower and higher gamma frequency ranges, respectively. Note that in controls, there is a pronounced decrease of gamma-band activity in the lower gamma frequency range over negative channels. Gamma-band power is increased over positive channels both in the lower and higher frequency ranges; sustained activity is only present in the higher gamma-band. (B) The same analysis as in panel A, but for chronic schizophrenia patients. Gamma-band power was averaged across the significant channels from the task versus baseline contrast in patients. (C) Gamma-band power in controls (continuous lines) and in patients (dashed lines) averaged across the significant channels of the between-group statistical analysis. Red lines represent average gamma-band power over channels that showed significantly increased activity in controls compared to patients, whereas blue lines represent average gamma-band power over channels that showed significantly decreased activity in controls compared to patients. In patients, gamma-band power over negative channels in the lower frequency range is not as strongly decreased as in controls. The increase in gamma-band activity over positive channels is reduced compared to controls, especially in the higher gamma-band, i.e. modulation amplitudes of task-related effects were always reduced in schizophrenia patients.

We did not find any significant correlations between gamma-band power over negative cluster channels and PANSS factors (for an overview of all correlations, refer to Table A.2 in the Appendix).

Correlation between Gamma-Band Power and Behavioral Performance

We computed correlations between gamma-band power and behavioral indexes for the face condition in controls and schizophrenia patients (hits, discrimination index A' and reaction times). Measures of gamma-band activity for each subject were computed separately for positive and negative channels, and for the lower and higher gamma-band. In chronic schizophrenia patients, we found a significant positive correlation between high-frequency gamma-band power and the discrimination performance ($r = 0.51$, $p = 0.04$). Interestingly, the discrimination performance and the hit rate were negatively correlated to

lower gamma-band power over negative channels ($r = -0.55$, $p = 0.04$ and $r = -0.55$, $p = 0.04$). In controls, we did not find any significant correlations between gamma-band power and behavioral performance (see Table A.2 in the Appendix for an overview of all correlations).

Spatiotemporal Reconstruction of Gamma-Band Activity

In controls, the strongest activation in response to face stimuli in the high-frequency gamma-band was observed in the fusiform gyrus (FusG) in the medial temporal lobe (Fig. 3.9 A). Additional clusters were found in the parietal and lateral temporal lobe, more specifically in the right superior temporal gyrus (STG) (BA39), in the transverse temporal gyrus (BA41), and in the inferior parietal lobule (IPL). Finally, upright Mooney faces elicited activation in frontal regions, including the right middle frontal gyrus (MiFG), right superior frontal gyrus (SFG), and the medial frontal gyrus (MeFG). In the lower gamma band (Fig. 3.9 D), the strongest activations were observed in prefrontal areas, with a peak in the left SFG, extending to the MeFG (BA11). Another frontal cluster was found in the right inferior frontal gyrus (IFG) (BA7). Furthermore, parietal regions, specifically the right angular gyrus and the left supramarginal gyrus, and occipital areas, specifically the inferior and middle occipital gyrus (IOG and MOG) showed enhanced activation in response to upright Mooney faces.

In schizophrenia patients, there was a pronounced reduction in task-related source power compared to controls in the high-frequency gamma-band in several regions especially in the right hemisphere (Fig. 3.9 C), including the postcentral gyrus, IFG (BA45), inferior temporal gyrus (ITG), primary visual cortex and FusG. Interestingly, we found enhanced source power in the high-frequency gamma-band in patients relative to controls in the posterior cingulate cortex, extending to the precuneus, as well as in a small cluster in the left SPL and the right precentral gyrus. While source power in schizophrenia

patients in the high-frequency gamma-band was largely decreased, the lower gamma-band was characterized by increased activation in patients compared to controls in several regions, including frontal areas (SFG, MiFG), again posterior cingulate and cuneus, and also the right ITG (Fig. 3.9 F). Clusters located in the left and right SFG and also in the right IPL showed enhanced activation for controls compared to patients (Fig. 3.9 F). The coordinates for all clusters are given in Tables A.3 and A.4 in the Appendix.

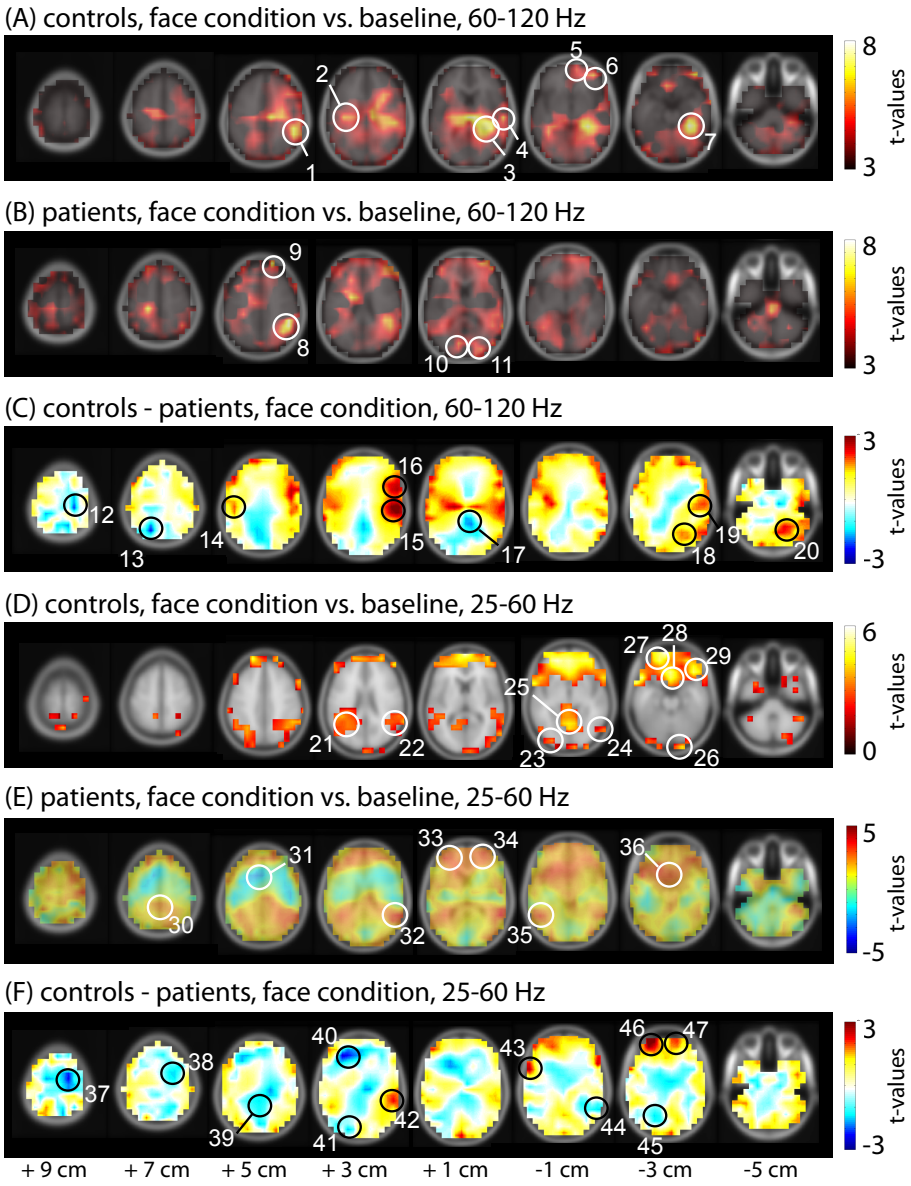

Figure 3.9. Source reconstruction in controls and chronic schizophrenia patients.

Figure 3.9. Source power in the face condition for controls and patients. In (A), (B), (D), and (E) red clusters represent stronger activation in the face condition compared to baseline for controls and patients, whereas blue clusters represent stronger activation in the baseline relative to the task. (C) and (F) correspond to the differences between controls and patients in the face condition, where red clusters denote stronger activation in controls compared to patients and blue clusters stronger activation in patients compared to controls. Note that t-values are corrected for multiple comparisons (FDR, $q < 0.05$) except in (E), which represents uncorrected t-values for the patient group in the lower gamma-band. 1: inferior parietal lobule (IPL); 2: postcentral gyrus; 3: transverse temporal gyrus; 4: superior temporal gyrus (STG); 5: superior frontal gyrus (SFG); 6: middle frontal gyrus (MiFG); 7: fusiform gyrus (FusG); 8: IPL; 9: SFG; 10: cuneus; 11: middle occipital gyrus (MOG); 12: precentral gyrus; 13: superior parietal lobule (SPL); 14: postcentral gyrus; 15: postcentral gyrus; 16: inferior frontal gyrus (IFG); 17: posterior cingulate; 18: lingual gyrus; 19: FusG; 20: cerebellum; 21: supramarginal gyrus; 22: angular gyrus; 23: inferior occipital gyrus (IOG); 24: MOG; 25: cerebellum; 26: lingual gyrus; 27: SFG; 28: medial frontal gyrus (MeFG); 29: IFG; 30: paracentral lobule; 31: cingulate gyrus; 32: STG; 33; MiFG; 34: MiFG; 35: middle temporal gyrus; 36: MeFG; 37: SFG; 38: MiFG; 39: cingulate gyrus; 40: SFG; 41: cuneus; 42: IPL; 43: STG; 44: inferior temporal gyrus; 45: cerebellum; 46: SFG; 47; SFG.

3.2.4 Discussion

The present study investigated the role of low- and high-frequency gamma-band oscillations and their neural generators in the pathophysiology of schizophrenia with MEG. Here, we provide novel evidence for deficits in high-frequency gamma-band oscillations in schizophrenia that were accompanied by impairments in perceptual organization and involved altered activation in occipito-temporal, parietal and frontal brain regions.

Gamma-Band Oscillations and Perceptual Organization in Healthy Controls

In healthy control participants, gamma-band power was increased over parieto-occipital channels, both in the low- ($25-60$ Hz) and high-frequency ($60-120$ Hz) gamma-band ranges; in contrast, gamma-band power was decreased over fronto-central channels. The increases in spectral power in the lower gamma range were transient and most likely reflected stimulus onset and offset. Only in the higher gamma-band range did we observe sustained activity that was

present for the entire stimulus duration, suggesting that the network relevant to perceptual organization operates predominantly in the high-gamma frequency range.

This finding is consistent with recent evidence from a series of studies that reported gamma-band responses between 60 and 200 Hz during a variety of cognitive tasks in MEG-recordings (Siegel et al., 2007; Guggisberg et al., 2008; Kaiser et al., 2004; Hoogenboom et al., 2006), invasive EEG recordings in humans (Crone et al., 2001; Lachaux et al., 2005; Brovelli et al., 2005), and invasive recordings in animals (Colgin et al., 2009; van der Meer and Redish, 2009). Together these studies suggest that in addition to activity in the low-frequency gamma band, high-frequency gamma oscillations are a functionally relevant phenomenon in cortical networks.

Source reconstruction of high-frequency gamma-band oscillations in healthy controls revealed that the processing of upright Mooney faces was associated with enhanced source power in multiple regions. Specifically, pronounced gamma power was observed in the fusiform gyrus, which is crucially involved in face perception (Kanwisher et al., 1997; Kanwisher and Yovel, 2006). Furthermore, source power was enhanced in a parietal region corresponding to the IPL, which is involved in memory retrieval (Wagner et al., 2005). Accordingly, this activity could reflect a retrieval of face templates from long-term memory, interacting with the sensory information from the Mooney stimuli for face detection.

In addition, upright Mooney faces induced activation in several frontal brain areas (MiFG, SFG and MeFG), which could reflect the maintenance of the task and enable comparisons between the stimuli and face-templates retrieved from long-term memory (Summerfield et al., 2006). Finally, we observed enhanced activation in the middle temporal gyrus, which is involved in the ventral stream that processes visual features such as form, colour and shape, and mediates object recognition (Ungerleider and Mishkin, 1982; Goodale and Milner, 1992).

Gamma-Band Oscillations and Perceptual Organization in Chronic Schizophrenia Patients

An earlier study by Uhlhaas et al. (2006a) reported that the amplitude of induced gamma-band oscillations in the $40 - 70$ Hz frequency range in EEG data during the same task was relatively intact while beta/gamma long-range synchronisation was strongly reduced. The current study provides complementary results for high-frequency gamma-band oscillations. We found a highly significant deficit in high-frequency gamma-oscillations ($60 - 120$ Hz) over parieto-occipital channels in schizophrenia patients that has not been reported previously. The present findings suggest that schizophrenia patients are characterized by a widespread deficit in gamma-band oscillations, involving both stimulus-locked and non-stimulus-locked gamma-band activity. Interestingly, schizophrenia patients showed stronger power over frontal and central channels in the lower gamma-band relative to controls, which in fact represented a deficit in the downregulation of gamma-band power over these channels in patients.

These alterations of gamma-band activity in patients were accompanied by a deficit in perceptual organization in line with the study by Uhlhaas et al. (2006a). The behavioural deficit was specific to the face condition where stimulus features needed to be grouped for a coherent percept. Since a dysfunction in the integration of stimulus elements into coherent object representations has been found for a wide range of Gestalt stimuli in schizophrenia (Uhlhaas and Silverstein, 2005), the current behavioral deficit is unlikely to reflect a specific impairment in face perception (Onitsuka et al., 2006).

We had expected to find impaired gamma-band oscillations mainly in the face condition where grouping was required; however, we also observed a significant reduction in high-frequency gamma power during the non-face condition (Figures A.1 and A.2 in the Appendix), suggesting a more general dysfunction of local neural circuits during visual processing in schizophrenia. Evidence for a

functional role of high-frequency gamma-band activity is provided by correlations between spectral power in the high-frequency gamma-band and discrimination performance as well as the disorganisation syndrome in the patient group. However, we did not observe a relationship between high-frequency gamma-band power and behavioral performance in healthy controls; a possible reason for the different findings in patients and controls may be a ceiling effect in the performance of controls such that the high detection accuracy in controls is not further improved by higher gamma-band power. Further research including larger sample sizes may be needed to clarify this issue.

Source reconstruction of gamma-band power in chronic schizophrenia patients revealed abnormal activation patterns in various occipito-temporal, parietal and frontal areas, suggesting that dysfunctional processing in a number of regions relevant to perceptual organization underlies the impaired behavioural performance and the changes in gamma-band power we observed at the sensor level. More specifically, in the higher gamma-band, source power was reduced in primary visual areas, in the fusiform gyrus, and in the IFG, which might lead to impaired interactions between face recognition areas and areas related to cognitive control in schizophrenia.

Interestingly, chronic patients also showed enhanced source power compared to controls in the posterior cingulate that has been linked to the default mode network (Greicius et al., 2003; Fransson and Marrelec, 2008). One may speculate that this relatively enhanced activation underlies the reduced downregulation in the lower gamma-band over central channels in chronic schizophrenia patients. As default mode network activity is usually decreased during cognitive tasks in healthy controls (Raichle et al., 2001; Fox et al., 2005), our findings may suggest an impairment in the regulation of default mode network activity in schizophrenia patients that also contributes to the impairment in behavioral performance. This hypothesis is supported by the correlations between gamma-band power and performance we observed in chronic patients:

spectral power in the high gamma-band (over parietal-occipital channels) was positively correlated with the discrimination performance, whereas spectral power in the lower gamma-band (over fronto-central channels) was correlated negatively with the discrimination performance.

Recent research has emphasized dorsal stream dysfunctions in visual processing in schizophrenia (e.g., Butler and Javitt, 2005; King et al., 2008; Coleman et al., 2009). However, the present data provide evidence that processing in the ventral stream may also be impaired, which is consistent with a recent fMRI study that demonstrated reduced activation in schizophrenia patients in higher visual cortex areas related to shape perception (Silverstein et al., 2009). It remains to be clarified whether dysfunctions in higher occipito-temporal regions are due to impaired processing in primary visual areas.

Conclusion

The present study provides novel evidence for an impairment in high-frequency gamma oscillatory activity in schizophrenia patients that is accompanied by deficits in perceptual organization. Previous studies have largely concentrated on oscillatory activity in the lower gamma-band in schizophrenia, providing inconsistent results with some studies reporting a reduction of induced gamma-band activity around 40 Hz (Haig et al., 2000; Green et al., 2003), whereas another study found relatively intact spectral power between 40 and 70 Hz (Uhlhaas et al., 2006a). The current results demonstrate that a pronounced deficit in induced gamma-band activity can be clearly observed in the high-frequency gamma-band range, with the underlying neural generators representing a distributed network in occipito-temporal, parietal and frontal regions. Our findings suggest widespread dysfunctions in local cortical network in schizophrenia patients, which may underlie the deficits observed in long-range coordination between different brain areas in schizophrenia patients (Uhlhaas et al., 2006a).

3.3 High-Frequency Gamma-Band Oscillations in Unmedicated First-Episode Schizophrenia Patients

3.3.1 Introduction

A number of EEG studies has demonstrated that patients with schizophrenia are characterized by abnormal neural synchronization in the gamma frequency range during visual processing (e.g., Green et al., 2003; Spencer et al., 2003, 2004; Wynn et al., 2005). This evidence has supported the view that abnormal temporal coordination might play an important role in the pathophysiology of schizophrenia (Phillips and Silverstein, 2003). However, most of the studies have been conducted with chronic medicated patients, leaving the question open to what extent an impairment in neural synchrony is present at the onset of the disorder and without the confounding influence of medication.

In the present study, we examined oscillatory activity in the $25 - 150$ Hz frequency range with MEG in a sample of first-episode unmedicated schizophrenia patients and a group of healthy control participants. We used the Mooney faces task to test perceptual organization, and MEG data were analysed in both sensor and source spaces as in the previous experiments. We expected that first-episode schizophrenia patients were impaired in their ability to detect Mooney faces, reflecting dysfunctional perceptual organization. Furthermore, we expected that a reduction of neural synchrony as indexed by spectral power in the gamma-band range would be already present at the onset of the disorder. We hypothesized that the deficits in gamma-band power and the associated impairment in perceptual organization would result from a reduction of source power in brain regions that had been shown to be involved in perceptual closure in our first study (Section 3.1, Fig. 3.4), such as parietal regions, areas in the inferior temporal cortex, and the inferior frontal gyrus.

3.3.2 Methods

Participants

Nineteen unmedicated first-episode patients with schizophrenia were recruited from the Cologne University Psychiatry Department. Twenty healthy controls were recruited from the local community in Frankfurt and screened for psychopathology with the German version of Structured Clinical Interview for DSM-IV-R Non-Patient Edition (SCID, Sass and Wittchen, 2003). Written informed consent was obtained from all participants following a description of the study procedures. DSM-IV diagnosis of schizophrenia was established with the SCID, by thorough chart review and in consultation with the treating psychiatrists. Patients and controls were excluded if they had any neurological or ophthalmologic disorders or if they met criteria for alcohol or substance dependence within the last month. Current psychopathology was assessed with the Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987). The symptoms were grouped into the factors "positive", "negative", "depression", "excitement" and "cognitive" (Lindenmayer et al., 1994). In contrast to the previous study with chronic schizophrenia patients, first-episode patients were not rated on the item inappropriate affect (Cuesta and Peralta, 1995); thus, it was not possible to assess the disorganization factor in this group. Note that the PANSS data presented in Table 3.4 represent only preliminary data from seven first-episode patients; the remaining data were not yet available but will be included in the manuscript for publication of this study.

Demographic information for patients and controls is given in Table 3.4. Healthy controls were on average about three years younger than the first-episode schizophrenia patients, and had on average two more years of education. No significant differences between groups were found for premorbid verbal IQ and handedness. Cognitive function in patients and controls was measured with the Brief Assessment of Cognition in Schizophrenia (BACS, Keefe et al., 2004). Compared to healthy controls, schizophrenia patients had

lower scores on all scales of the BACS (verbal memory, motor speed, verbal fluency and symbol coding) except for the tower of London test and the digit sequencing task.

Table 3.4. Demographic, cognitive and clinical characteristics of healthy controls and first-episode schizophrenia patients

		Controls ($N = 20$)		Patients ($N = 19$)		Statistics	
		Mean	SD	Mean	SD	χ^2-/t-value	p-value
Gender (m/f)		12/8		15/4		$\chi^2(1) = 0.87$	0.35
Age (years)		23.1	2.61	26.11	5.32	$t(37) = -2.26$	0.03
Education (years)		16.84	2.95	14.81	3.26	$t(34) = 2.57$	0.01
Handedness		62.92	36.67	62.24	48.28	$t(32) = 0.05$	0.96
MWT		30.82	2.65	28.63	4.33	$t(31) = 1.77$	0.09
BACS	Verbal memory	55.32	5.44	43.9	13.88	$t(34) = 3.31$	0.002
	Digit sequencing	23.89	3.9	22.06	6.06	$t(34) = 1.09$	0.28
	Motor speed	91.11	10.22	83.53	11.11	$t(34) = 2.13$	0.04
	Verbal fluency	58.84	12.25	43.29	18.94	$t(34) = 2.96$	0.006
	Symbol coding	65	8.27	53.29	13.49	$t(34) = 3.18$	0.003
	Tower of London	19.95	1.84	19.41	2.83	$t(34) = 0.68$	0.5
	Total score	314.11	20.98	265.53	46.7	$t(34) = 4.1$	0.0002
PANSS	Negative	–	–	19.71	6.97		
	Excitement	–	–	8.43	1.62		
	Cognitive	–	–	13.71	5.09		
	Positive	–	–	12.86	1.77		
	Depression	–	–	17.43	3.55		

Stimuli and Recordings

The procedure in the present study was identical to the one in our previous experiment: we used the Mooney faces task to examine perceptual organization in first-episode schizophrenia patients and healthy controls. Each run comprised 60 upright and 30 inverted-scrambled Mooney stimuli, and the task was to indicate whether a face was detected or not after each stimulus. Patients and controls completed four runs in the MEG. In addition, we obtained an anatomical scan from most of the participants that was used for the source analysis of the MEG data (for details on the task and the recordings, refer to Chapter 2).

Data Analysis

The MEG data analysis was performed with the Fieldtrip open source Matlab toolbox and followed a similar procedure as in our previous experiment (Section 3.2). The most important points will be summarized in the following paragraphs. Note that the focus of this study was on the comparison between first-episode schizophrenia patients and healthy controls. In addition, we conducted statistical comparisons between first-episode patients and the chronic patients of our previous study. The results of these comparisons will be described in this section; however, I will discuss and integrate the different studies in the General Discussion in the following chapter.

MEG Data Processing. Trials were classified according to the face condition, containing trials with upright stimuli, and the non-face condition, containing trials with inverted-scrambled stimuli. We used only trials with correct responses for all further analyses, i.e., hits in the face condition and correct rejections in the non-face condition. Trials contaminated by eye blinks, muscle activity or jump artifacts in the SQUIDs were discarded. Baseline-correction was performed by subtracting the mean amplitude during an epoch ranging from −500 to −100 ms before stimulus onset.

Analysis of Sensor-Level Spectral Power Changes. As in the previous experiments, time-frequency representations (TFRs) were computed by means of Morlet wavelets with a width of 5 cycles per wavelet at center frequencies between 25 and 150 Hz, in 1 Hz steps. For a statistical analysis of the changes in gamma-band power, we focused on the face condition and carried out three tests: first, we tested changes in gamma-band power within each group and compared the raw power during stimulus presentation (50 to 350 ms post-stimulus) to the raw power during baseline (−350 to −50 ms pre-stimulus) using dependent-samples t-tests.

Next, we compared gamma-band power between controls and first-episode

schizophrenia patients for the interval between 50 and 350 ms post-stimulus using an independent-samples t-test. The between-group analysis was computed on absolute power difference values, that is, the raw baseline power was subtracted from the raw task power for each subject. All statistical tests were computed for the frequency range of $25 - 140$ Hz and included all channels. We used false discovery rate (FDR, Genovese et al., 2002) with a criterion of $q < 0.05$ to correct for multiple comparisons.

In order to analyze correlations between gamma-band activity in the face condition and behavioral performance, we computed absolute power values for each patient and control subject by averaging gamma-band power between 50 and 350 ms, separately for the lower ($25 - 60$ Hz) and the higher ($60 - 140$ Hz) gamma-frequency range, and separately for significant positive and negative channels of each group. Significant positive and negative channels were determined by first multiplying the t-values given by the statistical analysis within each group (task vs. baseline) with the significance mask that contains zeros for all non-significant time-frequency-channel samples and ones for all significant samples. This yields a matrix where all t-values unequal zero are statistically significant. The matrix was then averaged across the time and frequency range used in the statistical analysis (50 to 350 ms and 25 to 140 Hz). To determine the channels showing on average a significant increase ("positive" channels) or decrease ("negative" channels) in power, we set a threshold of $t > 0$ (positive channels) and $t < 0$ (negative channels).

As mentioned above, we additionally compared the gamma-band power between first-episode schizophrenia patients and the chronic patient sample from the previous study using an independent-samples t-test that was computed on absolute power difference values. This statistical analysis was also computed for the frequency range of $25 - 140$ Hz across all channels, and FDR with $q < 0.05$ was used to correct for multiple comparisons.

Like in our previous experiment with chronic schizophrenia patients, the non-

face condition contained fewer trials than the face condition in the present study. We therefore carried out only a preliminary analysis of gamma-band power for the non-face condition, the results of which are shown in the Appendix (Figures A.3 and A.4).

Reconstruction of the Sources of Oscillatory Sensor-Level Components. We used an LCMV beamformer to localize the sources underlying oscillatory activity (van Veen et al., 1997, refer to Section 3.2 for a detailed description). Normalized leadfields and the same headmodel as in the previous studies were used. The head shape was derived from each individual subject's structural MRI.

The MEG data were filtered in the low ($25 - 60$ Hz) and high ($60 - 120$ Hz) gamma-band frequency ranges, and the covariance matrix was computed for each frequency band for all face trials, separately for controls and patients, and task (50 to 350 ms) and baseline epochs (-350 to -50 ms). Common filters were computed based on the average covariance matrices for baseline and activation epochs. Source power was subsequently estimated for each grid location by projecting the sensor data through the common filters for each trial, separately for task and baseline.

Three tests were carried out for a statistical analysis of the source power: first, we compared task and baseline raw source power within each group, using dependent-samples t-tests. Then, we compared task-related absolute source power between controls and patients, using an independent-samples t-test. Voxel-wise t-values were corrected with FDR ($q < 0.05$) to control for multiple comparisons. We excluded six subjects from the source analysis, three controls and three patients, because of a 50 Hz contamination in these subjects. As mentioned in the previous section, an offset due to sustained 50 Hz contamination does not affect the analysis of the raw (absolute) power differences at the sensor level, but may corrupt the results of beamformer source analysis, as the 50 Hz signal will influence the overall filter computation and therefore

have an effect at all frequencies. This may lead to shifted source locations. In addition, two controls and two patients were excluded from the analysis because anatomical data were not available from these subjects. Thus, the statistical tests of source power were based on 15 controls and 14 first-episode patients. Additionally, task-related absolute source power was compared between first-episode and chronic schizophrenia patients, using an independent-samples t-test.

3.3.3 Results

Performance

As in the previous experiment, we analysed the percentage of correct responses and reaction times for the face and the non-face conditions, as well as the discrimination index A', which gives a measure of the hit rate that is corrected for the number of false alarms (Grier, 1971). First-episode schizophrenia patients performed more poorly than controls in the non-face condition, as they classified more non-faces incorrectly as faces ($t(37) = 2.43$, $p = 0.02$) and had longer reaction times ($t(37) = -2.54$, $p = 0.02$) (Table 3.5). The detection accuracy in the face condition was not significantly different between the groups ($t(37) = 1.46$, $p = 0.15$), but there was a trend for longer reaction times in the patient group in this condition ($t(37) = -2.02$, $p = 0.05$). The discrimination index A' was significantly higher in controls than in first-episode patients

Table 3.5. Performance in healthy controls and first-episode schizophrenia patients

	Controls ($N = 20$)		Patients ($N = 19$)		Mean difference	
	Mean	SD	Mean	SD	t-value	p-value
Hits (%)	82.81	6.31	77.28	15.66	$t(37) = 1.46$	0.15
Correct rejections (CR) (%)	84.81	12.79	72.31	18.87	$t(37) = 2.43$	0.02
Discrimination index A'	0.91	0.04	0.84	0.09	$t(37) = 3.03$	0.0045
Reaction time (hits) (ms)	620.27	123.36	725.18	194.68	$t(37) = -2.02$	0.05
Reaction time (CR) (ms)	759.32	133.29	911.09	229.94	$t(37) = -2.54$	0.02

($t(37) = 3.03$, $p = 0.0045$), which reflects that controls had fewer false alarms for the same number of correctly detected faces compared to first-episode patients.

MEG Gamma-Band Power on Sensor Level

The time-frequency representation of relative gamma-band power in the face condition for controls revealed a similar pattern as in the previous study: gamma-band activity was characterised by an increase between 50 and 350 ms after stimulus onset with two prominent peaks around 50 ms and 250 ms in the $25 - 140$ Hz frequency range (Fig. 3.10 A). Sustained gamma-band activity was present between 100 and 300 ms, mainly in the high-frequency gamma-band between 60 and 120 Hz.

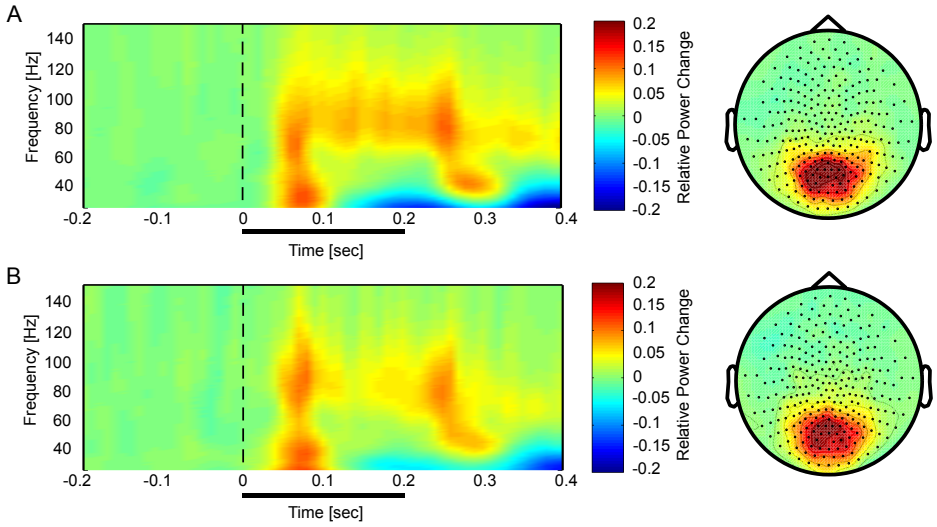

Figure 3.10. Time-frequency representations (TFRs) and topographies of gamma-band spectral power in the face condition for controls (A) and first-episode schizophrenia patients (B). The TFRs represent the average across all channels. The dashed vertical line marks stimulus onset. The topographies are averaged across the stimulus interval ($0 - 400$ ms) and between 25 and 150 Hz. The gamma-band signal is expressed as relative power change in the post-stimulus time window compared to baseline. In first-episode schizophrenia patients, the sustained response in the high-gamma frequency range and the late stimulus-offset response is reduced, whereas the early evoked component appears to be intact.

In first-episode schizophrenia patients, there were reductions in sustained high-

gamma band activity between 60 and 120 Hz and in the stimulus-offset response around $250-300$ ms, whereas the early stimulus-onset response around $50-100$ ms was intact (Fig. 3.10 B). A similar pattern of results is observed in the timecourses of absolute gamma-band power over parietal channels (Fig. 3.13 A, black and blue lines).

The statistical analysis in controls revealed a significant task-related increase of gamma-band power over parietal channels between 50 and 350 ms that was accompanied by a decrease in activation over frontal and central channels, mainly between 150 and 300 ms (Fig. 3.11 A). The results of the statistical analysis in first-episode patients were quite similar, although both the effects over parietal channels and fronto-central channels were not as strong as in controls (Fig. 3.11 B).

The statistical comparison of task-related gamma-band power between controls and first-episode patients revealed a complex pattern (Fig. 3.11 C); the main differences can be summarized as follows: compared to controls, first-episode patients were characterised by significant reductions in high-frequency gamma-band activity over parietal channels between 100 and 350 ms and in gamma-band activity over bilateral temporal channels mainly in the lower gamma-band range.

In addition, there was significantly stronger activity in patients relative to controls over frontal and central channels, mainly in the lower gamma-band, with this effect being most prominent over central channels between 100 and 250 ms. This relative increase in patients can be interpreted as a reduced down-regulation of gamma-band power over central channels in the patient group since gamma-band power in this frequency range was decreased in controls over central channels (Fig. 3.13 C, black and blue lines). Time-frequency representations and statistical analyses in the non-face condition showed similar results (Figures A.3 and A.4 in the Appendix).

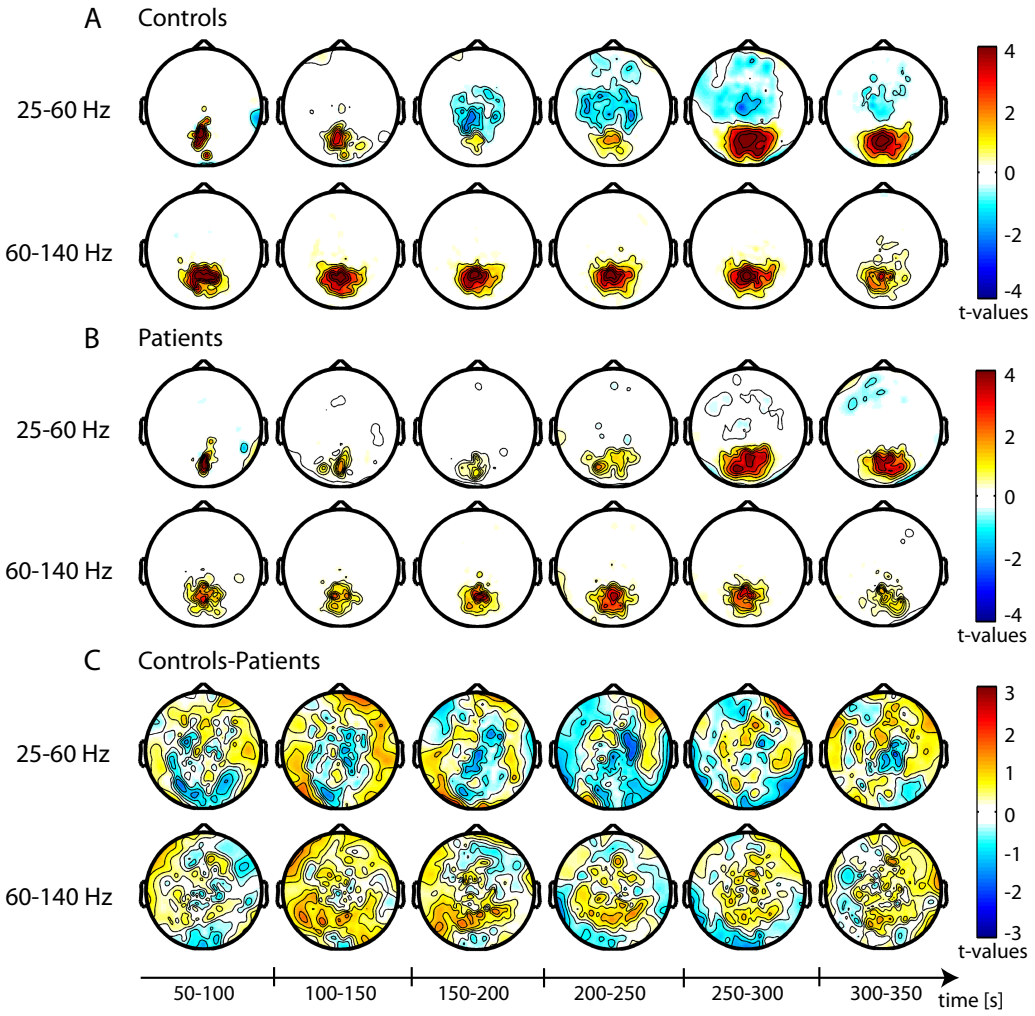

Figure 3.11. Statistical analysis of gamma-band power in response to upright Mooney faces for controls (A), first-episode schizophrenia patients (B), and for the difference between controls and patients (C). The topographies in (A) and (B) show significant differences between the face condition and the baseline, separately for the lower ($25-60$ Hz) and the higher ($60-140$ Hz) gamma-band. The effect is masked by the significance map derived from false-discovery rate (FDR, $q < 0.05$) statistical testing. Red denotes higher activation during stimulus presentation compared to baseline, whereas blue denotes less activation during stimulus presentation compared to baseline. The topographies in (C) show the difference for the face condition between controls and patients. Here, red denotes stronger activation for controls compared to patients, whereas blue represents stronger activation in patients relative to controls.

Correlation between Gamma-Band Power and Behavioral Performance

We computed correlations between gamma-band power and behavioral indexes for the face condition in controls and first-episode schizophrenia patients (hits, discrimination index A' and reaction times). Measures of gamma-band activity for each subject were computed separately for positive and negative channels, and for the lower and higher gamma-band. In healthy controls, we found a significant positive correlation between lower gamma-band power over negative channels and the discrimination performance ($r = 0.68$, $p = 0.008$) and a trend for a positive correlation with reaction times ($r = 0.43$, $p = 0.06$). First-episode patients showed a trend for a positive correlation between lower gamma-band power over negative channels and the discrimination performance ($r = 0.43$, $p = 0.07$). We did not find any significant correlations with low- or high-frequency gamma-band power over positive channels neither in controls nor in patients (see Table A.5 in the Appendix for an overview of all correlations).

Spatiotemporal Reconstruction of Gamma-Band Activity

In controls, the strongest activation in the high-frequency gamma-band was observed in the right superior temporal gyrus (STG)(Fig. 3.12 A). Enhanced source power for upright Mooney stimuli was also observed in the frontal cortex, more specifically in the left superior frontal gyrus (SFG) and in the right inferior frontal gyrus (IFG), and in posterior visual areas such as the middle occipital gyrus (MOG) and the cuneus. In the lower gamma band (Fig. 3.12 D), there was one major cluster in the SFG, and three smaller ones in the right IFG, STG, and inferior occipital gyrus (IOG).

In first-episode schizophrenia patients, there were pronounced reductions in task-related source power compared to controls in the high gamma-band in many cortical areas (Fig. 3.12 C). The peaks of these differences were mainly located in the frontal cortex, specifically in the medial frontal gyrus (MeFG),

the right middle frontal gyrus (MiFG), and the left IFG. Additional clusters were found in the right superior parietal lobule (SPL) and in the cuneus. The source power differences in the lower gamma band showed a similar pattern: first-episode patients were characterized by reductions in task-related source power in several regions, including primarily frontal areas such as bilateral SFG, MeFG, and left IFG.

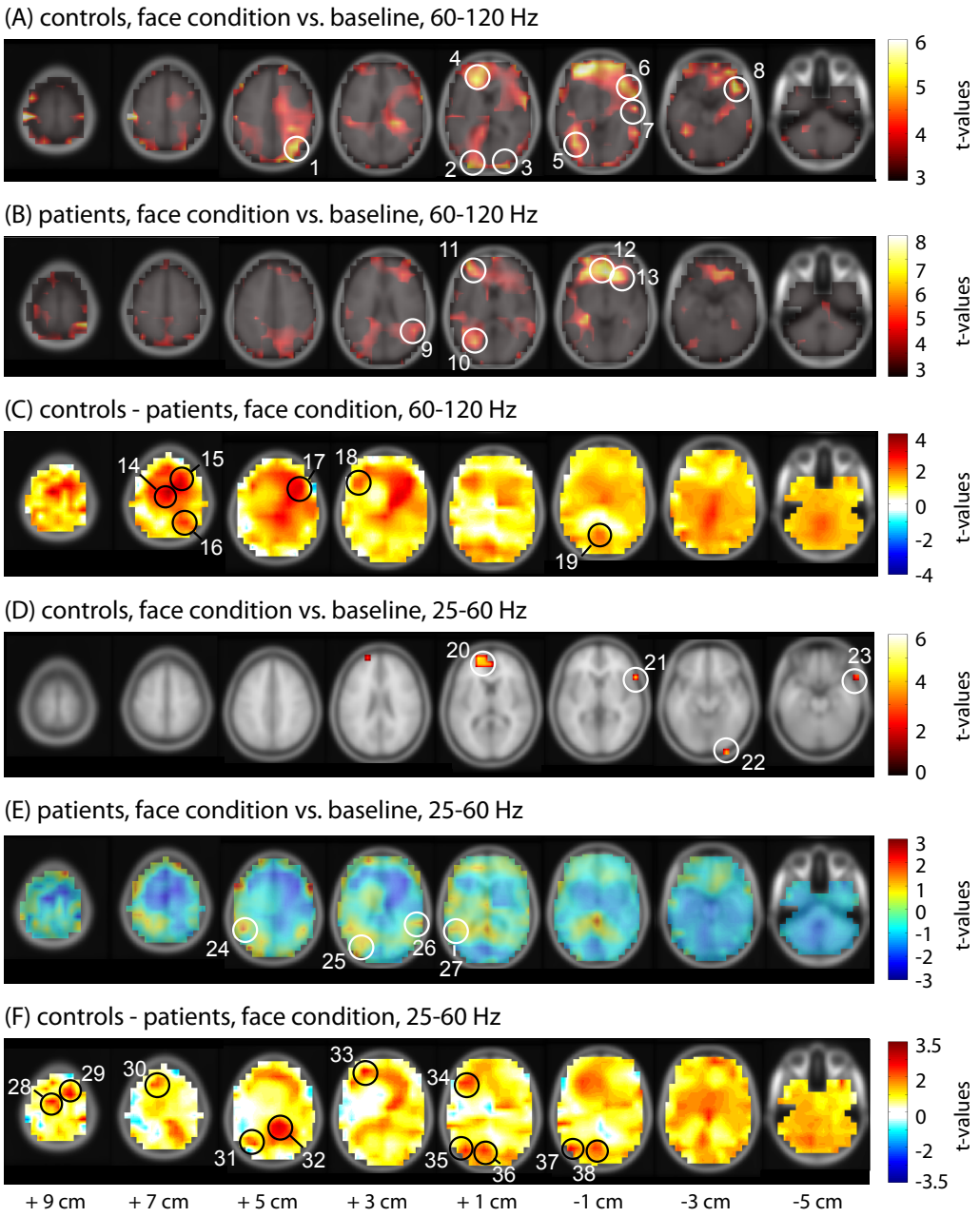

Figure 3.12. Source reconstruction in controls and first-episode patients.

Figure 3.12. Source power in the face condition for controls and first-episode patients. In (A), (B), (D), and (E) red clusters represent stronger activation in the face condition compared to baseline for controls and patients, whereas blue clusters represent stronger activation in the baseline relative to the task. (C) and (F) correspond to the differences between controls and patients in the face condition, where red clusters denote stronger activation in controls compared to patients and blue clusters stronger activation in patients compared to controls. The t-values are corrected for multiple comparisons (FDR, $q < 0.05$) except in (E), which represents uncorrected t-values for the patient group in the lower gamma-band. Note that the last three slices in (D) do not correspond to the slice distances indicated below the figure, but instead are at 0 cm, -2 cm, and -3 cm; these slices were chosen in order to show all the clusters for the respective statistical contrast. 1: precuneus; 2: middle occipital gyrus (MOG); 3: cuneus; 4: superior frontal gyrus (SFG); 5: MOG; 6: superior temporal gyrus (STG); 7: STG; 8: inferior frontal gyrus (IFG); 9: STG; 10: MOG; 11: middle frontal gyrus (MiFG); 12: medial frontal gyrus (MeFG); 13: IFG; 14: MeFG; 15: MeFG; 16: superior parietal lobule (SPL); 17: MiFG; 18: IFG; 19: cuneus; 20: SFG; 21: STG; 22: IFG; 23: inferior occipital gyrus (IOG); 24: STG; 25: superior occipital gyrus (SOG); 26: STG; 27: inferior parietal lobule (IPL); 28: MeFG; 29: SFG; 30: SFG; 31: IPL; 32: precuneus; 33: SFG; 34: IFG; 35: MOG; 36: cuneus; 37: MOG; 38: cuneus.

Furthermore, enhanced source power in controls compared to patients was observed in posterior visual cortex areas, more specifically in the MOG and the cuneus, and in parietal regions, including the precuneus and the left IPL. The MNI coordinates of all activation peaks are given in Tables A.6 and A.7 in the Appendix.

Comparison between First-Episode and Chronic Schizophrenia Patients

Fig. 3.13 presents timecourses of average gamma-band power and single-subject data of healthy controls, first-episode patients, and the chronic schizophrenia sample from the previous study in order to compare gamma-band activity between the different patient groups. Panel A in Fig. 3.13 reveals that high-frequency gamma-band power over parietal channels in the first-episode patient group lies in between the activation level in controls and chronic schizophrenia patients, as far as the sustained response and the late stimulus-offset response are concerned. Regarding the early stimulus-onset component ($50 - 100$ ms), the gamma-band response was markedly reduced in chronic patients, whereas controls and first-episode patients showed a similar

level of activation. The analysis of gamma-band activity in single subjects also reveals the general trend of decreasing gamma-band power over parietal channels from controls over first-episode patients to chronic patients; however, there was a considerable overlap of gamma-band power between the different groups (Fig. 3.13 B).

Panels C and D in this figure show the average gamma-band power in the low gamma-band range over central and frontal channels – i.e. channels that were associated with a pronounced decrease of gamma-band power in the task versus baseline contrast in controls in the statistical analysis, as well as with a relative increase of gamma-band power in first-episode patients compared to controls in the between-group analysis (Fig. 3.11 A and C, top rows). The analysis of absolute gamma-band power over frontal and central channels revealed that activation was decreased over these channels in healthy controls; both chronic and first-episode schizophrenia patients were characterized by a reduced downregulation of gamma-band power especially over central channels.

A statistical comparison of sensor-level gamma-band power and the reconstructed source power between first-episode and chronic schizophrenia patients revealed significant differences between the two patient groups (Fig. 3.14). Compared to chronic patients, first-episode patients were characterised by enhanced low- and high-frequency gamma-band power over parietal channels, reflecting a stronger upregulation of gamma-band power in first-episode patients, and by reduced low- and high-frequency gamma-band power over temporal and frontal channels, reflecting a reduced downregulation in chronic patients over these channels (Fig. 3.14 A). The comparison of reconstructed source power revealed mainly enhanced source power for chronic relative to first-episode patients in the lower gamma-band, with the peaks being located in the posterior cingulate and in the medial frontal gyrus (Fig. 3.14 B). In the high-frequency gamma-band, chronic patients were characterized by enhanced source power in the MOG and again in the posterior cingulate, whereas first-episode patients

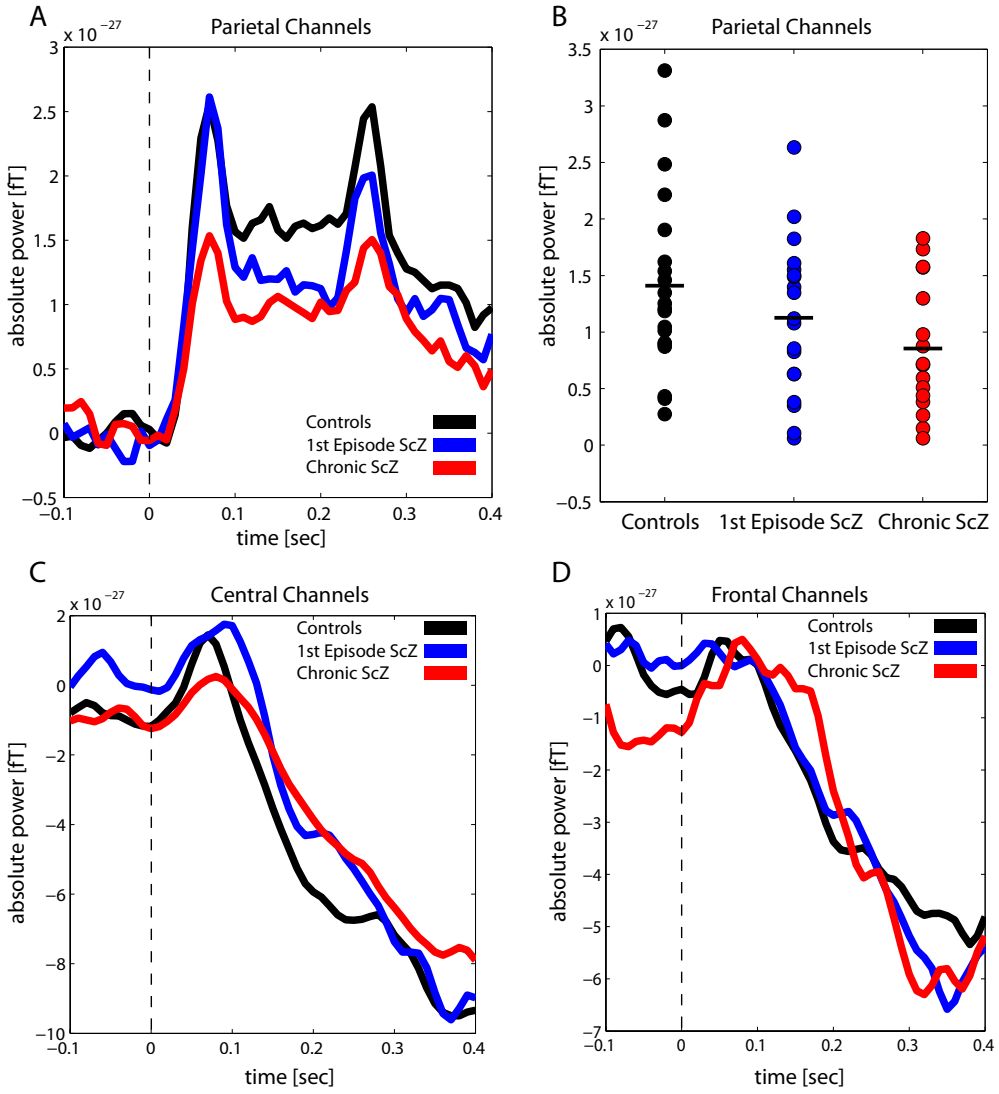

Figure 3.13. Gamma-band power in the face condition for healthy controls, first-episode schizophrenia patients, and chronic schizophrenia patients. Panel (A) shows the timecourses of absolute gamma-band power averaged across parietal channels and between 60 and 140 Hz. The dashed vertical line indicates stimulus onset. In panel (B), each circle represents the gamma-band power in an individual subject averaged across parietal channels, and between $50 - 350$ ms and $60 - 140$ Hz. Both patient groups show a decreased upregulation of high-frequency gamma-band power over parietal channels. Note that the level of gamma-band activity for the sustained induced response in first-episode patients is between that of controls and chronic patients. Panels (C) and (D) show the timecourses of absolute gamma-band power averaged across central and frontal channels, respectively, between 25 and 60 Hz. Both patient groups show a decreased downregulation of gamma-band power, mainly over central channels.

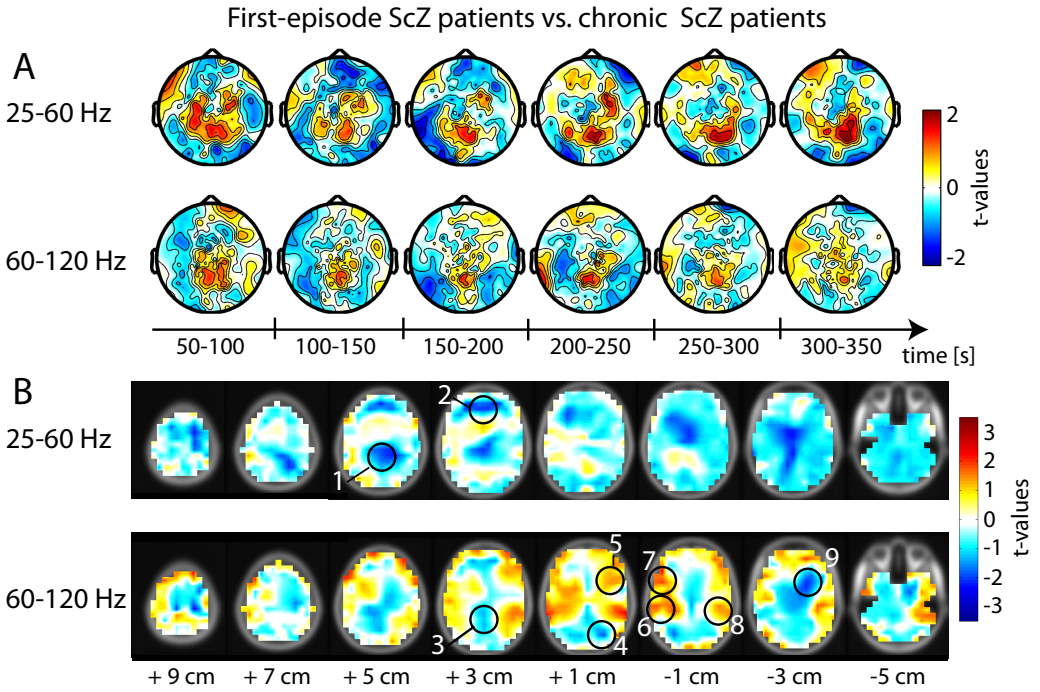

Figure 3.14. Statistical comparison of sensor-level gamma-band power (A) and reconstructed source power (B) between first-episode and chronic schizophrenia patients in the face condition. t-values are masked by the significance map derived from FDR statistical testing ($q < 0.05$). Red represents stronger activation for first-episode patients compared to chronic patients, whereas blue represents less activation in first-episode patients compared to chronic patients. The clusters marked with circles in (B) correspond to the following anatomic locations: 1: posterior cingulate (-2, -42, 18); 2: medial frontal gyrus (6, 42, 20); 3: posterior cingulate (0, -54, 16); 4: middle occipital gyrus (30, -78, 10); 5: inferior frontal gyrus (IFG) (52, 38, 0); 6: middle temporal gyrus (-62, -40, 2); 7: IFG (-50, 26, 2); 8: superior temporal gyrus (60, -40, 10); 9: IFG (28, 16, -24).

showed stronger activation in the IFG, and middle and superior temporal gyri. With regard to behavioral performance, we did not find any significant differences between first-episode and chronic patients. However, there was a trend for a superior classification of inverted-scrambled Mooney stimuli as non-faces in chronic compared to first-episode patients ($t(35) = -1.73$, $p = 0.09$).

3.3.4 Discussion

Studies in chronic medicated schizophrenia patients have provided evidence that this disorder is associated with an impairment in neural synchrony during

cognitive tasks (for a recent review, see Uhlhaas and Singer, 2010). Whether neural synchrony is already impaired at the onset of the disorder and without the confounding influence of medication remains largely unknown. The present study investigated the role of gamma-band oscillations and their neural generators during perceptual organization in unmedicated first-episode schizophrenia patients by means of MEG. In summary, the main findings are that first-episode patients were impaired in the discrimination between upright and inverted-scrambled Mooney stimuli, suggesting a loss in specificity of target (face) detection. Further, first-episode patients were characterized by a reduction in the sustained, induced high-frequency gamma-band response as well as in the stimulus-offset response, with neural generators of these deficits being located in a number of occipital, parietal and frontal brain regions. The following paragraphs focus on the discussion of these findings, i.e. the differences between first-episode patients and healthy controls; differences between first-episode patients and the chronic patient sample from the previous experiment will be discussed in the following chapter that integrates the different studies.

Perceptual Organization in First-Episode Schizophrenia Patients

Compared to healthy controls, first-episode schizophrenia patients were impaired in their ability to discriminate between face and non-face stimuli, which was due to an increased number of false alarms in patients, i.e. incorrect classifications of inverted-scrambled Mooney stimuli as faces. Contrary to our hypothesis, the patients did not show a reduced detection rate for faces among upright Mooney stimuli. Thus, patients had difficulties to decide whether a face was presented or not when a non-face stimulus was shown, but not when a face stimulus was presented. This notion is also reflected in the reaction times in patients, which were comparable with those of controls in the face condition, and significantly longer in the non-face condition.

Studies on perceptual organization in first-episode schizophrenia patients have

presented contradicting evidence: two earlier studies observed a deficit in perceptual organization in first-episode patients (Frith et al., 1983; Rabinowicz et al., 1996), whereas a recent study reported no impairments in first-episode patients for a task with known sensitivity to perceptual organization deficits in chronic schizophrenia patients (Silverstein et al., 2006a). The authors therefore suggested that dysfunctions of perceptual organization begin with increased chronicity of the illness. The pattern of results in the present study, however, suggests that patients already at their first psychotic episode are characterized by a subtle deficit in perceptual organization: the ability to integrate visual features into a coherent percept may still be intact at the onset of the disorder under circumstances when the input corresponds to common visual objects such as upright faces and therefore meets the observer's expectations; however, perceptual organization processes appear to break down when the input is irregular and complex as in the case of inverted-scrambled stimuli.

The processes underlying this impairment are not yet clear. One interpretation may be that the altered behavioral performance results from a disturbed interaction or balance between bottom-up, stimulus-driven visual processing and top-down processes driven by stored image representations and expectations. For example, if early sensory processing was corrupted, the percept in these patients would be mainly determined by top-down processes, such as the representation of a template of the target, i.e. a face in this case, not taking the information actually contained in the stimulus sufficiently into account.

An alternative explanation may be that these patients tend to attribute more significance to inverted-scrambled Mooney stimuli that are perceived as meaningless by healthy controls. Psychosis is characterized by a state of "heightened awareness and emotionality" and "a drive to make sense of the situation" which is interpreted by Kapur (2003) as an effect of aberrant assignment of salience to the elements of one's experience caused by changes in cerebral dopamine metabolism. Several studies using affective classification tasks have supported

this hypothesis, showing an alteration in behavioral performance that was characterized by a misattribution of salience to neutral stimuli (Holt et al., 2006; Phillips et al., 2000; Kohler et al., 2003; Schneider et al., 2006). For example, Holt et al. (2006) observed that, compared to patients without delusions and healthy controls, schizophrenia patients with prominent delusions were more likely to classify neutral words as unpleasant and they took longer to correctly classify neutral words. Preliminary clinical data in the present study show higher scores in first-episode patients compared to chronic patients for the "positive" factor that includes the severity of delusions, which may support the hypothesis that the altered behavioral performance in first-episode patients in the non-face condition is due to increased psychotic symptoms. However, further research is needed to gain insight into the processes underlying the subtle impairment in perceptual organization in first-episode patients.

Gamma-Band Oscillations and their Neural Generators in Healthy Controls

Similar to our previous studies (Sections 3.1 and 3.2), in healthy controls, gamma-band power was increased over parieto-occipital channels in response to upright Mooney faces, both in the low- ($25 - 60$ Hz) and high-frequency ($60 - 120$ Hz) gamma-band ranges, whereas gamma-band power was decreased over fronto-central channels in the low-frequency gamma-band. Sustained gamma-band activity was most pronounced in the higher gamma-band, whereas increases in the lower gamma-band were transient and most likely reflected stimulus onset and offset. As discussed in the previous sections, the prominent activity in the high-frequency gamma-band range is consistent with the view that high-frequency gamma oscillations may represent a functionally relevant phenomenon in cortical networks in addition to low-frequency gamma-band oscillations (e.g., Siegel et al., 2007; Guggisberg et al., 2008).

Source reconstruction of high-frequency gamma-band power in controls re-

vealed pronounced activations in frontal brain regions such as the left superior frontal gyrus (SFG) and the right inferior frontal gyrus (IFG). These activations are consistent with our previous findings in controls – albeit with a different lateralization –, with the left IFG showing enhanced activation for faces compared to non-faces in the perceptual closure time interval (Section 3.1, Fig. 3.4), and the right SFG showing enhanced activation for faces compared to baseline (Section 3.2, Fig. 3.9).

As mentioned before, frontal lobe regions have in general been shown to be involved in cognitively demanding tasks (Duncan and Owen, 2000). Recent fMRI studies have provided evidence for a specific role of the IFG during perceptual recognition, showing that activation of the IFG is related to the moment of object recognition (Ploran et al., 2007), and that in particular the right IFG selectively responds when important cues of a target object are detected (Hampshire et al., 2009). These findings suggest that IFG activation observed in the present study plays an important role in the detection of faces in the upright Mooney stimuli.

Further, we observed enhanced activation in the medial parietal cortex, in the precuneus, which has been proposed to be involved in the reconstruction of object (or face) representations from fragmentary evidence based on stored image representations (Fletcher et al., 1995; Dolan et al., 1997). Together with the results in our previous study (Section 3.1), the present findings support the view that memory-related top-down processes play a critical role for the perception of Mooney faces. Source power was also enhanced in several areas in the visual cortex which may be related to the processing of low-level cues of upright Mooney faces.

In contrast to the widespread increase of source power in the higher gamma-band, controls showed enhanced source power only in a few small clusters in the lower gamma-band, including the left SFG, right STG, right IFG, and right IOG. These clusters are largely consistent with the sources observed in

the higher gamma-band in controls in the present study, and also with the sources observed in the lower gamma-band in healthy controls in our second study (Section 3.2), although we found additional clusters in this earlier study in parietal regions, in the cerebellum, and in the medial frontal gyrus.

In summary, consistent with our results in the two previous studies, source reconstruction of gamma-band oscillations in healthy controls revealed a distributed network of enhanced source power during the processing of upright Mooney faces.

Gamma-Band Oscillations in First-Episode Schizophrenia Patients

First-episode schizophrenia patients exhibited a deficit in the sustained, induced gamma-band response over parieto-occipital channels in response to upright Mooney faces that was most pronounced in the high-frequency gamma-band range ($60 - 120$ Hz) between 100 and 250 ms. This deficit may underlie the observed impairment in perceptual organization, as induced gamma-band activity is supposed to reflect internally generated oscillatory activity and to be relevant for high-level cognitive processes, such as context processing and construction of coherent object representations (Tallon-Baudry and Bertrand, 1999).

A comparison of gamma-band power in the face condition between first-episode patients and the chronic patient group of our previous study revealed that the level of sustained high-frequency gamma-band activity over parieto-occipital channels in first-episode patients was intermediate between that of healthy controls and chronic patients, suggesting that the deficit of induced gamma-band activity may be progressive over the course of the illness. The differences between the two patient groups and likely underlying mechanisms will be discussed in Chapter 4.

Furthermore, we observed a reduction in gamma-band power of the late ($250 - 300$ ms) stimulus-offset response, whereas the early ($50 - 100$ ms)

stimulus-onset response to face stimuli was largely intact in amplitude. These results are consistent with another study in drug-free schizophrenia patients that reported a reduction of the late ($220 - 350$ ms) gamma-band response at 40 Hz over frontal electrodes in response to auditory stimuli, while the early ($20 - 100$ ms) gamma-band response was not impaired (Gallinat et al., 2004). Whereas the findings by Gallinat suggested abnormal interactions within a frontal lobe network, our results indicate that interactions within a parieto-occipital network may also be impaired at illness onset.

In contrast to our previous study, we found no correlation between sensor-level high-gamma power and discrimination performance in first-episode schizophrenia patients in the present study. In addition, in controls we observed a positive correlation between low-gamma power over fronto-central channels and the discrimination performance – contrary to the negative correlation for the same frequency band in chronic patients in the previous study. Thus, the present findings did not confirm the relationships between gamma-band power and performance observed in our previous study. The reasons for these differences are unclear at present, but it is possible that the sample sizes were too small to find robust correlations between gamma power and performance measures.

Another reason may be related to the method used to compute the correlations: for each subject, gamma-band power was averaged across the channels that showed a significant increase or decrease of power in the statistical analysis of the respective within-group task vs. baseline contrast. We opted for this method in order to select channels objectively and ensure that correlations within each group were performed with channels that showed a significant activation in the respective group. Even though positive and negative channels were similar across groups in general (parieto-occipital and fronto-central channels, respectively), the drawback of this method is that the channels are not completely identical for all groups, which may also contribute to differences in the correlation analyses. Further analyses and studies with larger sample sizes

may be needed to clarify the relationship between gamma-band activity and performance measures.

Source reconstruction of gamma-band activity in the time window between 50 and 350 ms revealed that first-episode schizophrenia patients exhibited pronounced reductions of source power compared to controls – both in the high- and the low-frequency gamma-band – in occipital, parietal and frontal regions, which are involved in perceptual organization as demonstrated by the results in healthy controls. Specifically, the reductions of source power in first-episode patients were most pronounced in various occipital and frontal regions, which indicates that interactions between areas related to the processing of low-level cues and areas maintaining a representation of the task or a template of the target stimulus may be disturbed in first-episode patients. These findings support the view that the impaired behavioral performance may result from a disturbed interaction between bottom-up and top-down processing as discussed above. In summary, our results suggest that patients at the onset of their first psychotic episode are characterized by widespread reductions of source power that may underlie the deficits in the induced and late stimulus-offset gamma-band response at the sensor level, and the associated behavioral impairments.

Conclusion

The present study provides novel evidence for an impairment in gamma-band oscillatory activity in drug-naïve schizophrenia patients at the onset of their first psychotic episode. Specifically, we found that first-episode patients are characterized by a deficit in the sustained, induced high-frequency gamma-band response as well as in the late stimulus-offset response, suggesting that the coordination of neural activity in local networks is already impaired early in the illness and without the confounding influence of medication. The underlying neural generators were located in a distributed network in occipital, parietal and frontal regions. Previous studies have provided inconsistent re-

sults regarding perceptual organization in first-episode patients (Frith et al., 1983; Rabinowicz et al., 1996; Silverstein et al., 2006a). In this study, perceptual organization of ambiguous face stimuli was impaired in first-episode patients as reflected by an impaired discrimination between upright and inverted-scrambled Mooney stimuli.

4 General Discussion

In this thesis we investigated the role of disturbed neural synchrony as a pathophysiological mechanism in schizophrenia. The previous chapter presented data from three experimental studies that examined gamma-band oscillatory activity during perceptual organization and the underlying neural network in healthy subjects, medicated chronic schizophrenia patients, and neuroleptic-naïve first-episode schizophrenia patients by means of MEG. In this chapter, an attempt is made to integrate the results across the three studies. I will first outline the main features of gamma-band activity during perceptual organization in healthy controls. Afterwards, the findings in chronic and first-episode schizophrenia patients will be compared and potential mechanisms of the differences between the two patient groups will be discussed. The chapter closes with a discussion of the limitations of the present studies and implications for further research.

4.1 Gamma-Band Oscillations during Perceptual Organization in Healthy Controls

Comparison of Sensor-Level Spectral Power in Healthy Controls across Studies

Gamma-band oscillations during perceptual organization were examined in three different groups of healthy subjects. The pattern of gamma-band activ-

ity during the processing of upright Mooney faces was very similar across these groups, with the main features being an increase of high-frequency gamma-band activity ($60-120$ Hz) over occipital-parietal channels, accompanied by a decrease of low-frequency gamma-band activity ($25-60$ Hz) over fronto-central channels. Thus, performance of the Mooney faces task was associated with both an upregulation and a downregulation of gamma-band activity; these modulations involved different frequency bands and probably different networks.

Our finding of prominent high-frequency gamma-band activity is consistent with recent evidence from MEG and intracranial EEG studies that reported gamma-band responses between 60 and 200 Hz during a variety of cognitive tasks (e.g., Crone et al., 2001; Kaiser et al., 2004; Brovelli et al., 2005; Lachaux et al., 2005; Hoogenboom et al., 2006; Siegel et al., 2007; Guggisberg et al., 2008), suggesting that in addition to activity in the low-frequency gamma-band, high-frequency gamma oscillations are a functionally relevant phenomenon in cortical networks.

The relationship between high-frequency gamma-band oscillations and the firing properties of the underlying neural population has only recently begun to be explored. Traditionally, it has been assumed that aggregate electrical activity of neuronal ensembles as measured with EEG or MEG reflects mainly synaptic activity (Klee et al., 1965). Recent studies, however, showed that local field potential (LFP) oscillations in the high-gamma range were tightly correlated with the spiking activity of the underlying neural population (Liu and Newsome, 2006; Nir et al., 2007; Ray et al., 2008a,b; Belitski et al., 2008; Rasch et al., 2008; Manning et al., 2009), suggesting that – in contrast to low-gamma activity – high-gamma activity has a relatively greater contribution from action potentials than from synaptic events. An alternative interpretation of the correlation between high-gamma oscillations and spikes may be that high-gamma activity reflects synaptic events where the associated spikes

are produced mainly locally – this interpretation provides further support for the view that synchronous high-gamma oscillations are primarily involved in local coordination of neural activity. Further studies using invasive techniques such as microelectrode recordings are expected to enhance our understanding of the neural correlates of high-frequency gamma-band activity.

The decrease of gamma-band activity over fronto-central channels during task performance might be interpreted in terms of the default-mode network, which refers to brain regions that are consistently activated when individuals are in a resting state, i.e. when they are awake and alert, but not actively involved in an attention demanding or goal-directed task (Raichle et al., 2001). It has been proposed that especially the anti-correlation between task-positive networks, being activated during task performance, and the default-mode network, being deactivated during task performance, is important for successful task performance (Fox et al., 2005). The resting state or default-mode network has so far been predominantly investigated with fMRI, and it has been proposed that the default-mode network is characterised by very low-frequency BOLD (blood oxygenation level dependent) signal oscillations (< 0.1 Hz). However, it appears that we find a similar functional coupling between deactivation and activation at a faster timescale in MEG during performance of the Mooney faces task.

Comparison of Source-Level Results in Healthy Controls across Studies

Source reconstruction of gamma-band activity in healthy controls revealed a distributed network of sources during the Mooney faces task. This finding was consistent across the three studies. Regarding the specific source locations, however, results in healthy controls showed some differences. These might be accounted for by the use of different beamforming techniques in the first

(frequency-domain DICS beamforming) as compared to the second and third study (time-domain LCMV beamforming). Some of the differences may also be due to the inaccuracy inherent in the beamforming technique. As mentioned above, beamforming fails in the presence of sources that are highly correlated (e.g., van Veen et al., 1997), leading to missing or mislocalized sources. Thus, some sources may have been only unilaterally reported because source power in the other hemisphere may have been extinguished due to inter-source correlation. For this reason, we opted for a conservative approach and disregarded the lateralisation of brain areas in the following.

Some brain regions were found to be consistently activated across different studies and both gamma-frequency bands during the processing of upright and inverted-scrambled Mooney faces in healthy controls, suggesting that they play an important role during our visual closure task. These include frontal brain regions (superior, middle and inferior frontal gyri), the superior temporal gyrus (STG), the inferior occipital gyrus (IOG), and parietal regions such as the inferior parietal lobule (IPL) and the precuneus. These findings suggest that the processing of Mooney face stimuli involves areas related to low-level feature processing (IOG), and areas related to higher level processes such as cognitive control and task maintenance (frontal cortex; Duncan and Owen, 2000) as well as memory-guided object reconstruction (parietal cortex; Dolan et al., 1997; Wagner et al., 2005). The role of the STG in our task is less clear; the STG has traditionally been implicated in cross-modal integration (e.g., Seltzer and Pandya, 1978; Calvert et al., 2000; Beauchamp et al., 2004) but a recent study has suggested that the STG is involved in solving verbal insight-problems (Jung-Beeman et al., 2004). It might be worth studying whether the STG has a more general role in solving insight-problems and may thus be also related to the detection of Mooney faces.

The network described above refers to the common sources that are activated during the processing of Mooney face stimuli in general. To examine the

processes specifically related to perceptual closure in healthy controls, we contrasted the face and non-face conditions and used time-resolved beamforming to analyze the spatio-temporal dynamics of visual closure processes in our first study. The findings confirmed our initial hypotheses that the extraction of 3D shape cues provided by shading (Kemelmacher-Shlizerman et al., 2008), which are processed in caudal ITG (Georgieva et al., 2008), is indeed essential for the perception of Mooney faces.

Furthermore, the recognition of Mooney faces is also guided by top-down processes (Kemelmacher-Shlizerman et al., 2008) such as object familiarity (Dolan et al., 1997; Moore and Cavanagh, 1998) and memory processes (Dolan et al., 1997) represented in posterior parietal cortex (Wagner et al., 2005). Moreover, we found that inferior temporal cortex areas specialized for the perceived object were activated at the moment of perceptual closure, i.e. the fusiform gyrus related to face processing (Kanwisher et al., 1997) for Mooney face stimuli. Interestingly, the IFG also showed activation for faces specifically in the closure interval, which supports the findings of recent studies, suggesting that this area is critically involved in visual detection processes (Ploran et al., 2007; Hampshire et al., 2009).

4.2 Gamma-Band Activity in Schizophrenia

As mentioned above, sensor-level gamma-band activity in healthy controls during the visual closure task was characterized by both an upregulation of high-frequency gamma-band activity over parieto-occipital channels and a downregulation of low-frequency gamma-band activity over fronto-central channels. In schizophrenia patients, modulation amplitudes of both task-related effects were reduced; thus, patients showed a reduced upregulation of high-frequency gamma-band activity accompanied by a reduced downregulation of low-frequency gamma-band activity.

Reduced Upregulation of High-Frequency Gamma Power

Our finding that chronic medicated schizophrenia patients showed a pronounced deficit in gamma-band activity is consistent with a number of studies that reported impairments in synchronous gamma-band oscillations in chronic patients during sensory processing (for a recent review see Uhlhaas and Singer, 2010), supporting the notion that the coordination of neural activity in local neural networks is disturbed in schizophrenia (Phillips and Silverstein, 2003; Uhlhaas and Singer, 2006). This impairment may result from alterations in brain gray matter structure (Harrison, 1999b; Arnold et al., 2005) and abnormalities in GABAergic (Lewis et al., 2005) and glutamatergic (Coyle, 2006) neurotransmitter systems in schizophrenia that are critically involved in the generation and synchronization of high-frequency oscillatory activity (Traub et al., 1997, 2004). Studies in chronic patients have so far focused on a narrow frequency range ($30 - 60$ Hz, mainly 40 Hz) (e.g., Green et al., 2003; Spencer et al., 2003; Wynn et al., 2005). Our results provide novel evidence for a widespread dysfunction in oscillatory activity in chronic schizophrenia patients that also includes the high-frequency gamma-band range (> 60 Hz).

Our third study showed that impaired high-frequency gamma-band activity is already present at the onset of the disorder, in drug-naïve patients, which suggests that the deficit in gamma-band activity in chronic patients cannot solely be due to medication effects or the chronicity of the illness. A comparison between first-episode and chronic schizophrenia patients revealed some differences in gamma-band power over parieto-occipital channels: first, compared to healthy controls, the early stimulus-onset response was markedly reduced in amplitude in chronic patients, but was intact in first-episode patients. Further, the amplitude of the sustained high-frequency response and of the late stimulus-offset response in first-episode patients was intermediate between the level of gamma-band activity in controls and chronic patients.

These results suggest that the deficit in gamma-band power may be progres-

sive over the course of the disorder. Recent longitudinal structural MRI studies have reported progressive decreases in gray matter volume during the initial years after the first episode that continue also in the more chronic phase of the illness (e.g., DeLisi et al., 1997; Gur et al., 1998a; Lieberman et al., 2001; Cahn et al., 2002; Ho et al., 2003). These structural brain changes may represent a possible neuroanatomical correlate of progressive reductions in spectral power in schizophrenia; however, it is unclear at present how changes in brain structural volume are related to changes in gamma-band spectral power.

Furthermore, it is unclear to what degree reductions in gamma-band activity in chronic patients compared to first-episode patients observed in our studies, as well as excessive brain volume loss after the first episode reported in the literature are due to disease progression, increasing age or the effects of antipsychotic drug treatment. Several studies in macaque monkeys have demonstrated that chronic exposure to antipsychotic treatment is associated with reduced brain volume (Dorph-Petersen et al., 2005; Konopaske et al., 2007, 2008). Lieberman et al. (2005) reported differential treatment effects of typical and atypical antipsychotics on brain gray matter volumes in first-episode patients that were followed over time. Thus, there is preliminary evidence for an effect of antipsychotic treatment on brain structure; however, the contribution of antipsychotic medication to progressive brain changes and worsening of alterations in synchronous oscillatory activity needs further study.

Impaired Downregulation of Lower Gamma-Band Activity

Interestingly, chronic and first-episode schizophrenia patients were characterized by enhanced task-related spectral power over frontal and central channels in the lower gamma-band relative to controls, representing in fact a reduction in downregulation of gamma-band activity in the patients. Similar to the deficit in high-frequency gamma-band activity, the impairment in the modulation of lower gamma-band activity appeared more pronounced in chronic

compared to first-episode patients, suggesting a progression of this impairment over the course of the illness. As mentioned above, the task in general elicited a downregulation of power in the lower gamma band over fronto-central channels, which may represent a decrease of default-mode network activity that is typically downregulated during cognitive tasks (Raichle et al., 2001; Fox et al., 2005). Therefore, one interpretation of our data might be that the transition from the resting-state network activity to the task-related network activity is dysfunctional in schizophrenia patients, which might underlie the impaired task performance in patients (discussed below). The current results fit with recent studies reporting atypical functional connectivity in resting state networks in schizophrenia (for a review see Broyd et al., 2009).

Abnormal Source Power in Multiple Brain Regions

In both patient groups, source reconstruction of gamma-band power revealed abnormal activation patterns in various occipito-temporal, parietal and frontal areas that were relevant to perceptual organization in healthy controls, suggesting that dysfunctional processing in these brain regions underlies the changes in gamma-band power observed at the sensor level and behavioral impairments in patients.

A direct comparison between first-episode and chronic schizophrenia patients revealed some differences between the two patient groups. First, chronic patients showed a stronger activation of the posterior cingulate cortex compared to first-episode patients. As this brain region has been related to the default-mode network in fMRI studies (Greicius et al., 2003; Fransson and Marrelec, 2008), the finding supports our hypothesis that especially chronic schizophrenia patients might be characterized by an impairment in the downregulation of the default-mode network during task performance. Second, we noted enhanced source power in first-episode compared to chronic patients in the IFG and temporal cortex, which indicates that object recognition processes might

be less impaired early in the disease compared to more chronic stages.

In summary, the pattern of widespread dysfunctions in chronic and first-episode patients is consistent with current theories of schizophrenia that emphasize impaired coordination of neural activity within and between various brain regions as compared to a single brain lesion underlying clinical symptoms and cognitive deficits (Phillips and Silverstein, 2003; Friston, 1999). This notion is supported by anatomical studies, showing that schizophrenia is associated with molecular and structural abnormalities in multiple brain regions (Harrison, 1999b; Shenton et al., 2001). Impaired neural coordination in various local networks as observed in the present studies may be related to dysfunctions in long-range synchronization schizophrenia patients (Spencer et al., 2003; Slewa-Younan et al., 2004; Uhlhaas et al., 2006a). However, it is currently unclear to what extent impairments in local circuits contribute to long-range synchronization deficits. It also needs to be taken into account that linking the two phenomena is complicated by the fact that impairments in local and long-range synchrony in schizophrenia patients involved different frequency bands: whereas our effects were observed in the high-frequency gamma-band range, impairments in long-range synchronization were observed at beta and lower gamma-band frequencies.

4.3 Perceptual Organization in Schizophrenia

We had expected that both patient groups would be impaired in the detection of upright Mooney faces, indicating a deficit in perceptual organization. Our results showed that chronic and first-episode patients were indeed impaired in perceptual organization, but to different degrees and with opposite behavioral patterns.

Chronic patients showed a normal performance in the non-face condition, but were characterized by longer reaction times and reduced detection rates in the face condition. We interpret this finding as an impairment in perceptual

organization in chronic patients, i.e. an impairment in the ability to integrate visual features into a coherent percept, which might result from the deficits in source power and sensor-level gamma-band activity described above. This finding is consistent with numerous studies that reported a deficit in perceptual organization in chronic schizophrenia patients (e.g., Rabinowicz et al., 1996; Silverstein et al., 1996, 1998; Doniger et al., 2001; Silverstein et al., 2000; Uhlhaas et al., 2005, 2006b; Kurylo et al., 2007; Silverstein et al., 2009).

In contrast, first-episode patients were not impaired in the detection of faces among upright Mooney stimuli; however, they showed an increased number of incorrect classifications of inverted-scrambled Mooney stimuli as faces, suggesting an impairment in the discrimination between face and non-face stimuli. These results indicate that there is a subtle impairment in perceptual organization at the onset of the disorder, which manifests under circumstances when the sensory input is irregular and complex as in the case of inverted-scrambled stimuli.

The processes underlying the performance impairment in first-episode patients are not yet clear. One might speculate that the loss in specificity of face detection in these patients results from a disturbed interaction between bottom-up and top-down processes, which would be consistent with the finding of reduced source power mainly in frontal brain regions and in the primary visual cortex in first-episode patients. Thus, top-down influences in the form of expectations or templates may take disproportional precedence in the construction of a percept.

Another interpretation might be that these patients attribute more significance to inverted-scrambled Mooney stimuli that are perceived as meaningless by healthy controls. This interpretation is based on the theory that psychosis is characterized by "a drive to make sense of the situation" and aberrant assignment of salience to the elements of one's experience (Kapur, 2003).

Further research is needed to understand to what extent bottom-up and top-

down processes in visual perception are impaired at the beginning of the disorder, and what mechanisms contribute to the worsening in perceptual organization in chronic compared to first-episode patients. Our finding that both effects of modulation of gamma-band amplitude (up- and downregulation) were more impaired in chronic compared to first-episode patients may suggest that a progressive deficit in neural coordination might underlie a worsening in visual integration over the course of the illness.

4.4 Limitations and Future Directions

Limitations of the Present Studies

A major aspect of this work has been the reconstruction of the neural generators associated with perceptual organization in healthy controls, chronic and first-episode schizophrenia patients, using beamforming source reconstruction techniques. The stability of the source reconstruction results, however, might be reduced due to relatively small samples sizes used in the analyses. This aspect might have affected results particularly in the chronic patient study where five patients needed to be excluded due to artifacts or missing anatomical data. Furthermore, the source locations obtained with MEG beamforming should not be taken to represent the true locations with zero error for the reasons discussed above. In our first study, we additionally estimated sources of differential activity from fMRI data and found a very good correspondence between source locations obtained from beamforming and fMRI. However, this finding is limited by the fact that the fMRI scans did not cover all brain structures; we therefore cannot draw any conclusions about a correspondence between MEG and fMRI activations regarding inferior frontal brain regions and anterior inferior temporal cortex.

It is also important to note that the coactivations of sources observed in our studies may suggest interactions between these sources – however, we did not

use any measures that would test for interactions directly, such as effective connectivity measures. Thus, definite conclusions about interactions between sources are not warranted by the current datasets.

Regarding our studies in patients, the experiments were not designed to statistically evaluate gamma-band power in the non-face condition in detail; it therefore remains unclear to what extent the results for gamma-band spectral power and source reconstruction are specific to the processing of upright as compared to inverted-scrambled Mooney faces in patients. Furthermore, the question remains at what stage visual processing is impaired in schizophrenia. As mentioned in Chapter 1, a number of studies has provided evidence that schizophrenia patients are characterized by deficits in early visual processing, and research has so far emphasized dysfunctions in the magnocellular pathway. Our findings suggest additional impairments in higher-level visual processing in the ventral stream in schizophrenia patients. It remains unclear, however, to what extent these impairments are due to dysfunctional processing in primary visual areas observed in the present studies. Furthermore, it is unclear to what extent dysfunctions in the magnocellular and/or parvocellular pathway contribute to the observed impairments. The Mooney faces paradigm we used in the present studies does not allow to disentangle these different possible mechanisms of dysfunctions in higher-level visual processing in schizophrenia patients.

Future Directions

In the following, I will suggest some ideas for future studies that may address some questions left open by the research presented in this thesis. First, we observed that first-episode patients were characterized by a deficit in high-frequency gamma-band spectral power that was less pronounced compared to chronic patients, suggesting that this impairment is progressive over the course of the disorder. To test this hypothesis, a longitudinal study to follow-up

the first-episode patients and investigate the course of change in gamma-band power would be necessary. Further, the present data leave open the question whether the worsening in gamma-band power in chronic patients compared to first-episode patients is due to disease progression, increasing age or the effects of antipsychotic drug treatment. The influence of increasing age on gamma-band power could be tested in a longitudinal study with healthy controls. The contribution of the other factors, however, will be difficult to clarify because this would require testing untreated subjects with schizophrenia, who cannot be used as a comparison group for obvious ethical reasons.

Second, brain structural abnormalities have been suggested as the anatomical correlate of impaired neural synchrony in schizophrenia patients. Further research is needed to investigate this relation; we plan to examine correlations between spectral power at specific source locations obtained with MEG beamforming and gray matter volume in corresponding brain structures to address this issue.

Third, an important question that needs further study is whether measures of neural synchrony during visual perception have a specific diagnostic value. So far, there is no consistent and specific biomarker for schizophrenia that would allow identifying at-risk subjects at an early stage of the disorder. Thus, further studies might investigate whether impairments in gamma-band spectral power are specific to schizophrenia patients as compared to other psychiatric groups. Our data, however, revealed a considerable overlap in the amplitude of high-frequency gamma-band activity across controls, first-episode patients and chronic patients, suggesting that this measure is not suited to differentiate between healthy subjects and schizophrenia patients. Further analyses may reveal whether other neurophysiological measures, such as event-related fields or source power associated with visual processing, provide a more precise differentiation of these groups.

Further, in our first study, we suggested that during perceptual closure, inferior

temporal cortex areas specialized for the perceived object are activated, i.e. the fusiform gyrus related to face processing for Mooney face stimuli in our case. To investigate this hypothesis, other Mooney stimuli – such as Mooney objects and houses – could be used; one should then see the closure effect in brain regions specialized for these stimuli, i.e. in the lateral occipital complex (Malach et al., 1995; Grill-Spector et al., 1998) and the parahippocampal gyrus (Epstein and Kanwisher, 1998; Aguirre et al., 1998).

As mentioned above, we suggested that the interaction between brain regions that were coactivated during the visual closure task, for example areas related to processing of 3D structure from shading cues (cITG), and areas associated with the activation of long-term memory templates (PPC), plays an important role for perceptual closure. However, interactions were not directly examined in the present studies. As a next step, we plan to reconstruct the time series at the source locations identified by our beamforming analyses and use a measure of effective connectivity such as transfer entropy (Schreiber, 2000) to examine the direction of effects for the nodes of the perceptual closure network.

Finally, our sensor-level gamma-band data indicate that different frequency ranges within the gamma-band are differentially modulated during visual processing, suggesting that they might serve different roles. More research will be necessary to understand the functions and underlying mechanisms of different gamma-frequency bands. We interpreted the downregulation of low-frequency gamma-band power over fronto-central channels in terms of the default-mode network that is typically deactivated during cognitive tasks. Data from MEG resting-state studies may provide further insight into this matter by determining predominant operating frequencies of the resting state network.

4.5 Conclusions

Our results provide evidence that high-frequency gamma-band oscillations play an important role during perceptual organization, and that the underlying

neural network comprises a number of distributed sources in occipito-temporal, parietal and frontal brain regions.

We found that both chronic and first-episode schizophrenia patients were impaired in perceptual organization, although patterns of behavioral impairment were different: whereas chronic patients exhibited a reduced ability to detect upright Mooney faces, first-episode patients were impaired in the classification of inverted-scrambled Mooney stimuli as non-faces. This suggests that the ability to integrate visual features into a coherent percept is impaired in chronic patients, but may still be intact to some degree at early stages of the disorder; first-episode patients, however, seem to be characterized by a loss in specificity of visual detection.

Abnormal modulations of task-related gamma-band activity as observed in our data may underlie the impairments in perceptual organization in schizophrenia patients. Specifically, our findings provide novel evidence for a deficit of high-frequency gamma-band oscillations in schizophrenia patients, which is present already at the onset of the disorder, in first-episode drug-naïve patients. The deficit of gamma-band activity was more pronounced in chronic compared to first-episode patients, suggesting a progressive deficit over the course of the disorder. These findings are consistent with abnormalities in GABAergic and glutamatergic neurotransmission in schizophrenia, and suggest that schizophrenia is characterized by a disturbance in the coordination of local neural activity. Furthermore, we observed that the downregulation of low-frequency gamma-band activity over fronto-central channels was reduced in patients, which might be interpreted as an abnormal modulation of the default-mode network in schizophrenia patients.

Our source reconstruction results demonstrated that schizophrenia patients were characterized by reduced power in a number of brain regions that were associated with perceptual closure in healthy controls. In addition, in chronic patients we found a reduced downregulation of source power in the posterior

cingulate gyrus compared to controls and first-episode patients, which may be related to a stronger activation of the default-mode network during task performance in chronic patients. Our findings of altered source power in multiple brain regions in schizophrenia patients support the current view that there is no single pathophysiological lesion in schizophrenia, but that this disorder likely arises from an impairment of neural coordination within and between brain regions.

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Appendix

Diagnostic Criteria for Schizophrenia according to DSM-IV

A. **Characteristic symptoms:** Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):

- Delusions
- Hallucinations
- Disorganized speech (e.g., frequent derailment or incoherence)
- Grossly disorganized or catatonic behaviour
- Negative symptoms (i.e., affective flattening, alogia, or avolition)

Note: only one Criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping a running commentary on the person's behaviour or thoughts, or two or more voices conversing with each other.

B. **Social/occupational dysfunction:** For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).

C. **Duration:** Continuous signs of the disturbance persist for at least 6

months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).

D. **Schizoaffective and Mood Disorder exclusion:** Schizoaffective Disorder and Mood Disorder With Psychotic Features have been ruled out because either (1) no Major Depressive Episode, Manic Episode, or Mixed Episode have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.

E. **Substance/general medical condition exclusion:** The disturbance is not due to the direct physiological effects of a substance (e.g., abuse of a drug, medication) or a general medical condition.

F. **Relationship to a Pervasive Developmental Disorder:** If there is a history of Autistic Disorder or another Pervasive Developmental Disorder, the additional diagnosis of Schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

Table A.1. Five factor model of schizophrenic symptoms according to Lindenmayer et al. (1994) and Cuesta and Peralta (1995). The numbers in brackets represent the item number of the PANSS.

Factor	Symptoms
1. Negative	Emotional Withdrawal (N2) Passive / Apathetic Withdrawal (N4) Lack of Spontaneity (N6) Poor Rapport (N3) Active Social Avoidance (G16) Blunted Affect (N1)
2. Excitement	Excitement (P4) Poor Impulse Control (G14) Hostility (P7) Tension (G4)
3. Cognitive	Conceptual Disorganization (P2) Disorientation (G10) Mannerisms and Posturing (G5) Poor Attention (G11) Difficulty in Abstract Thinking (N5)
4. Positive	Suspiciousness (P6) Delusions (P1) Grandiosity (P5) Unusual Thought Content (G9)
5. Depression	Preoccupation (G15) Guilt Feelings (G3) Depression (G6) Somatic Concern (G1) Anxiety (G2)
Disorganization	Conceptual Disorganization (P2) Inappropriate Affect Poor Attention (G11)
Other PANSS Items	Uncooperativeness (G8) Motor Retardation (M7) Stereotyped Thinking (N7) Lack of Judgment and Insight (G12) Disturbances of Volition (G13) Hallucinations (P3)

Brief Assessment of Cognition in Schizophrenia (Keefe et al., 2004)

- **List learning** to assess verbal memory. Subjects are presented with 15 words and then asked to recall as many as possible, in any order. The procedure is repeated five times. For data analysis, we computed a composite score for verbal memory, consisting of the total number of recalled words (range: $0 - 75$).

- **Digit sequencing task** to assess working memory. Subjects are presented with clusters of numbers of increasing length. They are asked to tell the numbers in order, from lowest to highest. The measure is the number of correct responses (range: $0 - 28$).

- **Token motor task** to assess motor speed. Subjects are given 100 plastic tokens and asked to place them two at a time into a container as quickly as possible within a 60 second time limit. The measure is the number of tokens correctly placed into the container (range: $0 - 100$).

- **Category instances** to assess verbal fluency. Subjects are given 60 seconds to name as many words as possible within a given category ("supermarket").

- **Controlled oral word association test** to assess verbal fluency. In two separate trials, subjects are given 60 seconds to generate as many words as possible that begin with a given letter (S and F). The measure is the number of words generated per trial. Here, we computed a composite score for verbal fluency, consisting of the total number of generated words in the category and word association tests.

- **Symbol coding** to assess attention and speed of information processing. Subjects are asked to write numerals $1 - 9$ as matches to symbols on a response sheet as quickly as possible within a 90 second time limit. The measure is the number of correct numerals (range: $0 - 110$).

- **Tower of London** to assess executive functions. Subjects are presented with a series of two pictures that show different arrangements of three balls on three pegs. They are asked to give the total number of moves necessary to make the arrangement in one picture identical to that in the other picture. The measure is the number of correct responses (range: $0 - 22$).

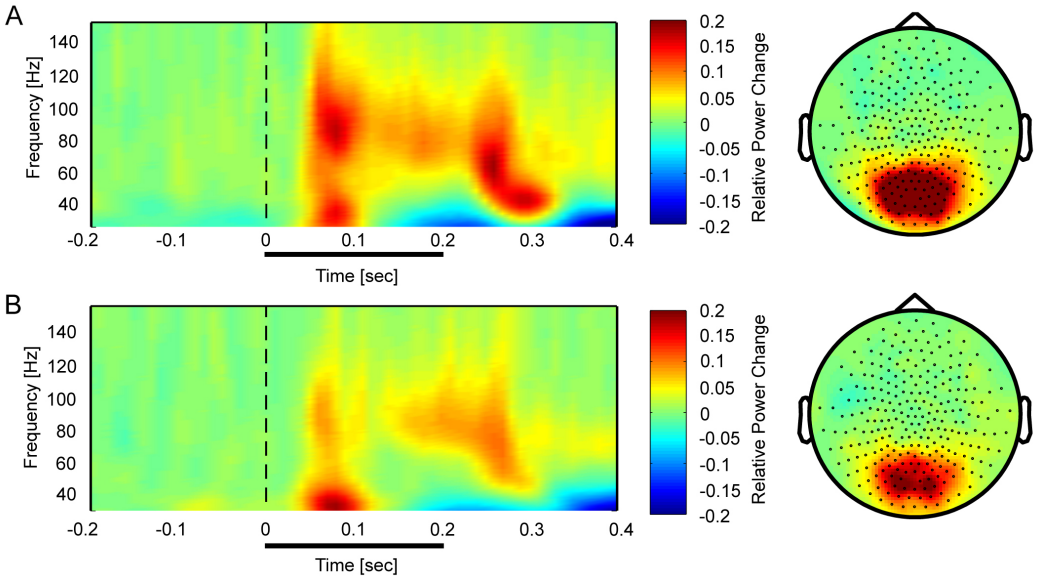

Figure A.1. Time-frequency representations (TFRs) and topographies of gamma-band spectral power in the non-face condition for controls (A) and chronic schizophrenia patients (B). The TFRs represent the average across all channels. The dashed vertical line marks stimulus onset. The topographies are averaged across the stimulus interval ($0 - 400$ ms) and between 25 and 150 Hz. The gamma-band signal is expressed as relative power change in the post-stimulus time window compared to baseline. In chronic schizophrenia patients, there is a marked reduction in spectral power, especially in the high-gamma frequency range ($60 - 120$ Hz).

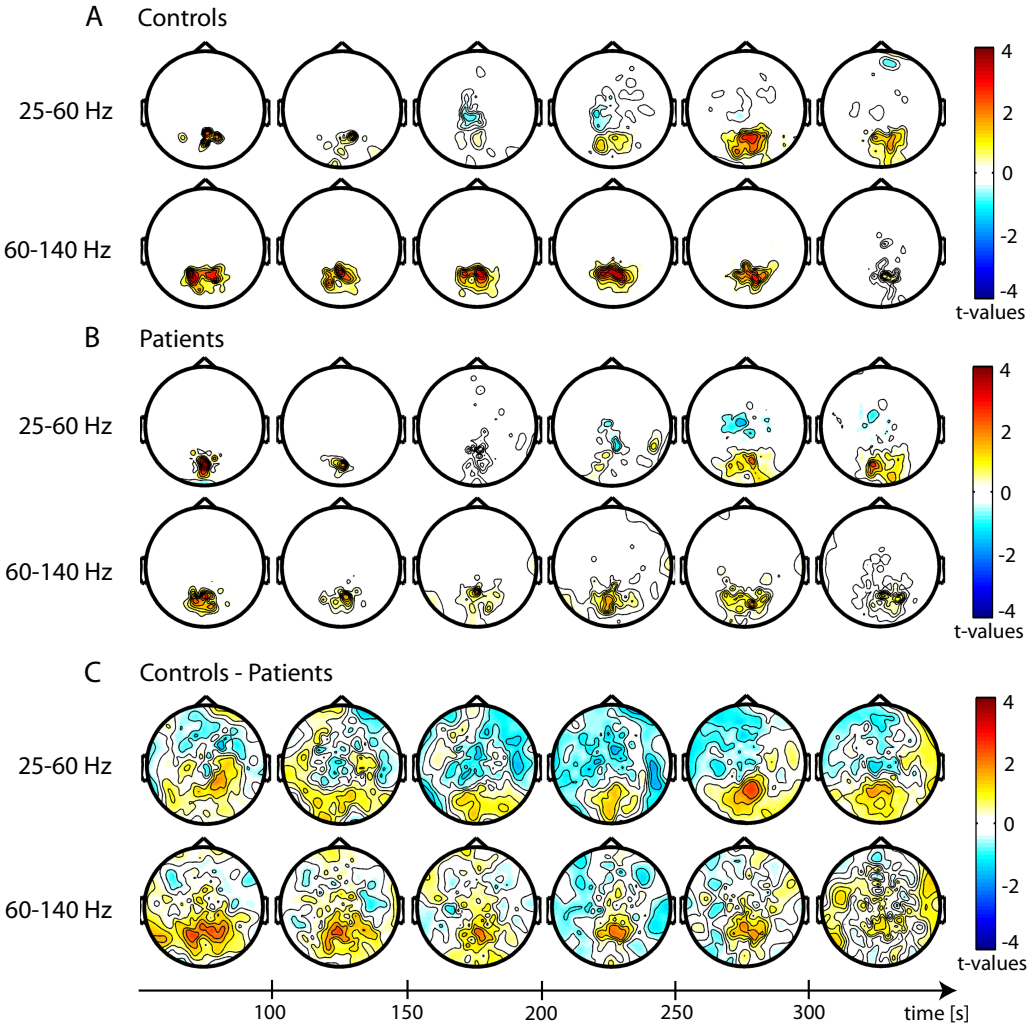

Figure A.2. Statistical analysis of gamma-band power in response to inverted Mooney faces for controls (A), chronic schizophrenia patients (B), and for the difference between controls and patients (C). The topographies in (A) and (B) show significant differences between the non-face condition and the baseline, separately for the lower ($25-60$ Hz) and the higher ($60-140$ Hz) gamma-band. The effect is masked by the significance map derived from false-discovery rate (FDR, $q < 0.05$) statistical testing. Red denotes higher activation during stimulus presentation compared to baseline, whereas blue denotes less activation during stimulus presentation compared to baseline. The topographies in (C) show the difference for the non-face condition between controls and chronic schizophrenia patients. Here, red denotes stronger activation for controls compared to chronic patients, whereas blue represents stronger activation in chronic patients relative to controls.

Table A.2. Correlations between gamma-band power, clinical symptoms and performance in controls and chronic schizophrenia patients

		Controls		Patients	
		r	p-value	r	p-value
		High Gamma, Positive Cluster			
Performance	Hits (%)	0.042	0.877	−0.056	0.836
	Discrimination index A'	0.022	0.936	0.512	0.042
	Reaction time (ms)	−0.125	0.646	−0.176	0.515
PANSS	Disorganization	–	–	−0.632	0.009
	Depression	–	–	−0.387	0.139
	Positive	–	–	−0.227	0.397
	Cognitive	–	–	−0.561	0.024
	Excitement	–	–	−0.245	0.36
	Negative	–	–	−0.35	0.184
		Low Gamma, Positive Cluster			
Performance	Hits (%)	0.36	0.171	−0.346	0.189
	Discrimination index A'	0.454	0.077	0.404	0.12
	Reaction time (ms)	0.044	0.872	−0.286	0.282
PANSS	Disorganization	–	–	−0.694	0.003
	Depression	–	–	−0.66	0.005
	Positive	–	–	−0.458	0.075
	Cognitive	–	–	−0.625	0.01
	Excitement	–	–	−0.265	0.321
	Negative	–	–	−0.374	0.154
		Low Gamma, Negative Cluster			
Performance	Hits (%)	0.3	0.26	−0.078	0.774
	Discrimination index A'	0.392	0.133	−0.44	0.088
	Reaction time (ms)	0.034	0.901	−0.258	0.335
PANSS	Disorganization	–	–	0.158	0.559
	Depression	–	–	0.23	0.391
	Positive	–	–	−0.041	0.879
	Cognitive	–	–	0.241	0.369
	Excitement	–	–	−0.013	0.963
	Negative	–	–	−0.158	0.559

Table A.3. MNI coordinates and anatomic locations for the sources of high-gamma activity in controls and chronic schizophrenia patients

60 − 120 Hz					
Cluster	x	y	z	t-value	Anatomic Location
Controls, Face vs. Baseline					
1	54	−46	44	6.26	inferior parietal lobule (IPL)
2	−36	−22	30	5.75	postcentral gyrus
3	42	−34	10	6.71	transverse temporal gyrus, BA41
4	62	−24	10	6.22	superior temporal gyrus (STG)
5	12	58	−10	5.6	superior frontal gyrus (SFG)
6	42	52	−10	5.5	middle frontal gyrus (MFG)
7	36	−38	−16	7.26	fusiform gyrus (FusG), BA37
Patients, Face vs. Baseline					
8	50	−44	40	7.62	IPL
9	22	56	40	6.14	SFG
10	−6	−80	10	5.44	cuneus, BA17
11	36	−92	10	4.61	middle occipital gyrus (MOG)
Controls – Patients					
12	22	−26	74	−1.57	precentral gyrus
13	−22	−66	54	−1.87	superior parietal lobule (SPL)
14	−48	−22	40	1.66	postcentral gyrus
15	60	−20	20	3.65	postcentral gyrus
16	62	16	22	2.51	inferior frontal gyrus (IFG), BA45
17	4	−54	12	−1.72	posterior cingulate
18	24	−78	−16	1.42	lingual gyrus, BA 18
19	54	−22	−30	2.28	FusG
20	22	−70	−36	2.06	cerebellum

Table A.4. MNI coordinates and anatomic locations for the sources of low-gamma activity in controls and chronic schizophrenia patients

25 – 60 Hz					
Cluster	x	y	z	t-value	Anatomic Location
Controls, Face vs. Baseline					
21	−46	−54	30	3.72	supramarginal gyrus
22	44	−58	36	3.33	angular gyrus
23	−32	−90	−14	3.59	inferior occipital gyrus (IOG)
24	54	−70	−12	2.68	MOG
25	4	−62	−10	4.93	cerebellum
26	14	−100	−22	3.56	lingual gyrus
27	−10	60	−20	6.52	SFG
28	4	28	−20	5.39	medial frontal gyrus (MeFG)
29	44	32	−16	4.52	IFG
Patients, Face vs. Baseline					
30	2	−42	52	2.63	paracentral loblue
31	−4	20	42	−2.08	cingulate gyrus, BA32
32	60	−50	10	4.07	STG
33	−26	50	16	2.90	MiFG
34	34	52	14	2.79	MiFG
35	−46	−60	0	3.67	middle temporal gyrus
36	6	18	−18	2.93	MeFG
Controls – Patients					
37	22	−8	68	−2.21	SFG
38	40	10	58	−1.82	MiFG
39	2	−42	36	−1.28	cingulate gyrus
40	−14	46	22	−1.95	SFG
41	−16	−88	20	−1.43	cuneus, BA18
42	64	−40	22	2.25	IPL
43	−58	10	−8	2.41	STG
44	64	−54	−8	−1.23	inferior temporal gyrus, BA21
45	−16	−74	−26	−1.26	cerebellum
46	−30	60	−24	3.34	SFG
47	22	56	−20	1.85	SFG

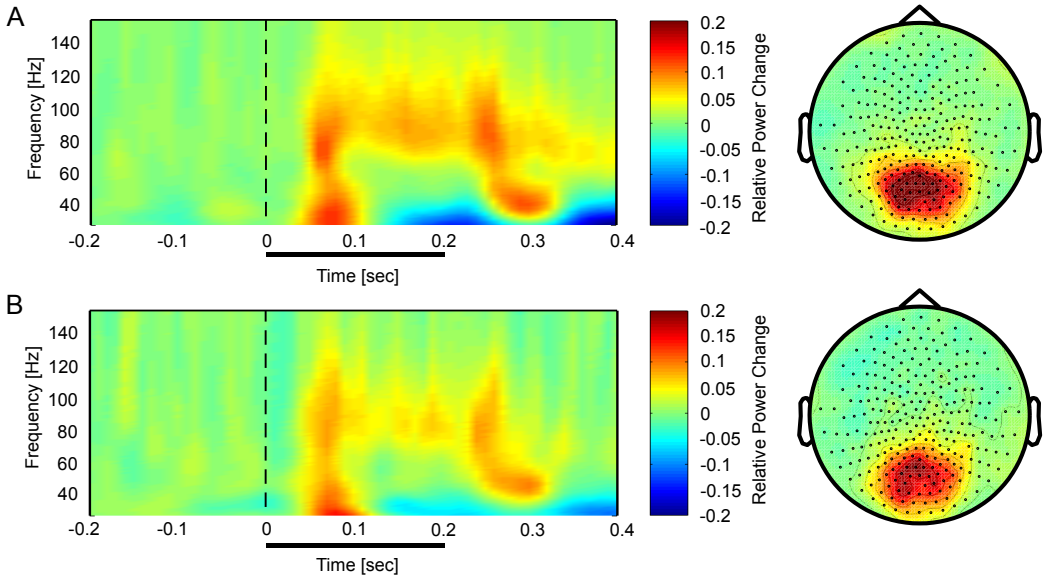

Figure A.3. Time-frequency representations (TFRs) and topographies of gamma-band spectral power in the non-face condition for controls (A) and first-episode schizophrenia patients (B). The TFRs represent the average across all channels. The dashed vertical line marks stimulus onset. The topographies are averaged across the stimulus interval ($0 - 400$ ms) and between 25 and 150 Hz. The gamma-band signal is expressed as relative power change in the post-stimulus time window compared to baseline. In first-episode schizophrenia patients, there is a marked reduction in spectral power, especially in the high-gamma frequency range ($60 - 120$ Hz).

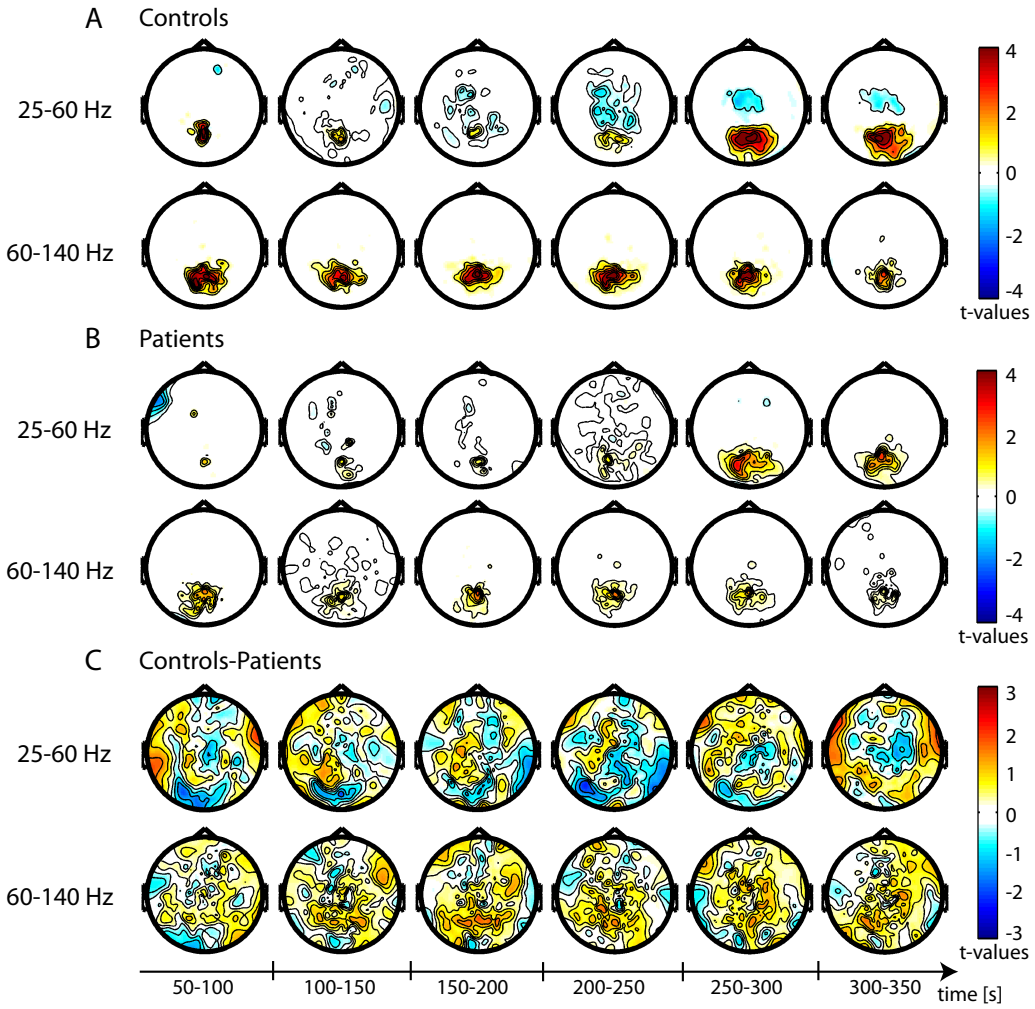

Figure A.4. Statistical analysis of gamma-band power in response to inverted Mooney faces for controls (A), first-episode schizophrenia patients (B), and for the difference between controls and patients (C). The topographies in (A) and (B) show significant differences between the non-face condition and the baseline, separately for the lower ($25-60$ Hz) and the higher ($60-140$ Hz) gamma-band. The effect is masked by the significance map derived from false-discovery rate (FDR, $q < 0.05$) statistical testing. Red denotes higher activation during stimulus presentation compared to baseline, whereas blue denotes less activation during stimulus presentation compared to baseline. The topographies in (C) show the difference for the non-face condition between controls and first-episode schizophrenia patients. Here, red denotes stronger activation for controls compared to first-episode patients, whereas blue represents stronger activation in first-episode patients relative to controls.

Table A.5. Correlations between gamma-band power and performance in controls and first-episode schizophrenia patients

	Controls		Patients	
	r	p-value	r	p-value
	High Gamma, Positive Cluster			
Hits (%)	0.07	0.77	0.26	0.28
Discrimination index A'	−0.2	0.41	0.31	0.2
Reaction time (ms)	−0.08	0.73	−0.05	0.8
	Low Gamma, Positive Cluster			
Hits (%)	−0.15	0.53	−0.03	0.91
Discrimination index A'	0.2	0.4	−0.28	0.25
Reaction time (ms)	0.06	0.79	0.12	0.63
	Low Gamma, Negative Cluster			
Hits (%)	−0.19	0.43	−0.08	0.75
Discrimination index A'	0.68	0.0008	0.43	0.07
Reaction time (ms)	0.43	0.06	−0.26	0.29

Table A.6. MNI coordinates and anatomic locations for the sources of high-gamma activity in controls and first-episode schizophrenia patients

60 – 120 Hz					
Cluster	x	y	z	t-value	Anatomic Location
Controls, Face vs. Baseline					
1	40	−72	40	5.15	precuneus, BA19
2	−10	−100	10	5.04	middle occipital gyrus (MOG), BA18
3	16	−104	2	4.48	cuneus
4	−26	52	−4	5.88	superior frontal gyrus (SFG), BA10
5	−28	−84	−2	4.70	MOG
6	60	12	2	5.72	superior temporal gyrus (STG)
7	60	−10	0	7.49	STG, BA22
8	44	30	−12	5.38	inferior frontal gyrus (IFG), BA47
Patients, Face vs. Baseline					
9	52	−50	20	5.26	STG
10	−30	−72	12	5.76	MOG
11	−30	50	2	7.16	middle frontal gyrus (MiFG)
12	4	46	−10	8.56	medial frontal gyrus (MeFG), BA11
13	22	36	−10	7.69	IFG, BA47
Controls – Patients					
14	−2	−10	60	4.18	MeFG, BA6
15	14	2	62	3.40	MeFG, BA6
16	28	−60	56	2.44	superior parietal lobule (SPL)
17	40	26	26	2.94	MiFG
18	−32	26	6	1.92	IFG, BA45
19	−2	−84	6	2.09	cuneus, BA17

Table A.7. MNI coordinates and anatomic locations for the sources of low-gamma activity in controls and first-episode schizophrenia patients

25 – 60 Hz					
Cluster	x	y	z	t-value	Anatomic Location
Controls, Face vs. Baseline					
20	−20	60	10	5.56	SFG
21	62	22	−22	2.76	STG
22	62	22	−2	4.18	IFG
23	32	−100	−10	3.80	inferior occipital gyrus (IOG)
Patients, Face vs. Baseline					
24	66	−40	20	2.20	STG
25	−38	−90	20	1.76	superior occipital gyrus (SOG), BA19
26	−50	−48	12	1.18	STG
27	−48	−46	40	1.36	inferior parietal lobule (IPL)
Controls – Patients					
28	−8	−14	70	2.20	MeFG
29	22	2	70	2.39	SFG
30	−14	18	60	1.92	SFG, BA6
31	−34	−66	40	1.62	IPL, BA39
32	20	−70	50	2.99	precuneus
33	−26	48	26	2.07	SFG, BA10
34	−48	30	16	2.17	IFG
35	−44	−80	2	1.92	MOG, BA19
36	−4	−80	2	1.77	cuneus
37	−48	−78	0	1.98	MOG
38	−10	−78	10	1.87	cuneus, BA23

Zusammenfassung

Einleitung

Das Ziel der vorliegenden Arbeit war es zu untersuchen, inwieweit Defizite in der Koordination verteilter Hirnaktivität als neuronales Substrat kognitiver Dysfunktionen, speziell visueller Wahrnehmungsstörungen, bei Patienten mit Schizophrenie vorliegen.

Kognitive Defizite stellen ein Kernsymptom der Schizophrenie dar. Sie betreffen viele Bereiche der Wahrnehmung und des Denkens und beeinträchtigen daher das Leben im Alltag und die berufliche Reintegration der Patienten erheblich. Neuere kognitive Modelle der Schizophrenie gehen davon aus, dass diese Defizite durch eine grundlegende Störung in der Informationsverarbeitung verursacht werden. Es wird angenommen, dass die Symptomatik der Schizophrenie auf einer Beeinträchtigung der Integration von Informationen beruht, welches sich in Störungen bei frühen Wahrnehmungsprozessen (Silverstein et al., 2000) und in Defiziten bei höheren kognitiven Funktionen wie Aufmerksamkeit, Exekutivfunktionen (Cohen and Servan-Schreiber, 1992), verbales und nonverbales Gedächtnis und Sprache (Blanchard and Neale, 1994) widerspiegelt.

Die kognitiven Modelle stehen im Einklang mit aktuellen neurowissenschaftlichen Theorien zur Pathophysiologie der Schizophrenie, welche die dysfunktionalen Informationsverarbeitungsprozesse auf eine Störung in der Koordination neuronaler Prozesse zurückführen (Phillips and Silverstein, 2003). Eine Reihe von Studien an Tieren und gesunden menschlichen Probanden hat gezeigt, dass

der Mechanismus für die Integration („Binding“) verteilter neuronaler Prozesse in der Synchronisation neuronaler Aktivität im Gamma-Frequenzband (um 40 Hz) bestehen könnte (Gray et al., 1989; Tallon-Baudry et al., 1999). Es wird vermutet, dass abnorme kognitive Prozesse bei Patienten mit Schizophrenie auf Veränderungen hochfrequenter Oszillationen im Gamma-Band zurückzuführen sind.

Diese Hypothese wird durch eine Reihe von Studien mittels Elektroenzephalographie (EEG) gestützt, welche zeigen konnten, dass die Amplitude oszillatorischer Aktivität sowie die Phasensynchronisation zwischen verschiedenen Hirnarealen während perzeptueller und kognitiver Aufgaben bei Patienten mit Schizophrenie reduziert sind (für einen Überblick siehe Uhlhaas and Singer, 2010). Da die meisten Studien jedoch an chronischen, medizierten Patienten durchgeführt wurden, bleibt offen, ob eine Veränderung oszillatorischer Aktivität bereits zu Beginn der Erkrankung und ohne den Einfluss von antipsychotischen Medikamenten vorhanden ist. Des Weiteren gibt es bislang keine Befunde zu den neuronalen Quellen, die den Defiziten oszillatorischer Aktivität bei Schizophrenie-Patienten zugrunde liegen.

Zudem wurde oszillatorische Aktivität bei Schizophrenie-Patienten bisher lediglich in einem eingeschränkten Frequenzband (meist um 40 Hz) untersucht. Daher bleibt unklar, ob auch im hochfrequenten Gamma-Band (> 60 Hz) eine Beeinträchtigung der oszillatorischen Aktivität vorliegt. Neuere Studien an gesunden Probanden haben gezeigt, dass hochfrequente Gamma-Band Oszillationen mit einer Reihe kognitiver Funktionen verbunden sind (z.B., Lachaux et al., 2005; Siegel et al., 2007; Guggisberg et al., 2008). Daraus lässt sich schließen, dass neben 40 Hz Oszillationen auch hochfrequente Gamma-Band Oszillationen eine wichtige Rolle in kortikalen Netzwerken spielen.

Im Rahmen dieser Dissertation sollte untersucht werden, inwieweit Defizite in der visuellen perzeptuellen Organisation bei Patienten mit Schizophrenie mit einer Beeinträchtigung hochfrequenter Gamma-Band-Aktivität einhergehen.

Dabei sind wir insbesondere der Frage nachgegangen, ob die Synchronisation hochfrequenter oszillatorischer Aktivität bereits in ersterkrankten, unmedizierten Patienten beeinträchtigt ist. Ein weiteres Ziel bestand in der Lokalisierung der neuronalen Generatoren oszillatorischer Aktivität in gesunden Probanden und Schizophrenie-Patienten. Hierzu wurde die Hirnaktivität während einer visuellen Gestaltaufgabe bei chronischen medizierten Schizophrenie-Patienten, ersterkrankten nicht-medizierten Schizophrenie-Patienten sowie bei gesunden Kontrollprobanden mittels Magnetoenzephalographie (MEG) gemessen.

Methoden

Die Methode der Magnetoenzephalographie wurde eingesetzt, da sie die Möglichkeit bietet, die neuronalen Korrelate perzeptueller Prozesse zeitlich hochaufgelöst zu untersuchen, und da sie im Vergleich zum EEG eine genauere Lokalisierung oszillatorischer Aktivität ermöglicht. Die MEG-Messungen wurden mit einem Ganzkopfsystem (Omega 2005, VSM MedTech Ltd., BC, Canada), welches 275 Sensoren umfasst, im MEG-Labor am Brain Imaging Center Frankfurt durchgeführt.

Zur Untersuchung visueller perzeptueller Organisation wurde die „Mooney faces“-Aufgabe verwendet (Mooney and Ferguson, 1951). Mooney faces sind Bilder menschlicher Gesichter, in denen sämtliche Graustufen entfernt wurden. Die Gesichter erscheinen somit unvollständig und erfordern die Integration der verschiedenen Elemente zu einem einheitlichen Ganzen, um ein Gesicht wahrnehmen zu können. Die Gruppierung der Elemente beruht auf dem Gestaltprinzip der Geschlossenheit („closure“) (Mooney and Ferguson, 1951). Typischerweise werden Mooney faces nur bei aufrechter Präsentation als Gesichter wahrgenommen, nicht jedoch bei räumlicher Inversion der Gesichter (Andrews and Schluppeck, 2004; George et al., 2005). Es wird angenommen, dass die Integration der Bildelemente zu einem kohärenten Objekt auf der Synchronisation neuronaler Aktivität beruht und daher einen geeigneten Mechanismus

darstellt, um die Beziehung zwischen Gamma-Band-Aktivität und Wahrnehmungsorganisation zu untersuchen.

Es wurden insgesamt 160 verschiedene Mooney faces-Stimuli verwendet, welche sich aus vier Kategorien zusammensetzten: 1) die 40 ursprünglichen Mooney-Stimuli in aufrechter Orientierung (aufrecht), 2) die ursprünglichen Stimuli gespiegelt an der vertikalen Achse (aufrecht-gespiegelt), 3) die ursprünglichen Stimuli gespiegelt an der horizontalen Achse (invertiert), 4) die invertierten Stimuli gespiegelt an der vertikalen Achse (invertiert-gespiegelt). Bei der Auswertung der Daten wurde jedoch nur zwischen aufrechten und invertierten Stimuli unterschieden. Bei den einzelnen invertierten Stimuli wurden die Elemente zusätzlich „durcheinander gewürfelt“, um sicherzustellen, dass in diesen Bildern keine Gesichter mehr zu erkennen sind.

Den Versuchspersonen wurde in jedem Durchgang eine zufällige Abfolge von aufrechten und invertierten Stimuli präsentiert. Die Stimuli wurden für jeweils 200 ms dargeboten, und das Inter-Stimulus-Intervall betrug $3500 - 4500$ ms. Die Probanden sollten nach jedem Stimulus so schnell wie möglich per Knopfdruck angeben, ob das Bild ein Gesicht darstellte oder nicht. Jeder Proband absolvierte insgesamt $4 - 6$ Durchgänge.

Bei der Auswertung der MEG-Daten wurden ausschließlich Trials mit richtigen Antworten berücksichtigt, d.h. Trials mit aufrechten Stimuli (Gesicht-Bedingung), die als Gesicht identifiziert wurden, und Trials mit invertierten Stimuli (Nicht-Gesicht-Bedingung), die als Nicht-Gesicht klassifiziert wurden. Die Auswertung der MEG-Daten beinhaltete auf der Sensoren-Ebene eine Auswertung der spektralen Power mittels Wavelet-Transformation zwischen 25 und 150 Hz, und auf der Quellen-Ebene eine Rekonstruktion der Generatoren oszillatorischer Aktivität mit Hilfe von Beamforming-Techniken (Gross et al., 2001; van Veen et al., 1997). Um auf Sensoren- und Quellen-Ebene diejenigen Aktivitätsmuster zu ermitteln, die spezifisch mit perzeptuellen Organisationsprozessen („closure“-Prozesse) verbunden sind, wurden die Aktivitätsmuster

der Nicht-Gesicht-Bedingung von denen der Gesicht-Bedingung abgezogen. Im Folgenden werden diese differentiellen Aktivitätsmuster als closure-spezifisch bezeichnet.

Experiment 1

Einleitung. Ziel der ersten Studie war es, die neuronalen Quellen zu lokalisieren, welche den Prozessen visueller Wahrnehmungsorganisation zugrunde liegen, und deren zeitliche Dynamik zu untersuchen. Dazu wurden 15 gesunde Probanden mit der oben beschriebenen Mooney faces-Aufgabe im MEG gemessen. Die Quellenlokalisation erfolgte mit einer zeitaufgelösten Beamforming-Methode (DICS, Gross et al., 2001), bei der die Quellen hochfrequenter Gamma-Band-Aktivität (60−100 Hz) in aufeinanderfolgenden kurzen Zeitfenstern (Dauer jeweils 200 ms, in Abständen von 50 ms) für die Differenz zwischen der Gesicht und Nicht-Gesicht-Bedingung rekonstruiert wurden. Um die Lokalisierung der Quellen zu validieren, wurde zusätzlich ein fMRT-Experiment mit der gleichen Aufgabe und 19 gesunden Probanden durchgeführt. In dieser Studie wurden neben der spektralen Power auch die ereigniskorrelierten Felder (EKFs) ausgewertet.

Es ist bereits bekannt, dass Mooney-Stimuli aus Schattierungsreizen bestehen, welche zur Rekonstruktion von 3D-Objekten beitragen und im caudalen inferioren temporalen gyrus (cITG) verarbeitet werden (Georgieva et al., 2008). Außerdem spielen top-down Prozesse eine wichtige Rolle beim Erkennen von Mooney faces (Kemelmacher-Shlizerman et al., 2008), wie z.B. Objektbekanntheit (Dolan et al., 1997; Moore and Cavanagh, 1998) und Gedächtnisprozesse (Dolan et al., 1997), welche in posterioren parietalen Arealen (PPC) repräsentiert sind (Wagner et al., 2005). Frühere fMRT-Studien haben weiterhin gezeigt, dass Mooney faces-Stimuli gesichtsspezifische Areale wie die fusiform face area (FFA) aktivieren (Kanwisher et al., 1998; Andrews and Schluppeck, 2004; McKeeff and Tong, 2007). Folglich erwarteten wir eine stärkere Aktivie-

rung in der Gesicht-Bedingung im Vergleich zur Nicht-Gesicht-Bedingung in diesen Arealen.

Ergebnisse. Die Ergebnisse der Zeitfrequenzanalyse zeigten, dass die Verarbeitung von aufrechten und invertierten Mooney-Stimuli mit einer erhöhten Aktivierung im hochfrequenten Gamma-Band ($60-100$ Hz) zwischen 100 und 300 ms einherging. Stärkere Gamma-Band-Aktivität für die Gesicht- im Vergleich zur Nicht-Gesicht-Bedingung war über okzipitalen und temporalen Sensoren zwischen 200 und 300 ms zu beobachten. Die Auswertung der EKFs ergab eine closure-spezifische Komponente („magnetic closure index“) zwischen 250 und 325 ms.
Die zeitaufgelöste Rekonstruktion der Quellen differentieller Aktivität zeigte eine stärkere Aktivierung für Gesichter im Vergleich zu Nicht-Gesichtern im cITG und PPC zwischen 0 und 200 ms. Im typischen „closure-Intervall“ zwischen 200 und 400 ms erstreckte sich die Aktivierung im cITG in den fusiform gyrus (FusG) hinein. Außerdem zeigte der linke inferiore frontale gyrus (IFG) in diesem Zeitintervall eine stärkere Aktivierung für Gesichter im Vergleich zu Nicht-Gesichtern. In späteren Zeitintervallen (Anfangszeiten von 250 bis 450 ms) ergab sich eine überwiegend stärkere Aktivierung für die Nicht-Gesicht- im Vergleich zur Gesicht-Bedingung in frontalen Arealen (middle frontal gyrus, inferior frontal gyrus, premotor cortex) und außerdem in primären visuellen Arealen.
Bei den Ergebnissen des fMRT-Experiments war eine hohe Übereinstimmung mit den Resultaten der MEG-Quellenrekonstruktion zu beobachten.

Diskussion. Unser Befund, dass hochfrequente Gamma-Band Oszillationen ($60-100$ Hz) bei der Verarbeitung von Mooney faces-Stimuli eine wichtige Rolle spielen, steht im Einklang mit neueren MEG und intrakraniellen EEG Studien, welche eine erhöhte Aktivität im hochfrequenten Gamma-Band während verschiedener kognitiver Aufgaben berichteten (z.B. Crone et al., 2001; Kaiser

et al., 2004; Brovelli et al., 2005; Lachaux et al., 2005; Hoogenboom et al., 2006; Siegel et al., 2007; Guggisberg et al., 2008). Beim Vergleich der beiden Bedingungen hinsichtlich der spektralen Power und der EKFs zeigte sich eine stärkere Aktivierung für die Gesicht-Bedingung in einem Zeitfenster zwischen 200 und 300 ms (Power) bzw. zwischen 250 und 325 ms (EKFs). Diese Ergebnisse sind konsistent mit früheren EEG-Studien, welche closure-spezifische Aktivierungen zwischen 200 und 400 ms fanden (Rodriguez et al., 1999; Doniger et al., 2000; Sehatpour et al., 2006).

Die Rekonstruktion der Quellen differentieller Aktivität zeigte, dass das mit perzeptueller Organisation verbundene Netzwerk verteilte Quellen in okzipitotemporalen, parietalen und frontalen Regionen umfasste. Die frühen closure-spezifischen Aktivierungen im cITG und in parietalen Arealen lassen vermuten, dass die perzeptuelle Organisation bei Mooney faces mit einer Interaktion zwischen Arealen, die mit der Verarbeitung von Schattierungsreizen verbunden sind (Georgieva et al., 2008) einerseits, und Arealen, die bei Langzeitgedächtnisprozessen eine Rolle spielen andererseits (Wagner et al., 2005; Dolan et al., 1997), beginnt.

Eine Aktivierung im IFG bei perzeptuellen Erkennungsaufgaben wurde in neueren fMRT-Studien ebenfalls gefunden und mit dem Zeitpunkt der Objekterkennung in Verbindung gebracht (Ploran et al., 2007; Hampshire et al., 2009). Im closure-Intervall beobachteten wir außerdem eine erhöhte Aktivierung in der fusiform face area, welche mit der Verarbeitung von Gesichtern in Verbindung gebracht wurde (Kanwisher et al., 1997). Unsere Ergebnisse deuten darauf hin, dass Areale, die der Verarbeitung von Formmerkmalen (LOC/cITG) dienen, und stimulus-spezifische Areale (FusG), die der Identifizierung des betreffenden Objekts dienen, im closure-Intervall zusammenarbeiten.

Frontale Aktivierungen wurden mit erhöhten kognitiven Anforderungen in Verbindung gebracht (Duncan and Owen, 2000). Die spätere stärkere Aktivierung

für Nicht-Gesichter im Vergleich zu Gesichtern in frontalen Arealen könnte mit einer größeren Aufgabenschwierigkeit der Nicht-Gesicht-Bedingung zu erklären sein, unter der Annahme, dass die Probanden versuchen in jedem Bild ein Gesicht zu entdecken.

Zusammenfassend lässt sich sagen, dass unsere Hypothesen bezüglich der aktivierten Areale während perzeptueller Organisationsprozesse bestätigt wurden. Unsere Studie liefert darüber hinaus neue Erkenntnisse über die zeitliche Abfolge der beteiligten Prozesse.

Experiment 2

Einleitung. In der zweiten Studie haben wir untersucht, ob bzw. in welchem Umfang hochfrequente Gamma-Band Oszillationen (> 60 Hz) bei Schizophrenie-Patienten beeinträchtigt sind, und ob ein Defizit in der Gamma-Band-Aktivität mit einer Beeinträchtigung der visuellen perzeptuellen Organisation einhergeht. Ein weiteres Ziel bestand in der Lokalisation der neuronalen Quellen, die den Defiziten der Gamma-Band-Aktivität zugrunde liegen.

MEG-Messungen wurden mit 16 medizierten chronischen Schizophrenie-Patienten, diagnostiziert nach DSM-IV, und 16 gesunden Kontrollprobanden durchgeführt. Zur Untersuchung der perzeptuellen Organisation wurde die gleiche Gestaltaufgabe (Mooney faces) verwendet wie in der ersten Studie. Von jedem Probanden wurden zusätzlich strukturelle Daten mittels MRT erhoben. Zur klinischen Charakterisierung der Schizophrenie-Patienten wurde die „Positive and Negative Syndrome Scale“ (PANSS, Kay et al., 1987) verwendet. Alle Probanden wurden außerdem mit einer neuropsychologischen Testbatterie (BACS, Keefe et al., 2004) untersucht.

Die Auswertung der MEG-Signale bestand aus der Auswertung der spektralen Power ($25 - 150$ Hz) sowie einer Rekonstruktion der Quellen mittels LCMV-Beamforming (van Veen et al., 1997) in der Gesicht-Bedingung. Da die erste Studie unterschiedliche Modulationen des tiefen und hohen Gamma-Bands ge-

zeigt hatte, haben wir die Quellenlokalisation in dieser Studie gesondert für $25-60$ und $60-120$ Hz durchgeführt.

Frühere Studien konnten bereits zeigen, dass Schizophrenie-Patienten Defizite in der Gestaltwahrnehmung (z.B. Silverstein et al., 1996, 2000; Doniger et al., 2001; Uhlhaas et al., 2005) und eine Reduktion der Gamma-Band Amplitude ($30-60$ Hz) (Haig et al., 2000; Green et al., 2003; Spencer et al., 2003; Wynn et al., 2005) aufweisen. Wir erwarteten, dass eine Beeinträchtigung oszillatorischer Aktivität bei Schizophrenie-Patienten auch im hochfrequenten Gamma-Band zu finden ist. Aufgrund der Ergebnisse unserer ersten Studie erwarteten wir Unterschiede in der Power auf Quellen-Ebene („Source Power“) zwischen Patienten und Kontrollprobanden in okzipitalen-temporalen, parietalen oder frontalen Arealen.

Ergebnisse. Die Ergebnisse der Verhaltensdaten zeigten eine verminderte Detektionsrate sowie längere Reaktionszeiten in der Gesicht-Bedingung in den Patienten im Vergleich zu den Kontrollprobanden. Dagegen zeigten sich keine signifikanten Gruppenunterschiede bezüglich Detektionsrate und Reaktionszeiten in der Nicht-Gesicht-Bedingung.

Die Auswertung der spektralen Power zeigte eine starke Reduktion der hochfrequenten Gamma-Band Power auf parieto-okzipitalen Sensoren bei Schizophrenie-Patienten im Vergleich zur Kontrollgruppe. Bei den Patienten korrelierte das Defizit in der hochfrequenten Gamma-Band Power zum einen mit der Beeinträchtigung in der perzeptuellen Organisation und zum anderen mit einem ausgeprägteren Disorganisationssyndrom.

Im unteren Gamma-Band ($25-60$ Hz) zeigten die Patienten eine stärkere Aktivität über fronto-zentralen Sensoren als die Kontrollprobanden. Eine Analyse innerhalb der Gruppen ergab jedoch, dass die Aktivität auf diesen Sensoren in den Kontrollprobanden und den Patienten während der Stimulus-Präsentation im Vergleich zur Baseline abnimmt. Dies bedeutet, dass die relative stärkere Aktivität im unteren Gamma-Band bei den Patienten eine verminderte Ab-

nahme der Aktivität im Vergleich zu den Kontrollprobanden darstellt.
Die Rekonstruktion der Generatoren oszillatorischer Aktivität in den Kontrollprobanden ergab – wie in der ersten Studie – ein verteiltes Netzwerk in okzipito-temporalen, parietalen und frontalen Arealen. Die Patienten zeigten im Vergleich zu Kontrollprobanden eine Reduktion der stimulusbezogenen Source Power im hochfrequenten Gamma-Band in einer Reihe von Arealen, einschließlich des postcentral gyrus, IFG (BA45), ITG, primary visual cortex, und FusG. Interessanterweise fanden wir eine stärkere Aktivierung in den Patienten im Vergleich zu den Kontrollprobanden im posterior cingulate cortex. Während die Source Power in Patienten im hohen Gamma-Band weitgehend reduziert war, zeigten sich stärkere Aktivierungen im tiefen Gamma-Band bei den Patienten in frontalen Arealen, im posterior cingulate gyrus und cuneus sowie im ITG. Aktivierungen im STG und IPL waren dagegen stärker in den Kontrollprobanden.

Diskussion. Gemäß unserer Hypothese zeigten die Verhaltensdaten eine verringerte Erkennungsrate für aufrechte Mooney faces bei medizierten chronischen Schizophrenie-Patienten. Dieses Ergebnis ist konsistent mit einer Reihe früherer Studien, die ein Defizit in der perzeptuellen Organisation bei Schizophrenie-Patienten berichteten (für einen Überblick siehe Silverstein and Uhlhaas, 2004).
Die Beeinträchtigung in der perzeptuellen Organisation ging einher mit einer starken Reduktion in der hochfrequenten Gamma-Band Power bei Patienten, was auf dysfunktionale Verarbeitungsprozesse in lokalen kortikalen Netzwerken hindeutet. Dies könnte auf Veränderungen in GABAergen (Lewis et al., 2005) und glutamatergen (Coyle, 2006) Neurotransmittersystemen bei Schizophrenie-Patienten zurückzuführen sein.
Die Quellenrekonstruktion in den Patienten zeigte veränderte Aktivationsmuster in okzipito-temporalen, parietalen und frontalen Arealen, was vermuten lässt, dass dysfunktionale Prozesse in Hirnregionen, die für perzeptuelle Or-

ganisation bedeutend sind, der beeinträchtigten Verhaltensleistung und der reduzierten Gamma-Band-Aktivität auf der Sensoren-Ebene zugrunde liegen. Beispielsweise zeigten sich im hohen Gamma-Band reduzierte Aktivierungen in primären visuellen Arealen, im fusiform gyrus, und im IFG, was darauf schließen lässt, dass die Interaktion zwischen Arealen zur Gesichtererkennung und Arealen zur kognitiven Kontrolle in Schizophrenie-Patienten beeinträchtigt sein könnte.

Neuere Studien haben Dysfunktionen im dorsalen Pfad der visuellen Informationsverarbeitung bei Schizophrenie-Patienten hervorgehoben (Butler and Javitt, 2005; King et al., 2008; Coleman et al., 2009). Die vorliegende Studie zeigt jedoch, dass Verarbeitungsprozesse im ventralen Pfad ebenfalls beeinträchtigt sein könnten. Unsere Befunde stehen im Einklang mit einer neueren fMRT-Studie, welche eine reduzierte Aktivierung bei Schizophrenie-Patienten in höheren visuellen Arealen gezeigt hat, die mit der Verarbeitung der Form eines Objekts in Verbindung stehen (Silverstein et al., 2009). Es ist bislang unklar, ob Defizite in höheren visuellen Arealen auf Dysfunktionen in primären visuellen Arealen zurückzuführen sind.

Die stärkere Aktivierung im posterior cingulate gyrus bei den Patienten im Vergleich zu den Kontrollprobanden könnte durch eine stärkere Aktivierung des Ruhenetzwerks, des sogenannten „Default Mode Network“ zu erklären sein, welches bei gesunden Probanden typischerweise während der Bearbeitung kognitiver Aufgaben herunter reguliert wird (Raichle et al., 2001; Fox et al., 2005). Eine reduzierte Abnahme der Default Mode Network-Aktivität bei den Patienten könnte möglicherweise der reduzierten Abnahme der oszillatorischen Aktivität im tiefen Gamma-Band auf fronto-zentralen Sensoren zugrunde liegen und zusätzlich zum Defizit in der hochfrequenten Gamma-Band-Aktivität zu einer beeinträchtigten Verhaltensleistung in den Patienten beitragen.

Zusammenfassend ergibt sich, dass diese Studie neue Erkenntnisse über eine beeinträchtigte Modulation oszillatorischer Aktivität im Gamma-Band bei

Schizophrenie-Patienten liefert, welche mit Defiziten der perzeptuellen Organisation und veränderten Aktivationsmustern in verschiedenen Hirnarealen einhergeht. Aus diesen Ergebnissen lässt sich folgern, dass ausgedehnte Dysfunktionen lokaler kortikaler Netzwerke bei chronischen Schizophrenie-Patienten vorliegen, die möglicherweise den Defiziten in der weitreichenden Koordination zwischen verschiedenen Hirnarealen bei Schizophrenie-Patienten zugrunde liegen könnten.

Experiment 3

Einleitung. In dieser Studie sollte die Frage untersucht werden, inwiefern eine Beeinträchtigung der Gamma-Band-Aktivität bereits zu Beginn der Erkrankung und ohne den Einfluss von antipsychotischen Medikamenten vorhanden ist. Dazu wurden MEG-Messungen an 19 nicht-medizierten ersterkrankten Schizophrenie-Patienten und 20 gesunden Kontrollprobanden durchgeführt, wiederum während der Mooney faces-Aufgabe. Von jedem Teilnehmer der Studie wurden zusätzlich strukturelle Daten mittels MRT erhoben. Zur klinischen Charakterisierung der Schizophrenie-Patienten wurde die „Positive and Negative Syndrome Scale“ (PANSS, Kay et al., 1987) verwendet. Alle Probanden wurden außerdem mit einer neuropsychologischen Testbatterie (BACS, Keefe et al., 2004) untersucht.

Die Auswertung der MEG-Daten umfasste wie in der zweiten Studie eine Auswertung der spektralen Power ($25-150$ Hz) sowie die Rekonstruktion der Quellen mittels LCMV-Beamforming (van Veen et al., 1997) für das hohe ($60-120$ Hz) und tiefe ($25-60$ Hz) Gamma-Band in der Gesicht-Bedingung.

Wie in der vorigen Studie erwarteten wir eine reduzierte Erkennungsrate für aufrechte Mooney face Stimuli bei den Patienten, einhergehend mit einer Reduktion der hochfrequenten Gamma-Band Power und verminderten Aktivierungen in okzipito-temporalen, parietalen oder frontalen Hirnregionen.

Ergebnisse. Das Verhalten in der Gesicht-Bedingung zeigte keine signifikanten Unterschiede zwischen den beiden Gruppen. In der Nicht-Gesicht-Bedingung jedoch wiesen die ersterkrankten Patienten längere Reaktionszeiten und eine verminderte Erkennungsrate auf, da sie mehr Nicht-Gesichter als Gesichter klassifizierten. Dies spiegelte sich auch in einem geringeren Diskriminationsindex A' der Patienten im Vergleich zu den Kontrollprobanden wider. Dieses Ergebnis zeigt, dass die Kontrollprobanden verglichen mit ersterkrankten Schizophrenie-Patienten weniger falsche Alarme (Nicht-Gesichter fälschlicherweise als Gesichter klassifiziert) bei der gleichen Anzahl richtig erkannter Gesichter machten.

Die Auswertung der spektralen Power zeigte eine Reduktion der hochfrequenten Gamma-Band-Aktivität bei den Patienten im Vergleich zu den Kontrollprobanden. Die Reduktion war jedoch weniger stark ausgeprägt als in den chronischen Patienten. Des Weiteren war eine reduzierte Abnahme der tiefen Gamma-Band Power auf fronto-zentralen Kanälen bei den Patienten im Vergleich zu den Kontrollprobanden zu beobachten; diese abnorme Modulation war ebenfalls weniger stark ausgeprägt in den ersterkrankten im Vergleich zu den chronischen Schizophrenie-Patienten.

Die Rekonstruktion der Quellen zeigte eine reduzierte Aktivierung in den Patienten im Vergleich zu den Kontrollprobanden in okzipitalen, parietalen und frontalen Hirnarealen, sowohl im hohen als auch im tiefen Gamma-Band. Die Unterschiede waren am deutlichsten in frontalen Arealen ausgeprägt, wie zum Beispiel im medial frontal gyrus, middle frontal gyrus und IFG. Verglichen mit den chronischen Patienten war bei den ersterkrankten Patienten eine stärkere Aktivierung im IFG und im temporalen Kortex zu erkennen, während die chronischen Patienten eine höhere Aktivierung im posterior cingulate gyrus aufwiesen.

Diskussion. Entgegen unserer Hypothese zeigten die Patienten keine Beeinträchtigung bei der Identifizierung von Gesichtern bei aufrechten Mooney face

Stimuli. Jedoch waren die Patienten in der Unterscheidung zwischen Gesichtern und Nicht-Gesichtern beeinträchtigt, was sich in einer erhöhten Zahl von falschen Alarmen äußerte. Bisherige Studien berichteten inkonsistente Ergebnisse bezüglich perzeptueller Organisation in ersterkrankten Schizophrenie-Patienten (Frith et al., 1983; Rabinowicz et al., 1996; Silverstein et al., 2006a). Die Ergebnisse unserer Studie deuten darauf hin, dass schon zu Beginn der Erkrankung ein leichtes Defizit in der perzeptuellen Organisation vorliegt: Die Fähigkeit, visuelle Merkmale zu einem kohärenten Perzept zu integrieren, ist zwar anscheinend noch intakt, wenn der visuelle Input den Erwartungen des Beobachters entspricht (Gesichter); wenn der visuelle Input jedoch komplex und unregelmäßig ist, versagt die Fähigkeit zur perzeptuellen Organisation. Die zugrundeliegenden Mechanismen sind dabei noch unklar. Die veränderte Verhaltensleistung könnte aus einer gestörten Interaktion resultieren zwischen bottom-up, stimulus-getriebenen visuellen Verarbeitungsprozessen einerseits, und top-down Prozessen, die durch Gedächtnisrepräsentationen und Erwartungen getrieben werden, andererseits. Alternativ könnte man die verminderte Diskriminationsleistung mit einer Tendenz der Patienten erklären, dass sie Nicht-Gesichtern mehr Bedeutung zuschreiben als die Kontrollprobanden (Kapur, 2003).

Wie erwartet zeigten die Patienten eine Reduktion der hochfrequenten Gamma-Band Power. Interessanterweise war dieses Defizit weniger stark ausgeprägt als in den chronischen Patienten. Im Verlauf der Krankheit könnte es somit eine progressive Beeinträchtigung in der Koordination neuronaler Aktivität geben. Zusammenfassend zeigen diese Daten, dass ein Defizit oszillatorischer Aktivität bereits zu Beginn der Erkrankung und ohne den Einfluss von Medikation vorhanden ist – welche Mechanismen jedoch der weiteren Reduktion in der Gamma-Band Power in den chronischen im Vergleich zu den ersterkrankten Patienten zugrunde liegen, lässt sich aus unseren Studien nicht ableiten. Mögliche Ursachen für die Unterschiede könnten antipsychotische Medikation,

zunehmendes Alter oder Fortschreiten der Erkrankung sein.

Die reduzierte Aktivierung in okzipitalen, parietalen und vor allem frontalen Arealen bei den Patienten im Vergleich zu Kontrollprobanden könnte der verminderten hochfrequenten Gamma-Band-Aktivität auf Sensoren-Ebene und der beeinträchtigen Verhaltensleistung zugrunde liegen. Im Vergleich zu den chronischen Patienten zeigten die ersterkrankten Patienten eine stärkere Aktivierung im IFG und im temporalen Kortex; diese Areale wurden mit perzeptuellen Erkennungsprozessen und Objekterkennung in Verbindung gebracht. Aus diesem Befund und der jeweiligen Verhaltensleistung ist zu folgern, dass visuelle Verarbeitungsprozesse, die der Identifizierung von Objekten dienen, zu Beginn der Erkrankung im Vergleich zu späteren chronischen Stadien weniger beeinträchtigt sind.

Fazit

Die Hauptbefunde der drei Experimente lassen sich wie folgt zusammenfassen: Das neuronale Netzwerk perzeptueller Organisation bei Mooney faces zeigt ausgeprägte oszillatorische Aktivität im hochfrequenten Gamma-Band ($>$ 60 Hz) und umfasst okzipito-temporale, parietale und frontale Areale, die zu verschiedenen Zeitpunkten der Informationsverarbeitung aktiviert werden. Unsere Ergebnisse lassen vermuten, dass perzeptuelle Organisationsprozesse bei Mooney faces auf einer frühen Interaktion zwischen Arealen beruhen, die mit der Verarbeitung von Schattierungsreizen zusammenhängen, gesichtsspezifischen Arealen, und Arealen, die mit dem Abruf von Informationen aus dem Langzeitgedächtnis in Verbindung stehen.

Bei medizierten chronischen und nicht-medizierten ersterkrankten Schizophrenie-Patienten zeigte sich ein Defizit in der hochfrequenten Gamma-Band-Aktivität. Dieses ging einher mit einer beeinträchtigten Verhaltensleistung bei der Mooney faces-Aufgabe und mit reduzierten Aktivierungen in den für perzeptuelle Organisationsprozesse relevanten Arealen. Aus diesen Ergebnissen

lässt sich schließen, dass die Koordination neuronaler Aktivität in lokalen Netzwerken bei Patienten mit Schizophrenie beeinträchtigt ist.

Das Defizit in der hochfrequenten Gamma-Band-Aktivität war in den chronischen im Vergleich zu den ersterkrankten Patienten stärker ausgeprägt, was auf einen progressiven Verlauf der Beeinträchtigung oszillatorischer Aktivität bei Schizophrenie-Patienten hindeutet. Die Patientengruppen unterschieden sich außerdem in ihrer Verhaltensleistung: Während die chronischen Patienten eine Beeinträchtigung in der Integration visueller Merkmale zu einem kohärenten Perzept (Gesicht) aufwiesen, zeigten die ersterkrankten Patienten ein Defizit in der Diskrimination zwischen Gesichtern und Nicht-Gesichtern. Die Ursachen für die Unterschiede zwischen den Patientengruppen im Verhalten und in der neuronalen Aktivität sind noch unklar; möglicherweise spielen Faktoren wie antipsychotische Medikation, zunehmendes Alter oder Fortschreiten der Erkrankung eine Rolle.

Erklärung

Ich erkläre hiermit, dass ich mich bisher keiner Doktorprüfung unterzogen habe.

Frankfurt am Main, 25.03.2010

Eidesstattliche Versicherung

Ich erkläre hiermit an Eides statt, dass ich die vorgelegte Dissertation über

"Neural Synchrony during Perceptual Organization in Schizophrenia"

selbständig angefertigt und mich anderer Hilfsmittel als der in ihr angegebenen nicht bedient habe, insbesondere, dass alle Entlehnungen aus anderen Schriften mit Angabe der betreffenden Schrift gekennzeichnet sind.

Ich versichere, nicht die Hilfe einer kommerziellen Promotionsvermittlung in Anspruch genommen zu haben.

Frankfurt am Main, 25.03.2010

Curriculum Vitae

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Ausbildung

06/2001	**Abitur**, Dietrich-Bonhoeffer-Gymnasium, Ratingen (Note: 1,0)
10/2001 – 09/2006	**Studium der Psychologie** an der Georg-August-Universität, Göttingen
09/2003 – 06/2004	**Auslandsstudium** an der University of California, Santa Cruz, USA (Studienstipendium der Universität Göttingen)
10/2005 – 09/2006	**Diplomandin** in der Abteilung Kognitive Neurowissenschaften (Prof. Dr. Stefan Treue), Deutsches Primatenzentrum GmbH, Göttingen Thema der Arbeit: *„Attentional modulation of psychophysical tuning curves for direction of motion“*
09/2006	**Diplom**, Georg-August-Universität, Göttingen (Note: 1,12)
11/2006 – 09/2010	**Doktorandin** in der Abteilung Neurophysiologie (Prof. Dr. Wolf Singer), Max-Planck-Institut für Hirnforschung, Frankfurt Thema der Arbeit: *„Neural synchrony during perceptual organization in schizophrenia“*
30.09.2010	**Disputation** (Note: summa cum laude)

Studienbegleitende Tätigkeiten

10/2002 – 08/2003	**Studentische Hilfskraft** am Georg-Elias-Müller-Institut für Psychologie, Georg-August-Universität, Göttingen
08/2004 – 10/2004	**Praktikantin** in der Klinik für Neurologische Frührehabilitation (Neuropsychologie), Städtische Kliniken Duisburg

02/2005 – 08/2005 **Studentische Hilfskraft** in der Abteilung Kognitive Neurowissenschaften, Deutsches Primatenzentrum GmbH, Göttingen

09/2005 – 10/2005 **Praktikantin** in der Abteilung Neurophysiologie, Max-Planck-Institut für Hirnforschung, Frankfurt

Fortbildungen

02/2008 FMRI Schulung, Maastricht Brain Imaging Center, Maastricht, Niederlande

04/2008 Schulung zu *„Advanced data analysis and source modelling of EEG and MEG data“*, Donders Centre for Cognitive Neuroimaging, Nimwegen, Niederlande

06/2008 *„Workshop on schizophrenia and related disorders“*, Cold Spring Harbor Laboratory, New York, USA

Konferenzbeiträge

Poster

08/2006 29th Annual Meeting der European Conference on Visual Perception, St. Petersburg, Russland

C. Tillmann, L. Busse, S. Katzner, and S. Treue

„Attentional modulation of psychophysical tuning curves for direction of motion“

11/2007 Society for Neuroscience, San Diego, USA

C. Tillmann, P. J. Uhlhaas, A. Kohler, W. Singer, and M. Wibral

„Using MEG and cluster randomization testing to investigate the role of oscillatory brain activity in face processing“

06/2008 1st Schizophrenia International Research Society Conference, Venedig, Italien

C. Tillmann, M. Wibral, M. Leweke, A. Kohler, W. Singer, D. Koethe, L. Kranaster, K. Maurer, and P. J. Uhlhaas

„High-frequency gamma-band oscillations during perceptual organization in chronic and first-episode schizophrenia patients“

11/2008 Society for Neuroscience, Washington, USA

C. Tillmann, M. Wibral, M. Leweke, A. Kohler, W. Singer, D. Koethe, L. Kranaster, K. Maurer, and P. J. Uhlhaas

„Source localization of high-frequency oscillations reveals widespread reductions in gamma-band activity during perceptual organization in chronic and first-episode schizophrenia“

Talks

05/2008 34. Tagung „Psychologie und Gehirn“, Magdeburg

C. Tillmann, M. Wibral, W. Singer, A. Kohler, K. Maurer, and P. J. Uhlhaas

„Hochfrequente Gamma-Band Oszillationen und Gestaltwahrnehmung bei Patienten mit Schizophrenie“

09/2008 20th Anniversary Conference of ISNIP, Frankfurt

C. Tillmann, M. Wibral, M. Leweke, A. Kohler, W. Singer, D. Koethe, L. Kranaster, K. Maurer, and P. J. Uhlhaas

„High-frequency oscillations during perceptual organization in schizophrenia“

03/2009 International Congress of Schizophrenia Research, San Diego, USA

C. Grützner, M. Wibral, F. M. Leweke, A. Kohler, W. Singer, D. Koethe, L. Kranaster, K. Maurer, and P. J. Uhlhaas

„High-frequency gamma-band oscillations during perceptual organization in chronic and first-episode schizophrenia patients“

05/2009 Neurobiologisches Forschungskolloquium, Stiftung Universität Hildesheim

C. Grützner

„MEG Gamma-Band Oszillationen und Gestaltwahrnehmung bei Patienten mit Schizophrenie“

Publikationen

L. Busse, S. Katzner, **C. Tillmann**, and S. Treue (2008). Effects of attention on perceptual direction tuning curves in the human visual system. *Journal of Vision* 8(9):2, 1-13.

C. Grützner, P. J. Uhlhaas, E. Genc, A. Kohler, W. Singer, and M. Wibral (2010). Neuroelectromagnetic correlates of perceptual closure processes. *Journal of Neuroscience* 30(24):8342-8352.

P. Wang, M. N. Havenith, M. Best, **C. Grützner**, W. Singer, P. J. Uhlhaas, D. Nikolic (2010). Time delays in the β/γ cycle operate on the level of individual neurons. *NeuroReport* 21:746-750.

C. Grützner, M. Wibral, W. Singer, K. Maurer, and P. J. Uhlhaas. Deficits in high-frequency ($>$ 60 Hz) gamma oscillations during perceptual organization in chronic schizophrenia. (in preparation).

C. Grützner, M. Wibral, M. F. Leweke, D. Koethe, L. Kranaster, W. Singer, K. Maurer, and P. J. Uhlhaas. High-frequency gamma-band oscillations in unmedicated first-episode schizophrenia patients. (in preparation).

Frankfurt am Main, 25.10.2010