Audiovisual Processing in Schizophrenia:

Neural Responses in Audiovisual Speech Interference and Semantic Priming

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List of Abbreviations

ACC Anterior Cingulate Cortex

EEG Electroencephalogram

GBA Gamma Band Activity

GBR Gamma Band Response

IFG Inferior Frontal Gyrus

LD Lexical decision

LGN Lateral Geniculate Nucleus

MEG Magnetoencephalography

MFG Middle Frontal Gyrus

MTG Middle Temporal Gyrus

SFG Superior Frontal Gyrus

SMG Supramarginal Gyrus

STG Superior Temporal Gyrus

SZ Schizophrenia

WM Working Memory

WP Word pronunciation

1. Summary

Schizophrenia is characterized by different fluctuating symptoms, all of which share the feature of a severe deterioration of the quality of life for affected patients. This is reflected in a diminished performance in a range of cognitive functions such as attention, working memory, executive functions, social perception and interaction, such as Theory of Mind or recognition of the emotional expression of others, speech and communication.

For a long time, deficits like these have been conceptualized primarily as consequences of deficient top-down processing. But within the last few decades, a paradigm shift from higher cognitive functions towards rather basic, sensory processing emerged (Javitt, 2009). In early visual processing, deficits in patients with schizophrenia were found in tasks involving the magnocellular pathway, which were reflected in lower responses to magnocellular-biased stimuli in occipital Steady-State Visual Evoked Potentials (SSVEP) in patients with schizophrenia (Butler, Schechter, Zemon, Schwartz, Greenstein, Gordon, Schroeder, Javitt et al., 2001). Behavioral impairments as well as reduced phase synchrony in the β-frequency range were found in tasks which require Gestalt perception (Uhlhaas, Linden, Singer, Haenschel, Lindner, Maurer and Rodriguez, 2006), and deficits in motion perception could be demonstrated behaviourally as well as in a diminished detection-related response in the EEG (Wang, Brown, Dobkins, McDowell, & Clementz, 2010). Auditory processing was also found to be impaired in schizophrenia as indicated by a reduction in 40 Hz power in the Auditory-evoked Steady-State Response (ASSR) to stimulation with trains of clicks at different presentation rates (Kwon, O'Donnell, Wallenstein, Greene, Hirayasu, Nestor, Hasselmo, Potts, Shenton & McCarley, 1999). Furthermore, a reduction of evoked power and phase-locking of the early γ-band response in the EEG in an auditory reaction task was found, in which patients with schizophrenia showed slower reaction times as well as an increased error rate as compared to non-clinical control subjects (Leicht, Kirsch, Giegling, Karch, Hantschk, Möller, Pogarell, Hegerl, Rujescu, Mulert, 2010). Information processing in everyday life is to a large extent characterized by simultaneous input from different sensory modalities rather than from input of one single modality. To understand sensory processing in schizophrenia, it is therefore vital to consider the multisensory aspect of everyday situations and study whether alterations exist in schizophrenia. Furthermore, multisensory processing is not independent of other cognitive processes, but is rather embedded in and can be modulated by prior experience, expectations, attention or memory amongst others (Talsma, Senkowski, Soto-Faraco, & Woldorff, 2010). To include two cognitive functions with a considerable influence on sensory processing, attention as well as semantic memory were incorporated in the

designs, which therefore comprise an audiovisual attention task in the EEG (study 1 and study 2) as well as a visual-to-auditory semantic priming paradigm in the MEG (study 3).

The auditory speech interference paradigm was first applied in healthy subjects (study 1) and presented a video stream of three speakers who produced syllables, with one target syllable - occasionally produced by the center speaker- as the target syllable. As distracting input, flanking speakers produced no speech stimuli (No Interference Condition), audiovisual speech (Speech Interference Condition), auditory noise (Auditory Noise Interference Condition) or lip movements only (Lip Movement Interference Condition). The video was presented using an on-off flicker in different frequencies, 19 Hz for the two distracting flanking speakers, and 25 Hz for the to-be-attended center speaker, so Steady-State Visual Evoked Potentials (SSVEP) could be recorded in the EEG. Results indicated longer reaction times in response to distracting audiovisual speech, higher hit rates in the No Interference as compared to the Speech Interference and Auditory Noise Interference condition as well as enhanced distracting speaker induced SSVEPs for audiovisual speech, reflecting enhanced behavioural as well as neuronal correlates of distractibility towards natural audiovisual speech as compared to other distractors on the neuronal level. Subsequently, the paradigm was adapted and used in patients with schizophrenia (study 2). SSVEP power differences failed to reach significance, but behavioural data show that naturalistic speech is a stronger distractor than auditory noise, which parallels the behavioural findings in healthy subjects (study 1).

The visual-to-auditory semantic priming study (study 3) involved an S1-S2 paradigm with naturalistic objects that were presented as pictures (S1) and subsequent sounds (S2) in a sample of patients with schizophrenia and matched control subjects (study 3). The semantic congruency of the object pairs was modulated and subjects were required to respond with an implicit judgment to the auditory S2. A behavioral priming effect, i.e. facilitated auditory object recognition, was found as indicated by significantly shorter reaction times on the auditory S2 for congruent as compared to the incongruent object pairs in all subjects. Furthermore, analysis of the MEG data showed reduced evoked power in patients with schizophrenia as compared to non-clinical control subjects between 30-40 Hz in the time window 20-80 msec as well as a significant statistic interaction for the factors group and condition. Additionally, correlations between 30-40 Hz power and different symptoms of the disease were found. Taken together, the findings of this thesis point to the relevance of early sensory processing in different mental actions and specifically, the correlation between MEG power and symptom strength in schizophrenia supports the notion of a possible impact for understanding dysfunctional neuronal functioning in schizophrenia.

2. Introduction

Schizophrenia (SZ), or the group of schizophrenias, as the title of one of the most famous publications in schizophrenia research states (Bleuler, 1911a), comprises psychotic disorders with a range of fluctuating symptoms. The World Health Organization (WHO) summarizes the most important symptoms of SZ as follows: "… thought echo; thought insertion or withdrawal; thought broadcasting; delusional perception and delusions of control; influence or passivity; hallucinatory voices commenting or discussing the patient in the third person; thought disorders and negative symptoms." ("WHO | International Classification of Diseases (ICD)," n.d.). All SZ subtypes share the feature of a severe deterioration of the quality of life for affected individuals, as indicated by a two- to threefold increased mortality as compared to the general population, with significantly elevated suicide rates as compared to the general population contributing to this enhancement (McGrath, Saha, Chant, & Welham, 2008).

Symptoms and Diagnostic categories

Symptoms of SZ have been divided into positive and negative symptoms (Crow, 1980). Positive symptoms include unusual thoughts or perceptions, including hallucinations, delusions, thought disorder and disorders of the movement, whereas negative symptoms are characterized by a loss or decrease in the ability to initiate actions, avolition, language impairments, deficits in the expression of emotions and anhedonia. Another category, cognitive symptoms, plays an important role in prognosis, social functioning, and rehabilitation. It subsumes deficits in attention, executive functions and memory and has been found to show a poor response to medication and at the same time to be most derogating for the patients in everyday life and with regard to occupational rehabilitation. In a frequently used diagnostic instrument for the assessment of symptom severity, the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987), symptoms are separated into the positive, negative symptoms and general psychopathology scales.

Interestingly, some symptoms of the three categories of positive, negative and cognitive symptoms partly overlap, while others differ substantially although subsumed in the same scale, specifically in the categories of negative and cognitive symptoms. Different factor structures of SZ symptoms in factor analyses of all the PANSS items have been found, with a five factor structure, consisting of positive, negative, cognitive/disorganization, excitement and depression/anxiety (Kim et al., 2012; Lindenmayer, Grochowski, & Hyman, 1995; Nakaya, Suwa, & Ohmori, 1999), being the most dominant finding and complemented by a sixth factor which was labelled "Withdrawn" in a recent study (Van den Oord et al., 2006).

Table 1. Overview of frequent schizophrenia subtypes as described in ICD-10 **("DIMDI - ICD-10-GM," n.d.)** and DSM-IV **(Saß & Houben, 1998)**.

Subtype	**Major Symptoms**
Paranoid Schizophrenia 295.30 / F 20.0x	· stable, often paraniod delusions, usually with hallucinations and perceptual disturbances · disturbances of affect, volition and speech and catatonic symptoms are absent or rare
Hebephrenic Schizophrenia F 20.1x	· affective changes are prominent, delusions and hallucinations fleeting and fragmentary · behaviour irresponsible and unpredictable, mannerisms common · shallow, inappropriate mood, disorganized thought, speech incoherent · tendency to social isolation, rapid development of „negative symptoms" (particularly flattening of affect and loss of volition)
Disorganized Schizophrenia (295.1)	· thought disorder and flat affect
Catatonic Schizophrenia 295.20 / F 20.2x	· prominent psychomotor disturbances that alternate between extremes like hyperkinesis and stupor, or automatic obedience and negativism · constrained attitudes and postures, may be maintained for long periods · episodes of violent excitement, catatonic phenomena may be combined with a dream-like (oneiroid) state with vivid scenic hallucinations
Undifferentiated Schizophrenia 295.50 / F 20.3x	· psychotic conditions meeting general diagnostic criteria for schizophrenia but not conforming to any of the subtypes in F 20.0-F20.2
Post-schizophrenic Depression F 20.4x	· depressive episode, which may be prolonged, arising in the aftermath of schizophrenic illness, with some positive or negative symptoms still present · depressive states are associated with increased risk of suicide
Residual Schizophrenia 295.50 / F 20.5x	· chronic state in development of schizophrenic illness · long-term negative symptoms like psychomotor slowing, poverty of quantity or content of speech, poor nonverbal communication by facial expression, poor self-care, underactivity, blunting of affect
Simple Schizophrenia F 20.6x	· characteristic negative features of residual schizophrenia without being preceded by any overt psychotic symptoms

Table 1.

One approach, favouring the notion of the positive, negative and disorganized syndrome, of which the latter have been shown to correlate with neurocognitive dysfunctions, even led to

the development of a diagnostic tool extending the PANSS (Kay et al., 1987), the Positive and Negative and Disorganized Symptoms Scale (PANADSS) (Moritz et al., 2001).
In attempts to describe the symptoms of SZ and in the search for underlying pathological mechanisms, different perspectives on the clinical features of the disorder have been proposed. In general, a categorical approach states that SZ can be subdivided into different, exclusive groups, such as the different subtypes of the disease as they are used today in diagnostic decisions (see Table 1), whereas the dimensional model favors the idea of clusters of symptoms that can coexist and overlap. The sum of findings indicates that a combined approach of the categorical and dimensional model represents characteristics of the disease more accurately than one single perspective alone (see Van Os, 2010).

Correlations between the different symptoms and cognitive functioning as well as between symptoms and sociodemographic variables revealed an association between an illness duration of more than 2 years and cognitive dysfunction as well as correlations between positive symptoms and impairments in memory and attention (Talreja, Shah, & Kataria, 2013). The two latter important domains of cognitive functioning, memory and attention, each comprise several different components and specific impairments in SZ and will be discussed in chapter 2.2 and 2.3 of this introduction. Since both memory and attention in general depend at some point on the processing of sensory input, sensory processing in SZ is covered first (chapter 2.1).

2.1.Sensory Processing in Schizophrenia

In contrast to several domains in which a decreased performance in SZ is obvious and empirically replicated, sensory processing was originally considered one of the few well preserved functions which were not specifically impaired (Bleuler, 1911). Although Bleulers assumption of unimpaired sensory processing in SZ has been challenged early in the history of SZ research by Kraepelin, who assumed that the excitation of sensory centers might be involved SZ, this traditional view was dominant until the 1960s (Javitt, 2009). Notably, most deficits in SZ have been regarded primarily as consequences of deficient top-down processing. Within the last two decades, the main focus of neurophysiological experimental research on SZ has shifted from the formerly more pronounced focus on higher cognitive functions and top-down processing towards a growing interest in rather basic, sensory

processing, which will be covered in chapter 2.1 of this introduction. Chapter 2.4 describes the measures of neural activity and introduces the methods that were used in the experiments of this thesis.

2.1.1. Unisensory Processing in Schizophrenia

Sensory processing and neurophysiological measures for assessment have again received attention in SZ research within the last decades. After long periods in which a lot of experimental work in SZ focused on relatively complex, higher-order cognitive functions, recent studies on basic perceptual processing and the links between early sensory processing and higher-order functions as well as symptoms of SZ have added to the field and provided insights into impairments in fundamental aspects of sensory functions.

Differences in sensory processing between patients with SZ and non-clinical control subjects have also been shown in other sensory modalities recently, such as olfaction (Kayser et al., 2013; Rupp, 2010), and tactile stimulation (Teale, Pasko, Collins, Rojas, & Reite, 2013), and findings such as hypoalgesia in SZ (Potvin & Marchand, 2008) point to interesting deviations from non-clinical subjects in sensory processing that have to be investigated further in the future. Nevertheless, this chapter of the introduction focuses on visual and auditory processing, since these two modalities are related to the experiments of this thesis and have been investigated extensively in SZ.

Visual Processing

Impairments in visual sensory processing in SZ have been investigated on different levels and with different methods recently. Patients with SZ show deviations from non-clinical control subjects on different stages of visual processing, even on the level of motor aspects of visual processing such as eye movements and saccades, fixation stability and fixation dispersal during free-viewing. Patients with SZ also show deficits in binocular depth perception (Schechter et al., 2006), motion perception (Spencer, Sekuler, Bennett, & Christensen, 2013), smooth pursuit tasks and visual scanpath (Beedie, Benson, Giegling, Rujescu, & St Clair, 2012).

Several studies characterized bottom-up contributions to higher-order cognitive impairments. In a recent study with the aim of investigating the intersection of visual sensory processing and visual neural plasticity, a simple monocular deprivation (MD) setup was used for the induction of short-term Visual Evoked Potential (VEP) amplitude changes (Foxe, Yeap, & Leavitt, 2013). VEPs were recorded during monocular and binocular viewing periods and

yielded a larger amplitude of the summed monocular VEPs as compared to the amplitude of the binocular viewing period in healthy subjects, which was interpreted in terms of plasticity. This effect was lacking in patients with SZ. This finding was interpreted by the authors as a lack of those short-term compensatory mechanisms that provide non-clinical subjects with the ability to generate robust VEPs in monocular deprivation conditions.

In early stages of visual processing, two separate but parallel streams can be distinguished: the magnocellular (M) and parvocellular (P) stream. Both convey information from retinal ganglion cells to higher visual areas, project to different layers of the LGN and differ functionally throughout the processing stream from the retina to the cortex. The magnocellular system is primarily involved in motion processing, coarse, colourless object processing, whereas the parvocellular system provides high-definition and colour vision. These two processing streams have been shown to constitute segregated streams until higher stages of visual processing in the monkey (Maunsell, Nealey, & DePriest, 1990). Patients with SZ show deficits specifically in tasks demanding the magnocellular pathway, which is reflected in lower responses to magnocellular-biased stimuli in Steady-State Visual Evoked Potentials (SSVEP) in patients with SZ as compared to matched control subjects (Butler et al., 2001). Furthermore, in a study investigating the influence of early visual processing as well as cognitive deficits on visual Working Memory (WM) in SZ, ERPs were recorded, contrast sensitivity was tested to assess magnocellular/parvocellular function and participants had to perform the AX-CPT to assess WM (Dias, Butler, Hoptman, & Javitt, 2011). Results showed amplitude reductions for early sensory as well as later ('cognitive') ERP components, and sensory impairments were found to predict cognitive ERP deficits. An association between performance and contrast sensitivity was found, but only for low spatial frequency, pointing to magnocellular impairments and influences of sensory processing on performance. The authors interpret these findings as support for the encoding hypothesis, i.e., for deficits in WM encoding rather than in WM retention, which had been stated previously.

Presentation of more complex visual stimuli, such as ambiguous pictures, figures embedded in noisy backgrounds or Gestalt stimuli yielded diminished behavioural performance in detection tasks as well as aberrant neural responses: In a Gestalt task in which participants indicated if an illusory square was either absent or present, occipital response-locked oscillations elicited by the squares were found in healthy controls and in patients with SZ, but with a lower frequency range in patients with SZ (22.1 – 24.1 Hz) as compared to non-clinical control subjects (31.3 - 44.2 Hz) (Spencer et al., 2004). The topography did not differ significantly between the two groups, supporting the notion of a common underlying

mechanism. Furthermore, the occipital response-locked effect was correlated with conceptual disorganization. The findings point to abnormalities in gamma-band synchrony in SZ and demonstrate a relation to positive symptoms of the disorder.

Furthermore, deficits in the performance of patients with SZ were found in tasks which require Gestalt perception, i.e. upright and inverted mooney faces, and these behavioural deficits were accompanied by reduced phase synchrony in the β-band (Uhlhaas et al., 2006). A relation between disorganized symptoms in SZ and a reduction in high-frequency oscillatory power was found in an MEG study in which the same stimuli as in the previously mentioned study (Uhlhaas et al., 2006) were presented (Grützner et al., 2013).

The role of the above mentioned findings on visual perception and aberrant high-frequency oscillations in SZ is further supported by recent evidence for the relation of resting GABA concentration in the visual cortex and gamma oscillation frequency as measured by MEG (Muthukumaraswamy, Edden, Jones, Swettenham, & Singh, 2009) and therefore provide a link to discussed pathophysiological mechanisms of SZ (Lisman et al., 2008).

Auditory Processing

Sensory processing deficits in SZ have also been found in the auditory domain, such as impairments in an interaural time difference discrimination task (Matthews et al., 2013). Interestingly, these basic auditory processing deficits have been linked to higher-order cognitive deficits, in assessing not only the patients` performance in the interaural time difference discrimination task, but also how binaural cues are used in auditory scene analysis of complex auditory environments, yielding deficits in patients with SZ in both tasks.

Some of the auditory processing deficits in SZ are also related to symptoms: Deficits in auditory processing were related to auditory hallucinations as assessed by tasks involving pitch discrimination of unmodulated tones and auditory streaming, and hallucinating as well as non-hallucinating patients with SZ had a diminished performance in discrimination of modulated tones and affective prosody (McLachlan, Phillips, Rossell, & Wilson, 2013).

Early auditory processing was found to be impaired in SZ as indicated by a reduction of evoked power and phase-locking of early evoked Gamma-Band Response in the EEG in an auditory reaction task compared to healthy control subjects. Furthermore, auditory encoding processes in patients with SZ and healthy controls throughout the cortex was investigated using MEG, to localize differences in early auditory processing between patients with SZ and healthy control subjects (Chen et al., 2013). Participants performed a paired-click task and maps of activity derived from Vector-based Spatial-temporal Analysis using L1-minimum-

norm (VESTAL) were analysed. For both groups, bilateral STG activity was found, with a stronger activity in non-clinical control subjects as compared to patients with SZ. Furthermore, group differences for frontal areas and supramarginal gyrus (SMG) were also found, pointing to deviations in SZ from non-affected individuals not only in STG, but rather on the level of an auditory network.

Auditory processing deficits have been investigated extensively in event-related potential (ERP) components in SZ (see chapter 2.4.1). The mismatch negativity (MMN), an ERP elicited by auditory deviants, has even been recorded in early illness schizophrenia (ESZ) patients, clinical high-risk individuals (CHR) and healthy controls, and within the CHR patients it was recorded after a follow-up period (Perez et al., 2013). An MMN reduction in ESZ and CHR was found as compared to healthy control subjects, and in clinical high-risk individuals who converted to psychosis as compared to those who did not. Time to psychosis onset was predicted by MMN to deviants that differed from the standards regarding duration and frequency.

Taken together, impairments in different sensory modalities in patients with SZ have been investigated experimentally using paradigms favouring low-level processing as well as higher-order integrative functions. Although these deficits are not necessarily pathognomonic to SZ, they can reveal insights into early stages of information processing with possible implications for higher-order cognitive processes, functioning in everyday life, symptom severity and might be useful to improve predictions about recovery and remission in the future.

2.1.2. Multisensory Processing in Schizophrenia

Information processing in everyday life is to a large extent characterized by processing of information form different sensory modalities rather than from input of one single modality. Specifically, a rapid integration of visual and auditory stimuli is relevant in any kind of social interaction where speech is involved, which works on a fine-graded temporal scale with small critical time windows for the integration of signals from the two modalities. An extensive amount of literature indicates that humans (e.g. (Thomas & Shiffrar, 2013; van Ee, van Boxtel, Parker, & Alais, 2009) as well as animals (Chandrasekaran, Lemus, & Ghazanfar, 2013; Kayser, Logothetis, & Panzeri, 2010; Komura, Tamura, Uwano, Nishijo, & Ono, 2005) can derive information from input of an additional sensory modality and that this gain is reflected in behaviour and neurophysiological measures.

Since deficits in unisensory processing are well replicated for several sensory modalities in SZ, the question arises whether alterations in multisensory processing can also be found in SZ patients. Indeed, patients differ from non-affected individuals in their performance in multisensory tasks: a reduced reaction time facilitation to bimodal targets as compared to non-clinical control subjects in a target detection task was found in patients with SZ, with stronger negative symptoms being associated with the least reaction time facilitation (Williams, Light, Braff, & Ramachandran, 2010). Interestingly, the weaker multisensory benefit was also associated with the presence of both auditory and visual hallucinations as compared to the presence of auditory hallucinations.

The McGurk effect (McGurk & MacDonald, 1976) is a well-known perceptual fusion that emerges in cases of mismatch of simultaneously presented auditory and visual syllables, as for instance when an visual "ba" and an auditory "ga" is presented, often "da" is perceived. Interestingly, in schizophrenia has been investigated yielding opposing findings: patients were less susceptible to the fusion than healthy control subjects, although their performance in a separate spatial sound localisation task was found to be unimpaired (de Gelder, Vroomen, Annen, Masthof, & Hodiamont, 2003), but others found a susceptibility comparable to that of non-clinical subjects (Myslobodsky, Goldberg, Johnson, Hicks, & Weinberger, 1992; S. A. Surguladze et al., 2001). In a study investigating the McGurk effect in adult and adolescent patients with SZ, a significantly lower mean of McGurk-positive responses was found in adolescent patients with SZ as compare to healthy adolescents, but not between adults with SZ and their matched control subjects (Pearl et al., 2009). This finding is in line with the aforementioned results by (Myslobodsky et al., 1992) on adults. In general, the findings on the McGurk fusion in SZ indicate a failure to integrate auditory and visual information in affected patients, but also revealed an effect of age which points to developmental aspects of multisensory integration aside from SZ.

Furthermore, it has been shown that patients with SZ have a specific deficit in multisensory integration in a speech recognition task when audiovisual and auditory words were presented with noise imposed on a proportion of the regular stimuli. Noise diminished the performance for patients and healthy control subjects, but in the group of patients with SZ, a specific deficit in multisensory speech processing was found in the absence of a unisensory impairment of the behavioral performance. Interestingly, this specific deficit which was most present at an 'intermediate' signal-to-noise ratio for which in healthy subjects the gain of audiovisual stimulation is maximal (Ross et al., 2007).

Impairments in SZ have also been shown in complex social functions using multisensory paradigms. For instance, in audiovisual emotion recognition as assessed with a paradigm requiring emotional voice categorization following the synchronous presentation of the picture of an emotional face and an emotional voice, a diminished crossmodal influence of the emotional visual stimuli on the voice classification was found in patients with SZ (de Jong, Hodiamont, Van den Stock, & de Gelder, 2009). Interestingly, this effect was not present in a sample of non-SZ psychosis patients, which points to a specific multisensory processing deficit in SZ.

Neurophysiological investigations of multisensory processing

Multisensory enhancements as indicated by larger responses in neurophysiological measures following multisensory as compared to the sum of the responses to unisensory stimuli are well-replicated (Tyll et al., 2013; Werner & Noppeney, 2010). Neuronal indicators of multisensory processing in SZ were investigated recently, as for example in an EEG study comparing the unisensory auditory and visual responses with simultaneous audio-visual evoked responses in SZ, a larger response to audiovisual stimuli in SZ as compared to healthy controls was found, i.e., an enhanced multisensory facilitation (Stone et al., 2011). A picture of a soccer field with goal and goalie (visual) was presented as well as a low tone of 550 Hz, aiming to simulate a soccer ball (auditory) in SZ, with an additional variation of the visual image of a soccer ball which was presented in a "NEAR" (aimed at evoking peripheral responses) and "FAR" (aimed at evoking responses from central retina) condition. Correspondingly, the auditory stimulus was also presented in a "NEAR" (80 dB) and FAR (64 dB) variation of the volume. Subjects were asked to indicate whether the soccer ball was presented near or far and to maintain fixation on the goalie throughout the task. Behavioural results revealed faster RTs for the audiovisual than the auditory and visual condition as well as an interaction between stimulus type and group, i.e., in patients with SZ, visual and audiovisual RT differences were larger. Patients with SZ showed not only an increase in multisensory facilitation, but significant differences in the amplitude in early unisensory visual evoked potentials for an occipital region of interest as well as in auditory evoked potentials in a fronto-central and right-temporal region of interest for the "NEAR" condition and in a right-temporal region for the "FAR" condition. The authors interpreted the finding of an increased multisensory facilitation as being related to the unisensory deficits.

In an EEG study using natural audiovisual events in which visual information predicted the onset of the sound, an N1 reduction as compared to healthy control subjects was found in

patients with SZ when the sound was accompanied by a video, as well as a diminished congruency effect on the P2 (Stekelenburg, Maes, Van Gool, Sitskoorn, & Vroomen, 2013).
Notably, there are also some studies indicating that patients with schizophrenia do not differ from unaffected individuals in multisensory integration in specific tasks and neurophysiological measures: In a study using a target detection task with unisensory and multisensory stimuli, auditory and visual ERPs were recorded in patients with SZ and healthy controls and demonstrated only small and non-significant neural and behavioural differences between the groups and an absence of a deficit in multisensory integration in SZ (Wynn, Jahshan, & Green, 2014). Furthermore, another study on audiovisual integration in SZ did not find impairments in multisensory intergration: A visual temporal order judgment task with click sounds to evoke the temporal ventriloquism yielded a diminished sensitivity in judging visual temporal order, but benefitted as healthy controls from the additional auditory information (temporal ventriloquism) (de Boer-Schellekens, Stekelenburg, Maes, Van Gool, & Vroomen, 2013).
Recently, beyond visual and auditory processing, other modalities have been investigated in multisensory experiments in SZ (Seubert et al., 2010), but the selection of findings summarized in this section was limited to audiovisual multisensory experiments, because the focus of this thesis is the combined processing of these two modalities and so far and the existing empirical background is the largest as compared to other modalities.

2.2. Attention in Schizophrenia

Attention can be viewed as a cognitive function comprising dynamic processes enabling animals and humans to select relevant stimuli among the available information. Attentional orienting refers to the alignment of attention with specific input channels or contents of memory (Posner, 1980), implicating the enhanced deployment of processing ressources towards attended information. In general, one basic problem in perception refers to the selection of relevant information, since several models of attention postulate a limited processing capacity (often referred to as a 'bottleneck') (Broadbent, 1958; Desimone & Duncan, 1995; Treisman, 1964), which necessitates selection. Endogenous, controlled and intentional components of attention ('top-down') in which an individual orients attention willingly can be distinguished from exogenous influences ('bottom-up'). The latter are assumed to be stimulus-driven, automatic and occurring in response to salient an external event rather than in line with the individuals expectations, decisions and plans. Out of all cognitive domains that have been shown to be impaired in SZ, attention has been described as

one of the most severely affected functions in SZ and has been described early in the beginning of research on SZ and investigated experimentally for decades.

Models of attentional impairments in schizophrenia

In investigations of attention in SZ, in part general attention models (Broadbent, 1958) are used to explain experimental findings in SZ (Hemsley, 1975), and beyond this, more specific models and theories for the application in neuropsychological disorders and SZ research have been developed, two of which are summarized in this section.

In contrast to early psychoanalytic theories on psychosis emphasizing the breakdown of ego functions, a hypothesis on SZ symptoms viewing impairments from a rather clinical perspective stated a cognitive disorder as an underlying core deficit in SZ (McGhie & Chapman, 1961), and proposed that the emergence of several symptoms occurs in response to this basic cognitive impairment. According to the authors, the consequences of this cognitive impairment can be observed primarily in the domains of attention and perception. Specifically, a breakdown of normally intact selective-inhibitory control of attention is hypothesized in SZ, which includes a general factor of distractibility. The neurological mechanisms leading to this supposed basic cognitive disorder were assumed to reside in the reticular system, since it was considered to be the physiological system controlling selection of sensory information and inhibition. Pathological changes as a consequence of this central deficit of attentional control include according to the hypothesis 1) a decline in the perceptual process leading to global and undifferentiated perception, 2) diffuseness of normally discrete sensory channels, with a possible association to synaesthesia, 3) disturbed control and direction of motility, leading to enhanced conscious awareness of the respective functions, and 4) decreased concentration and progression of thought disorder which is related to the lack of control over incoming information.

Experimental findings on selective attention in SZ using psychomotor tests as well as tests on perception and immediate memory demonstrate impairments in a range of tasks (McGhie, Chapman, & Lawson, 1964). The authors conclude that the consequences of a deficit in selective attention in SZ could be reflected in an inability to block irrelevant information that leads to an overload in short-term memory. This overload in short-term memory in turn could cause a deterioration of the performance in subsequent cognitive functions. This interpretation links the deficits in the cognitive functions of attention and memory in SZ and illustrates that deficits in central cognitive functions are interrelated with other functions as well as

symptoms of the disease. For instance, it has been demonstrated that selective attention in SZ is related to cortical activation and social withdrawal (Venables, 1963).

Furthermore, although not specific to SZ, a neuropsychological model comprising four factors of attention was proposed (Mirsky, Anthony, Duncan, Ahearn, & Kellam, 1991), providing a framework for investigating disorders of attention. The four processes, 'Focus-Execute', 'Sustain', 'Shift', 'Encode', which were derived from principal component analyses on extensive neuropsychological test batteries, were also linked to cerebral structures. Rather than providing a new theory, the model aimed at providing an empirically validated set of relevant elements of attention that can be used in clinical diagnostic assessment.

Neurophysiological experiments on attention in schizophrenia

Following the development of theories of attention, EEG, MEG and neuroimaging studies have made considerable progress in investigating neural substrates of attention and relating these findings to original assumptions of the basic attention theories (Fox et al., 2005; Herrmann & Knight, 2001; Posner & Petersen, 1990; Shapiro, 2009). Impairments in SZ in tasks requiring attention have not only been shown behaviourally, for instance in tasks involving spatial working memory and sustained attention (O'Gráda et al., 2009) and speeded and non-speeded measures of selective attention (Egeland, 2003), but also on the level of neurophysiological processing.

Attentional deficits in SZ have been investigated for instance in ERP studies and the results could be partly linked to symptoms, subtypes and behavioral impairments of the disorder. For instance, in an ERP experiment on distractibility in SZ, an enhanced vulnerability of patients was found as indicated by a smaller P3a amplitude in the EEG in response to auditory distractors as well as a change in behavioral performance (Grillon, Courchesne, Ameli, Geyer, & Braff, 1990). Neurophysiological correlates of attentional impairments in SZ have not only been shown in experiments using stimuli with a short duration, but also within the course of longer intervals. To investigate if deficits in auditory selective attention in schizophrenia are present later in the processing stream or at early stages of auditory processing, ERPs were recorded while patients with SZ and matched controls performed a cross-modal selective attention task (Mathalon, Heinks, & Ford, 2004). Loud and soft speech sounds as well as bright and dim checkerboard patterns were presented and participants were required to respond with a button press to soft speech sounds in the auditory attention task and to dim checkerboards in the visual attention task. Evidence of cross-modal selective attention was found at 50 msec for patients and controls, but sustained until 300 msec in controls as

compared to a range until 100 msec in patients. The authors suggest that an early attentional filter is applied in controls as well as in patients with SZ, but that this filter does not sustain until later processing stages in patients with SZ.

Beyond amplitudes of ERPs and local power changes in neural activity and oscillations in SZ deviated from those of non-clinical control subjects in attention studies, but also measures of connectivity reveal alterations SZ which are related to attention. In an MEG experiment on connectivity within the frontoparietal network (FPN) in SZ (Roiser et al., 2013), effective connectivity was assessed using dynamic causal modeling (DCM) of evoked responses. Patients with SZ and control subjects performed a visual change test activating the FPN and attention was tracked with a flicker-detection task. During processing of the attended visual changes, the two groups differed regarding the recruitment of the FPN according to the DCM analyses. The authors interpreted these results as aberrant top-down modulation of evoked responses, in case of attended changes. Interestingly, data of patients and controls were explained by different Bayesian models: patients` data were best explained by a DCM with attention dependent changes in top-down and bottom-up connections, and the control subjects` data were best represented by a model with bottom-up changes. Connectivity estimates the right IPS-TPJ connection revealed a reduced connectivity during attended stimulus changes in SZ, which was associated with lower intelligence. This study not only provides insight into attentional deficits in SZ, but also further validates the disconnection hypothesis of SZ with its proposed coupling impairments based on deficient regulation of NMDA-dependent synaptic plasticity.

Taken together, the small selection of findings on attention in SZ summarized above provides an overview of the diversity of the levels of cognitive impairment in the disorder. However, contrary to the general assumption of impairments in multiple cognitive domains and almost any kind of cognitive task in SZ (O'Carroll, 2000), there are also findings indicating unimpaired or even enhanced performance in attention tasks in SZ, such as in the shift of spatial attention (Spencer et al., 2011). Attentional processes in SZ is relevant for all three experiments of the present thesis: Whereas in the first two experiments, distractibility is explicitly implemented in the experimental setup, and this specific facet of attention has been shown to be impaired in SZ (see above). Furthermore, attention has been suggested to be influenced by multisensory integration, and vice versa (Talsma et al., 2010), which amongst other aspects refers to interrelations between memory and attention, being of specific interest in the third study of this thesis.

2.3. Semantic Memory in Schizophrenia

Sensory modalities provide input that is attended and processed on the sensory level, and at a subsequent stage of processing this input is stored and organized in memory. Several distinctions regarding different memory systems can be made. In general, in the domain of long-term memory the episodic memory is distinguished from the semantic memory (Tulving, 1972). Given the enormous amount of sensory input that is processed, organized and stored in the human nervous system, the question arises how such a memory system is organized and how storage of and access to information is provided and maintained, specifically given continuously growing amounts of input.

Theories of Semantic Memory

Early theoretical and empirical work on organizing principles of memory established a model memory that could be implemented within computer programs and evaluated regarding its performance in human-like language behavior (Quillian, 1967). The purpose of this work was to provide design principles and methods for the implemented programs that could enable a machine to use it in performing memory-dependent tasks and give rise to theories of organization of semantic memory. In the memory model put forward by Quillian, concepts correspond to senses of words and can be represented as nodes in a network. Interconnected nodes have associative links with different properties between them.

Search in memory in this model is thought of as a parallel tracing process along links from the node of each concept provided by input words, with a spread of activation to the nodes connected with the first node, and subsequently to all nodes connected with each of these nodes and so on. Nodes that have been involved in the search process get activation tags with specifications of the starting node as well as direct neighbors that have been activated before. Intersections between two nodes arise when tags from nodes with different starting nodes meet and in the following, the paths leading to the intersection can be evaluated if the constraints of syntax and context are met. Priming, or preparation, in Quillian's model, refers to a parallel process of at least two subsequently activated nodes in which the spread of activation of one of the activated nodes meets tags left by a previously activated node. Whereas Quillian's theory of semantic memory search and semantic preparation (Quillian, 1967) can be regarded as a predecessor for subsequently developed theories of semantic processing, most of the basic assumptions of it are still referred to implicitly or explicitly in current approaches and experimental studies.

The Spreading-activation Theory of human semantic processing (Collins & Loftus, 1975) was developed as an extension of the theory of semantic memory search and semantic preparation (Quillian, 1967). It was intended not to challenge the core assumptions of the latter, but to expand the scope of applicability to human experiments, whereas Quillian's theory was designed to model and implement semantic structure and related human-like behavior on computers. The extensions pertain to local processing assumptions, such that assumed features of human information processing are included in the theory, as well as to memory structure and processing more general. Specifically, semantic similarity as an organization principle of the conceptual (semantic) network is proposed. Furthermore, the existence of a lexical network is proposed, which is organized according to phonemic similarity and involved in storage of names of concepts. Semantic matching occurs as a process of evaluation if a semantic match exists for two concepts. An assumption of the theory with important consequences for predictions in priming experiments on semantic structures is that in case of processing of an item, the extent of activation of other items is proportional to the relatedness to that item.

A distinction can be made with regard to activation in the semantic network: automatic activation processes are postulated which occur without awareness, intention and conscious effort (Posner, & Snyder 1975), and these are distinguished from controlled, conscious processing operations which take place in a system of limited capacity and which, once occupied with an operation, lacks capacities for others.

Semantic Memory in Schizophrenia

Amongst the many different symptoms of SZ, most of the symptoms relevant for a diagnosis of SZ are expressed in language, which inspires discussions if SZ can be viewed as a genuinely human disorder.

Not only the content of spoken or written language, but also the formal aspects of utterances feature characteristic deviations from those of unaffected individuals. Clinical observations lead to numerous descriptions and empirical investigations of utterances of patients with SZ, with phenomena such as the repetition of linguistic units, object-chaining, associative intrusions, punning, or word schemes (Maher, 1983). Specifically, investigations of object-chaining contributed to the development of a model of associational intrusion in schizophrenic discourse (Maher, Manschreck, Hoover, & Weisstein, 1987), which includes a vulnerability to intrusions supposed to be influenced by syntax boundaries. The "Tentative Theory of Schizophrenic Utterance" (Maher, 1983) states that the pathology of SZ is

associated with a deficit in keeping external or internal material from intrusion into consciousness which would in normal functioning be excluded based on its task-irrelevance. In normal functioning, this active process is related to the control of attentional deployment by redundancies in input and inhibition of associated elements from entering preverbal plans and protocols (i.e., speech).

Interestingly, it is hypothesized that associational bonds and networks themselves in patients with SZ do not necessarily differ with regard to content or development from those of healthy subjects, with the consequence that not bizarre associations are the core of the problem in SZ, but rather regular associations appearing at inappropriate places. Although the theory states that in general, networks of patients with SZ and healthy subjects do not differ per se, the plastic nature of associational networks which includes experience-dependent changes and adaptation to alterations in input entails that anomalous associations can emerge in cases of experiences of disturbed sensory and associational utterance. Thereby, during later stages of SZ, one of the predictions of the theory would indeed pertain to altered associations as compared to healthy subjects as well as for example as compared to recent-onset SZ. It has been hypothesized and tested in a series of experiments if patients with formal thought disorder (FTD) have a stronger associational activation than patients with SZ with lower or no FTD, and if this would in turn be reflected in performance. Indeed, a greater associational activation was found in an LD task in patients with SZ with FTD (Maher, Manschreck, Hoover, & Weisstein, 1987).

To operationalize semantic memory experimentally and to quantify the spread of activation in semantic memory, different semantic priming paradigms are suitable depending on the type of priming that is investigated.

In general, associative priming can be distinguished from semantic priming. Associative relations are given when items are in some way associatively related but from different semantic categories (e.g., spoon, soup), whereas items are semantically related when they belong to the same semantic category (e.g., teacher, student). Direct semantic priming refers to direct relations between targets and primes, such as ‘black – white’, and can be distinguished from indirect semantic priming (see Pomarol-Clotet, Oh, Laws, & McKenna, 2008), which refers to paradigms with indirectly related targets and primes, such as ‘lemon-sweet’ (with the word ‘sour’ mediating the relation). In contrast, repetition priming refers to priming in which the same word is represented by prime and target (Neely, 1991).

In lexical decision tasks (LD), after presentation of a prime, a word/non-word decision should be made to the consecutively presented target, often a single-letter string, or the target should be said out loud (word pronounciation task (WP)). The target word can either be related or unrelated to the prime, and a possible priming effect is usually quantified by subtraction of RTs for targets that follow related primes from RTs for targets that follow unrelated or neutral primes. Depending on the baseline condition, resulting differences are either called overall priming effect (when unrelated targets serve as baseline) or in case of targets that follow neutral primes targets facilitation, a positive difference is called facilitation and a negative difference inhibition (Neely, 1991).

Neurophysiological investigations of semantic memory

The electrophysiological N400 is a brain component varying with semantic language comprehension, peaking approximately at 400 ms after stimulus presentation as a negative-going deflection (Kutas & Federmeier, 2000). In healthy subjects, an N400 in response to semantic violations in a sentence reading task was found, i.e., when sentences occasionally contained a semantically incongruent word (Kutas & Hillyard, 1980).

The question whether semantic priming differences between non-clinical control subjects and patients with SZ refer to stable characteristic of the disorder or whether deviations fluctuate in time has been investigated recently in a 1-year test-retest study. The authors found N400 amplitudes improved at restest, but behavioural priming was still impaired (Besche-Richard, Iakimova, Hardy-Baylé, & Passerieux, 2014).

In SZ research, empirical findings of any neurophysiological measures are at some point evaluated regarding their applicability as an endophenotype or biomarker for the disease state. In a priming study with long and short SOA (300ms and 750 ms), the EEG was recorded while patients with SZ, their unaffected relatives as well as healthy controls subjects performed a visual word pair priming task (Kiang, Christensen, & Zipursky, 2014). Smaller N400 amplitudes for related versus unrelated words were found in controls and relatives. The N400 did, however, not differ between related and unrelated targets in SZ. N400 amplitudes were generally larger in SZ patients as compared to their unaffected relatives as well as healthy controls for related targets. The authors suggest that N400 priming deviations in SZ may be a biomarker of SZ, rather than an endophenotype, since no abnormalities were found in the unaffected relatives.

Several attempts have been made to disentangle the behavioural as well as neurocognitive heterogeneity in SZ, and to investigate whether specific subgroups of patients with SZ share

specific features. Interestingly, a preliminary study with a small sample of SZ patients demonstrated a positive correlation between semantic priming effects and the P50 gating ratio (Vinogradov et al., 1996), pointing to a relation between inhibitory processes in sensory information processing and the spread of activation in semantic memory.

Using a semantic priming paradigm in SZ while recording fMRI, (Sass et al., 2014) investigated processing abnormalities in patients as compared to healthy controls subjects regarding semantic distance (direct and indirect semantic relations, unrelated word-pairs, pseudoword-target stimuli) and sensory modality (visual or auditory-visual stimulus presentation). Participants were asked to perform visual lexical decisions on word-pairs. Analyses of the reaction times showed a significant main effect of relation, and within the group of the control subjects, a priming effect for directly related stimuli was found. No significant priming effects were found for the patients. A general semantic priming effect on the neural level was observed with a bilateral network of the left superior frontal gyrus (SFG), middle temporal gyrus (MTG), precuneus, inferior occipital gyrus, cerebellum and anterior cingulate cortex (ACC). Differences between the groups regarding the priming effect were reflected in an enhancement of responses in patients and a response suppression in controls in right angular gyrus (AG) and precuneus. Patients and controls differed regarding the modality effect within left MTG, fusiform gyrus, cerebellum, ACC, SFG, and right AG. Within left MTG and SFG, controls as well as patients showed a response enhancement for crossmodal and a response suppression for unimodal priming effects. Effects of semantic distance were reflected in a bilateral temporo-parietal nework, comprising MTG, fusiform gyrus, precuneus and right thalamus, with group differences in the thalamus, left MTG, fusiform gyrus, and precuneus. The authors suggest that a delay and enhancement of the spread of activation might have contributed to the result of enhanced activation in SZ.

2.4. Measures of Neuronal activity

The earliest attempts to record electric neural activity in humans led to the discovery of rhythmic activity (Berger, 1929), paralleling earlier findings by Richard Caton in animal recordings ("Forty-Third Annual Meeting of the British Medical Association," 1875), who not only showed that electric currents as assessed by a galvanometer exist in the brains of monkeys and rabbits, but also proposed a relation between functional activity of the grey matter and changes in these electric currents. Some of Berger's early seminal recordings in humans were done with needle electrodes, in some cases over brain areas where patients had

trepanations before so that parts of the bone were removed. His observations of waves featuring cycles of different frequencies led Berger to expect that, analogous to the electrocardiogram for diseases of the heart, the "Elektrenkephalogramm", as he termed it, could one day provide an objective diagnostic method to detect disorders of the nervous system. The notion of a sensitivity of the EEG as we know it today for changes in the electric potential and thereby for information processing in the nervous system, sensory and cognitive functions and mental states was supported by simultaneous intracranial recordings (Zelmann, Lina, Schulze-Bonhage, Gotman, & Jacobs, 2013).

In the early stages of the development of the electroencephalogram (EEG), the analyses were primarily focusing on features of the raw ongoing EEG. Small amplitudes of the recorded ongoing signals as well as artifacts, muscle activity, eye movements and other kinds of noise limited the possible applications of the EEG and the scope of interpretation of the findings. Neural activity as assessed with EEG or MEG today is often analyzed according to one of the following two approaches: as event-related potentials (see chapter 2.4.1) or frequency-specific activity (see chapter 2.4.2).

2.4.1. Event-related Potentials

Sensory and cognitive functions have been investigated extensively by analyzing event-related brain potentials (ERPs). ERPs are calculated by averaging epochs of scalp-recorded brain activity in response to a certain stimulus event (Handy, 2005). Importantly, the activity that is reflected in the EEG or averaged ERP reflects activity from summed potentials of large numbers of synchronously active neurons (Nunez & Srinivasan, 2006). Stimulus events eliciting a brain response can be internal or external, they can be of any sensory modality, such as the visual (Hillyard & Anllo-Vento, 1998; Martínez et al., 1999), auditory (Hillyard, Squires, Bauer, & Lindsay, 1971), tactile (e.g. (Kekoni et al., 1997), olfactory (Haehner, Gruenewald, Dibenedetto, & Hummel, 2011) or gustatory (see Ohla, Busch, & Lundstrom, 2012). ERPs are characterized by specific waveforms with sequences of peaks that reflect the activity of extracellular currents that give rise to the scalp-recorded electrical activity. Importantly, this neural activity can be measured with millisecond precision in MEG and EEG, so that these two methods have been termed "real-time measures" in comparison to for instance fMRI. Whereas the spatial resolution of fMRI is superior as compared to EEG and MEG, its time resolution is much poorer because measures as obtained with fMRI are bound to blood flow. Therefore, activity as measured with fMRI can only be analyzed within large

time windows, probably of a length of several seconds. Some of the most important ERP components assessing sensory processing and cognitive functioning in SZ that have also been proposed as potential biomarkers are briefly mentioned in the following part of this chapter (except the N400, which is discussed in chapter 2.3, pp 25, in the context of semantic memory in SZ).

P50

The repeated presentation of an identical sensory stimulus usually leads to habituation. In healthy subjects, the amplitude as measured with EEG in response to the second of two consecutively presented stimuli is usually weaker as compared to the response the first stimulus. This finding has been interpreted as response habituation. Sensory gating, an organisms` ability to suppress irrelevant sensory input, is often investigated in neurophysiological studies assessing the auditory evoked P50 in the event-related potentials (ERP). An experimental setup that has been frequently used in patient studies is the sensory gating paradigm. This paradigm comprises two identical successively presented auditory stimuli (e.g. clicks), so the auditory evoked P50 in response to the first and to the second stimulus can be directly compared. Healthy Participants usually show a suppression of the P50, i.e. a smaller amplitude in response to the second stimulus as compared to the response to the first stimulus. Interestingly, in patients with schizophrenia, this habituation seems to be much weaker or is even absent, which has also been shown in the MEG and combined EEG-MEG studies: beyond less P50 gating in SZ, left hemisphere M50 gating was correlated with EEG gating and also related to sustained attention and working memory (Thoma et al., 2003). Findings on P50 suppression and correlations with symptoms raise the question if the P50 as a basic measure of early sensory processing is also related to the performance in more demanding tasks and higher functions. To examine the role of early sensory processing deficits in sensitivity to distracting noise in SZ, the relation between performance in an auditory attention task and P50 gating ratios was investigated (Smucny, Olincy, Eichman, Lyons, & Tregellas, 2013). Specifically, this study tested for an association between the effects of noise distraction and the behavioural performance in an auditory attention task. Main findings of this study were a stronger distraction effect of noise on reaction times (RTs) and higher P50 auditory gating ratios in patients than in non-clinical control participants, with the magnitude of noise-induced RT increase being correlated with P50 gating ratio. The distracting influence of noise on RTs was also positively correlated with the symptom of

delusion and the P50 gating ratios were correlated with delusion and hallucinations in the patients (Smucny et al., 2013).

It has been argued that the P50 shows some similarities to the evoked Gamma Band Response (GBR) which raises the question whether the reduced GBR might account for the P50 suppression effect in SZ: in a simultaneous EEG and MEG study, support for this notion was found, with the MEG GBR and the M100 even being superior over P50 in the EEG for schizophrenia-normal group separations (Clementz, Blumenfeld, & Cobb, 1997). Most studies that have found inefficient suppression of irrelevant sensory information in the sensory gating paradigm in individuals with SZ have used simple auditory stimuli (Dalecki, Croft, & Johnstone, 2011). This raises the question if similar findings can also be found when more naturalistic sensory stimuli would be presented. Recently, an MEG study including patients with SZ found significantly larger P50m sensory gating ratios in response to human voices, with higher left P50m gating ratios being associated with more severe auditory hallucinations and higher right P50m gating ratios with more severe negative symptoms (Hirano et al., 2010). The authors suggested that auditory hallucinations in schizophrenia might be associated with sensory overload to voices in auditory cortex. Taken together, the findings of abnormal P50 suppression in SZ indicate substantial deviations of sensory gating from healthy participants.

However, in an audiovisual P50 paradigm, patients with SZ showed decreased responses to the first (auditory) of two P50 stimuli, which supports the notion of deficits in early auditory processing (Magnée, Oranje, van Engeland, Kahn, & Kemner, 2009). Furthermore, in a study comparing the P50 of patients with SZ with atypical neuroleptics (clozapine, olanzapine, risperidone) with the P50 of patients who received conventional neuroleptics, a substantially lower P50 suppression was only found for patients with SZ with conventional neuroleptics (Light, Geyer, Clementz, Cadenhead, & Braff, 2000). Taken together, the findings on P50 suppression yield interesting insights into neurophysiological mechanisms in SZ, but also raise additional questions about sensory gating and influencing factors in SZ.

Mismatch Negativity (MMN)

In a mismatch negativity paradigm, series of repetitive auditory stimuli are presented with some stimuli in between which deviate from the series of repetitive standards regarding one physical feature, such as duration, intensity or spectral frequency. Deviating stimuli elicit a characteristic ERP component featuring a negative deflection, even in the absence of active attention, and have been suggested to reflect N-methyl-d-aspartate receptor-mediated

neurotransmission (Javitt, Steinschneider, Schroeder, & Arezzo, 1996). The MMN is believed to capture aspects of the processing of auditory sensory memory (Umbricht & Krljes, 2005), which refers to the processing of context-dependent information. In SZ, an extensive amount of findings on deficits in MMN exists (see Näätänen & Kähkönen, 2009; Nagai et al., 2013; Todd, Harms, Schall, & Michie, 2013). Although the MMN is in general an auditory paradigm, there has also been a visual MMN study in SZ, yielding comparable results as the majority of auditory MMN studies in SZ, i.e., a significantly smaller vMMN (Urban, Kremlácek, Masopust, & Libiger, 2008).

A meta-analysis on MMN in SZ summarized 62 studies and the authors concluded that the MMN might be useful to monitor changes in the auditory cortex in SZ, since deficits in frequency MMN were found to be associated with illness duration and unimpaired MMN was found in first-episode schizophrenia (Umbricht & Krljes, 2005). Interestingly, the MMN provides a link to another factor that has been implicated in the development of psychotic symptoms: MMN amplitudes to frequency deviants was significantly reduced in cannabis users as compared to healthy participants, and furthermore, the duration MMN in long-term users was found to be reduced as compared to healthy participants as well as short-term users (Greenwood et al., 2014).

N1

The N1 of the evoked potential, a negative wave peaking between 50 and 150 ms (Näätänen & Picton, 1987), has been investigated in SZ for decades and a large body of evidence shows robust deviations from healthy participants (Dias et al., 2011; Foxe et al., 2011; Leicht et al., 2010a; Neuhaus et al., 2011). The N1 seems to be suitable to distinguish patients with SZ from prodromal participants as indicated by a study applying a visual oddball paradigm in which the visual N1 responses in first-episode SZ and prodromal participants were assessed. Participants performed a silent target detection task while the EEG was recorded and the N1 amplitude was found to be reduced in SZ, but not in prodromal participants (Oribe et al., 2013). Interestingly, the N1 also indicates suppression during talking compared to listening of the same self-generated speech sounds, and this suppression was reduced in patients with SZ and patients with a history of psychosis (Ford et al., 2013), which points to deficits in corollary discharge mechanisms and provides possible links to the emergence of positive symptoms. Similar results were obtained in early illness SZ (Perez et al., 2012). Further support for the notion that the auditory N1 yields relevant insights in SZ research comes from studies on auditory gating of the P50 in high-risk participants with the 22q11.2 deletion

syndrome (Rihs et al., 2013), where differences in the N1 component were found between patients with the 22q11.2 deletion syndrome and healthy participants, such that the patients showed increased amplitudes over central regions to the first N1 and a reduction of activation of primary and secondary auditory cortex during the second N1, whereas the P50 did not differ between the patients and healthy participants.

Taken together, the findings briefly mentioned in this section indicate that sensory processing abnormalities in SZ are reflected in the early visual and auditory ERP, which therefore provides an appropriate measure for neurophysiological alterations in SZ.
The ERP is usually recorded as a brain response to a stimulus with a marked onset in time and epochs of these brain responses are averaged and analyzed time-locked to the onset of a stimulus. In contrast, ongoing, spontaneous brain activity is present before a stimulus, accompanies the presentation of a stimulus and lasts afterwards, and it even occurs independent of any external sensory events. It consists of mixed oscillations, allowing descriptions of the signal in the spectral domain and offering the opportunity to investigate neural processes that are not strictly time-locked to a stimulus. Although neuronal oscillations and event-related potentials are not independent of each other, their analysis yields different views on EEG data as briefly outlined in the following section 2.4.2.

2.4.2. Frequency-specific Neuronal Activity

The function of neural oscillations at different frequencies has already been discussed in Berger's work, as he observed alterations of the predominant frequency of the ongoing EEG depending of the participants´ state (Berger, 1929). When the eyes were closed, he observed rhythmic activity primarily in frequencies in the alpha band (8-12 Hz), whereas opening of the eyes led to a decline of alpha activity. Activity in the beta band (Hz) was dominant during a more alert state of the participant (Berger, 1937). Importantly, rhythmic neuronal activity on the level of brain networks is not only characteristic for arousal or a general or specific state of an organism, but its synchronization has also been proposed to provide an essential coordinating mechanism in perception.
Specifically, information provided by the sensory channels has to be integrated into coherent structures to be perceived as entities such as objects rather than as aggregations of independent parts. Solutions for this so called "binding problem" have been suggested, such

that coding of features of the same object has been hypothesized to imply synchronous neuronal discharges, thereby providing a mechanism in sensory segmentation (Malsburg & Schneider, 1986; Milner, 1974) and feature integration (Treisman, 1996), a notion also referred to as the temporal binding hypothesis (Engel, Fries, König, Brecht, & Singer, 1999). The hypothesis that stimulus-specific synchronization of neuronal responses provides a mechanism for binding of object features is supported by evidence from animal (Gray, König, Engel, & Singer, 1989; Gray & Singer, 1989; Roelfsema, Engel, König, & Singer, 1997) as well as human (Joliot, Ribary, & Llinás, 1994; Keil, Müller, Ray, Gruber, & Elbert, 1999; Rodriguez et al., 1999; Tallon-Baudry, Bertrand, Delpuech, & Pernier, 1996) neurophysiological findings. However, the functional role of gamma band activity has been questioned (Ray & Maunsell, 2010; Ray, Ni, & Maunsell, 2013), although recent animal work indicates that these findings do not necessary challenge the hypothesis in general (Roberts et al., 2013).

Related to this hypothesis is the Feature-Integration Theory of Attention (Treisman & Gelade, 1980), which specifies and emphasizes the role of focused attention and top-down processing in the formation of relations between features. Top-down processing can be distinguished from bottom-up processing (Engel, Fries, & Singer, 2001; Treisman & Gelade, 1980; Varela, Lachaux, Rodriguez, & Martinerie, 2001): bottom-up, stimulus-driven perception is assumed to follow a feedforward or bottom-up hierarchy from lower to higher stages of processing, whereas top-down processing refers to the influences of prior experience and expectations on processing and thereby offers the opportunities of selection and prediction. The Feature-Integration Theory of Attention (Treisman & Gelade, 1980) states that focused attention provides the resource to establish relations between features and thereby provide a percept, and that awareness emerges via focal attention or top-down processing, which usually work in parallel.

Since the early work of Berger, several attempts have been made to investigate the functional role of the different frequencies that characterize rhythmic neural activity (for an overview of early work see (Gray, 1994). Functions of neuronal activity at different frequencies have been investigated for the delta (Harmony, 2013; Nácher, Ledberg, Deco, & Romo, 2013), theta (Buzsáki & Moser, 2013; Hasselmo & Stern, 2014; Yamaguchi et al., 2007), alpha (Jensen & Bonnefond, 2013; Jensen, Gelfand, Kounios, & Lisman, 2002; Klimesch, 2012; Palva & Palva, 2007; Pfurtscheller, 2003), beta (Andreas K Engel & Fries, 2010) and gamma (Lachaux et al., 2000; Pantev et al., 1991; Tallon-Baudry, Bertrand, Delpuech, & Permier, 1997) frequency range.

Beyond local power changes in single brain regions and separate frequency bands, patterns of correlations on the network level within and between different frequencies as well as large-scale interactions have been examined recently (Hipp, Engel, & Siegel, 2011; Hipp, Hawellek, Corbetta, Siegel, & Engel, 2012; Siegel, Donner, & Engel, 2012). Furthermore, the role of rhythmic neuronal activity and its alterations have also been elucidated in sensory deprivation such as blindness (Schepers, Hipp, Schneider, Röder, & Engel, 2012), in specific mental states such as during anaesthesia (Supp, Siegel, Hipp, & Engel, 2011), multisensory processing (Schneider, Debener, Oostenveld, & Engel, 2008; Schneider, Lorenz, Senkowski, & Engel, 2011; Senkowski, Schneider, Foxe, & Engel, 2008) and in ongoing brain activity (Andreas K. Engel, Gerloff, Hilgetag, & Nolte, 2013).

Evoked activity in SZ

In studies on neuronal responses to stimuli, evoked activity, which is strictly phase-locked to the stimulus, is distinguished from induced activity, which contains activity that is not phase-locked to a stimulus (Herrmann, Rach, Vosskuhl, & Strüber, 2013), and total activity, which contains phase-locked as well as non-phase locked activity. Evoked activity is calculated by averaging the evoked responses and subsequently transferring the responses into the frequency domain, whereas the total activity is obtained by frequency analyses on single trials prior to averaging. Whereas evoked activity is thought to reflect basic sensory processing, since responses occur primarily in close temporal proximity to the sensory stimulus eliciting the evoked response, whereas total oscillatory activity is assumed to reflect further processing beyond basic perception.

A specific case of evoked activity is the Steady-state evoked potential (SSVEP), which is obtained by presenting a repetitive stimulus at a certain frequency in for instance the visual modality in form of a visual flicker, and analyzing the neuronal responses in the frequency domain with regard to the frequency domain of the driving stimulus. SSVEPs not only reflect the frequency of the driving external stimulus, they were also found to be enhanced in amplitude in the specific frequencies of the to-be-attended stimulus as compared to other stimuli and to show resonance phenomena, i.e., preferred frequencies eliciting enhanced responses (Herrmann, 2001).

In a study with healthy subjects, SSVEPs accompanying task-relevant auditory or visual information have been used to investigate intermodal and crossmodal spatial attention (Zhang, Hong, Gao, Gao, & Röder, 2011). Differences in evoked power in Steady-State Evoked potentials (see chapter 4) between schizophrenia patients and non-clinical control

subjects have been replicated several times for the auditory and the visual modality. For the auditory system, the Auditory Steady State Response (ASSR) in schizophrenia has been investigated using a stimulation with trains of clicks with presentation rates of 20, 30 or 40 Hz, showing a reduction specifically at 40 Hz power in SZ as compared to lower stimulation frequencies in comparison to non-clinical control subjects (Kwon et al., 1999). Baseline 40 Hz gamma power in left auditory cortex was found to be enhanced in patients with SZ as compared to healthy control subjects (Spencer, 2011). ASSR power to modulated tones was investigated in the EEG and found to be reduced in SZ over a broad band of frequencies (Krishnan et al., 2009). In an SSVEP study applying seven different stimulation frequencies, power at beta and gamma frequencies, but not at 4 and 8 Hz at an occipital region, was reduced in patients with SZ as compared to non-clinical controls subjects (Krishnan et al., 2005) and noise power, the power at frequencies around the stimulation frequency, was higher in patients.

Table 5. Steady-State Evoked Potentials in SZ. The sensory modality is indicated with a different colour (auditory = yellow, visual = blue)

First author	***Publication date***	***Method***	***Main finding in SZ***
Krishnan et al.	2005	SSVEP	Lower SSVEP power in beta and gamma frequency range in SZ
Butler et al.	2001	SSVEP	Lower SSVEP responses to magnocellular-biased stimuli in SZ
Calderone et al.	2013	SSVEP	Reduced SSVEP in response to magnocellular-biased condition
Kim et al.	2006	SSVEP	reduced SSVEP amplitude elicited by magnocellular-biased stimuli correlated with impairments in velocity discrimination
Spencer et al.	2011	ASSR	Higher 40 Hz baseline power as compared to control particitpants in left auditory cortex correlated with ASSR power in SZ
Hong et al.	2004	ASSR	Reduced 40 Hz ASSR power in relatives of patients with SZ; no difference between patients with SZ and healthy participants, but enhanced 40 Hz power in patients with SZ taking new generation antipsychotics as compared to patients taking conventional antipsychotics
Mulert et al.	2011	ASSR	Diminished current source density of the 40 Hz ASSR response in SZ in right STG and MTG; reduced interhemispheric phase locking for primary auditory cortices; correlation between severity of hallucination and phase synchronization between primary auditory cortices
Light et al.	2006	ASSR	Reduced power and intertrial phase synchronization at 30 and 40 Hz stimulation; association between reduced working memory performance and 40 Hz intertrial coherence
Tsuchimoto	2011	ASSR (MEG)	Reduced ASSR power and dipole moments to 40 and 80 Hz frequencies; less right-greater-than-left 40 Hz ASSR in SZ; correlation between enhanced hallucination severity and smaller left 80 Hz ASSR

Kwon et al.	1999	ASSR	Reduction in 40 Hz power in SZ as compared to control participants and compared to lower stimlation frequencies
Krishnan et al.	2009	ASSR	Reduced ASSR power in SZ over broad range of frequencies in the gamma range, with the largest deficit in the range between 35-45 Hz for power and PLF

Table 5.

Deficits in SZ in contrast sensitivity have recently also been investigated in a study combining psychophysical measures, fMRI and SSVEP, offering the opportunity to investigate relations between these measures (Calderone et al., 2013). Whereas a psychophysical contrast-sensitivity task indicated deficient contrast sensitivity in SZ across different spatial frequencies and also the SSVEP responses revealed a specific processing deficit in SZ in magnocellular-biased stimuli, the fMRI results revealed that activation strengths did not differ between patients with SZ and control participants in a contrast-sensitivity task, but yielded a lower volume of activation measures in SZ. The results suggest that a reduced volume of activation might be related with processing deficits of stimuli featuring a low spatial frequency rather than activation strength in general and point to the sensitivity of SSVEP and psychophysical measures in the investigation of basic sensory processing deficits in the visual domain in SZ. In a study using SSVEP while manipulating luminance contrast of the stimuli and assessing velocity discrimination thresholds in patients with SZ and control participants (Kim, Wylie, Pasternak, Butler, & Javitt, 2006), deficient velocity discrimination correlated with reductions in SSVEP amplitude in response to magnocellular-biased stimuli which is interpreted by the authors as influences of deficient bottom-up input to V1 on higher cognitive functions. Although the majority of findings suggest deficits in SZ in the entrainment to an external stimulus as assessed by steady-state evoked potentials, it should be noted that results on SSVEP and ASSR in SZ are not fully consistent (Hong et al., 2004). Extensive reviews of studies using the steady-state evoked potential in SZ can be found elsewhere (Brenner et al., 2009).

Models of Schizophrenia

Beyond investigations of specific features of SZ in the domains of neurotransmission, psychophysiology, genetics, behavioural performance, cognitive abilities, electrophysiology and neuroimaging in SZ, integrative models have been developed to provide suggestions for the etiology of SZ and to take into consideration the complexity of different empirical findings in SZ. Challenges for any model of SZ arise partly due to features of the disease such as the fluctuations of symptoms over time, the heterogeneity of subtypes of SZ, prevalent

additional diagnoses, and the frequent observation that patients with SZ differ from non-affected individuals in countless variables, but that these differences are sometimes hard to replicate, not always consistent and not pathognomonic. An ideal model of SZ would explain the etiology of the disorder, the emergence of positive, negative and cognitive symptoms, it would have to address the numerous structural alterations in SZ that can be found throughout the nervous system, and it would have to incorporate hypotheses on dynamic changes in neurotransmission accounting for the changes of symptoms during the course of the disorder. Ideally, it would also include explanations for findings in related disciplines that might indirectly influence functioning of the nervous system such as evidence for inflammatory processes in the nervous system in SZ (Müller, Myint, & Schwarz, 2012), and the enhanced rate of obstetric complications in SZ (Cannon, Jones, & Murray, 2002). The purpose of this section was not to provide an exhaustive review of all the models of SZ, but to mention the most influential models briefly that have an impact on current theories or which were developed and supported by empirical findings recently.

As mentioned in previous sections, within the last few decades a paradigm shift in schizophrenia research became apparent, changing from a predominantly "top down" perspective towards bottom-up and basic sensory processing. Given the existing findings which are interpreted as demonstrating deficient top-down processing as well as the aforementioned sensory impairments at early stages of sensory processing (see chapter 2.1), the question arises -amongst others- whether deficits in SZ might be located anatomically in primary sensory areas that exhibit a specific dysfunction or whether impairments in SZ should rather be investigated and conceptualized primarily as related to top-down processing, suggesting a perspective of disruptions emerging on the network level. Since conceptualizations of SZ are also directly or indirectly linked to models of neurochemistry, assumptions about alterations in neurotransmission are related to the top-down versus bottom-up distinction. Taken together, Javitt suggested a "top down" vs "generalized" view rather than an oversimplified top-down vs bottom-up distinction (Javitt, 2009b), which is in line with recent approaches in SZ research that incorporate several aspects of basic sensory and higher-order cognitive processing. In general, distributed models which include bottom-up as well as top-down components are associated with recent glutamatergic and gamma-aminobutyric acid(GABA)ergic models of SZ, whereas top-down models are related to dopaminergic theories, emphasizing the prefrontal cortex.

In an early integrative model based on MRT and PET data the term "cognitive dysmetria" was coined for a range of impairments in SZ, i.e., deficient coordination and

response to information as well as diminished abilities to prioritize and process input (Andreasen, Paradiso, & O'Leary, 1998). It emphasizes the interaction of cortical and subcortical structures, specifically connectivity of prefrontal regions, thalamic nuclei and the cerebellum and regards cognitive deficits in SZ as emerging on the level of distributed circuits and their disruptions rather than in distinct local areas.

The "disconnection hypothesis" (Friston, 1998) proposes functional disconnection as primarily involved in the pathomechanisms leading to SZ, i.e. deficient functional integration of neuronal systems. Specifically, the connections between neuronal systems and long-term changes in the strength of these connections is emphasized, such that not plasticity in general is considered to be impaired, but its regulation. Notably, Friston`s notion of disconnection refers to functional, effective rather than anatomical disconnection, in contrast do very early hypotheses about the etiology of psychoses.

For decades, the dopamine hypothesis of SZ was the dominant model of neurochemistry in SZ, on grounds of the early finding that psychotic symptoms similar to those observed in SZ can be evoked by psychostimulants such as amphetamine (Meltzer & Stahl, 1976; Snyder, 1976). Support for the dopamine hypothesis comes from the observation that positive symptoms of SZ can be treated with antipsychotics targeting D2 receptors. Shortcomings of these treatments were obvious: The effects were restricted to the treatment of positive symptoms, whereas the treatment of negative symptoms of the disorder as well as functional recovery remain challenges to date (Insel, 2010). Second, even in successful treatment of positive symptoms, the devastating side effects such as extrapyramidal symptoms like tremor and rigidity, which sometimes even resemble symptoms of Parkinson´s disease, diminish the quality of life for patients substantially. Advances were made in the development of atypical antipsychotics, but most of the times do not exceed efficacy of conventional antipsychotics in treatment of positive symptoms. However, since the dopamine hypothesis was the dominant perspective in SZ research for a very long time, several modifications were proposed. A review and detailed description of tree different versions of the dopamine hypothesis throughout the decades can be found elsewhere (Howes & Kapur, 2009).

Glutamatergic models of SZ (Javitt, Steinschneider, Schroeder, & Arezzo, 1996b; Javitt, 2012; Lisman et al., 2008; Moghaddam & Krystal, 2012; Mulert & Scarr, 2012; Olney & Farber, 1995) emerged following the observation that schizophrenia-like symptoms are elicited by the administration of phencyclidine (PCP) and ketamine. Blocking of neurotransmission at N-methyl-D-aspartate (NMDA)-type glutamate receptors was identified

as the mechanism leading to the emergence of the symptoms, bringing about the "NMDA receptor hypofunction hypothesis" (Coyle, 2012). Interestingly, not only positive symptoms were replicated, as was the case for psychostimulants, which led to the dopamine hypothesis, but also negative and cognitive symptoms of the disorder. Regarding the two predictions of the model, namely, 1) a relation between cognitive deficits of SZ and NMDAR dysfunction and 2) agents enhancing NMDAR function yield beneficial treatment effects, recent work yielded tremendous advances, experimentally as well as with regard to the development of treatments (Javitt, Zukin, Heresco-Levy, & Umbricht, 2012). Furthermore, the glutamate hypothesis of SZ received considerable support by a pharmacological nonhuman primate model of SZ, that was developed based on ERP recordings in humans and rhesus macaques in an auditory oddball paradigm (Gil-da-Costa, Stoner, Fung, & Albright, 2013). Homologous MMN and P3a ERPs were recorded, and beyond that, ketamine was administered to the macaques. An expected decrease in both ERP amplitudes that parallels findings in patients with SZ was found. This finding demonstrates nicely another aspect the glutamate hypothesis adds to existent knowledge in SZ research, namely, the opportunity to model sensory impairments, a relevant group of symptoms in SZ, via administration of ketamine in macaques that can be recorded noninvasively and compared to well-replicated neurophysiological measures in animals as well as humans.

Recently, attempts have been made to integrate dysfunctions of different systems of neurotransmission into models of interactions. This has for example yielded new perspectives on the integration of dopamine and glutamate transmission at NMDA receptors (Laruelle, 2014) as well as hypotheses about the relations between rhythmic neuronal activity as recorded with EEG and MEG and underlying alterations in neurotransmission in SZ, pointing to a necessity for a broader integrative approach. For instance, gamma oscillations in SZ and their association with the aforementioned models of neurochemistry is probably based on parvalbumin (PV)-containing gamma-amino butyric acid (GABA) neurons, which are involved in the generation of gamma oscillations (Sohal, Zhang, Yizhar, & Deisseroth, 2009), so the abovementioned deviations in gamma synchrony in SZ as compared to healthy participants may be due to alterations in PV neurons in SZ. Furthermore, it has been suggested that NMDA receptors could be involved in the emergence of PV alterations (Gonzalez-Burgos & Lewis, 2012).

An integrative approach on alterations in SZ on the level of circuits incorporating neuronal oscillations, neurotransmission and gene interactions has recently been suggested (Lisman et al., 2008; Lisman, 2012). Beyond the inclusion of risk genes affecting

glutamatergic, nicotinic and GABAergic transmission in the framework, GABA and NMDAR hypofunction are both incorporated. This is due to findings indicating GABA impairments, i.e., reductions in GABA in SZ in post mortem studies, as well as the finding that phencyclidine (PCP) and ketamine can induce schizophrenia-like symptoms due to their properties as NMDA receptor antagonists. The relevance of NMDA transmission for recent SZ research and specifically in this framework is further emphasized by the finding that NMDA antagonists reproduce negative and positive symptoms of the disease. Furthermore, the generation of the mismatch negativity evoked potentials has been shown to be related to NMDA channels, thereby suggesting that the MMN might be a useful measure for NMDA hypofunction.

This is supported by the findings of reduced mismatch negativity in SZ. One of the advantages of the framework is the investigation of the interaction between systems of neurotransmission, such as the interaction between NMDA and GABA, leading to a disinhibition which plays a major role in circuitry: GAD-67, a GABA-synthesizing enzyme, has been shown to be reduced in SZ in post mortem studies, probably favoring disinhibition, and furthermore, NMDA antagonists have been assumed to contribute to disinhibition of pyramidal cells due to blocking of NMDAR-mediated EPSP of interneurons. Beyond GABA and NMDA, dopamine is also involved in pathophysiology according to the framework, specifically, it was suggested that NMDAR hypofunction can be related to a hyperdopaminergic state. As a region involved in the emergence of a hyperdopaminergic state, the hippocampus has been identified, and a hyperactive hippocampus has been found to cause an enhanced firing in the dopamine system of the ventral tegmental area (VTA).

The chapters of this introduction sketched indicators of neural activity as well as some important domains of human cognitive functioning, namely sensory processing, attention and semantic memory. All of these are highly relevant for cognitive, social and occupational tasks and personal well-being, and specifically, none of these functions works isolated from the others. The aim of this study is to combine the investigation of multisensory processing and of attention (study 1 and 2) and of semantic memory (study 3) in three neurophysiological experiments in patients with SZ. Specifically, the purpose was to elucidate whether dysfunctions are present on the behavioural level, and if do whether these dysfunctions are accompanied by deviations in neural activity as measured by EEG and MEG in comparison to non-clinical control subjects. Furthermore, the possible relationship between behavioural performance, neural activity and symptom severity was explored.

3. Experimental Section 1: "SSVEPs as a neurophysiological Correlate of Distractibility under audiovisual Speech Interference Conditions in Healthy Subjects (EEG)"

3.1. Introduction

In everyday life, speech signals from a person that we are listening to are often accompanied by distractions, such as auditory and visual stimuli from surrounding people. These distracting stimuli can capture attention and interfere with the recognition of speech. How exactly distracting auditory and visual speech stimuli affect the recognition and processing of attended speech is, to date, not well understood.

Speech recognition, in particular in noisy conditions, is considerably improved when matching visual inputs, i.e. lip movements, are presented (Ross, Saint-Amour, Leavitt, Javitt, & Foxe, 2007; Ross, Saint-Amour, Leavitt, Molholm, et al., 2007; Sumby & Pollack, 1954). Moreover, a recent functional magnetic resonance imaging study showed that attending to lip movements that match a stream of auditory sentences leads to an enhanced target detection rate and to stronger activity in a speech-related multisensory network compared to attending to non-matching lip movements (Fairhall & Macaluso, 2009). This suggests an important role of top-down attention for multisensory processing of speech In this high-density electroencephalography (EEG) study, we investigated how different types of speech and non-speech stimuli influence the processing of attended audiovisual speech. Participants were presented with three horizontally aligned speakers who produced syllables. The faces of the three speakers flickered at specific frequencies (19 Hz for flanking speakers and 25 Hz for the center speaker), which induced steady-state visual evoked potentials (SSVEP) in the EEG that served as a measure of visual attention (Koelewijn, Bronkhorst, & Theeuwes, 2010; Talsma, Senkowski, Soto-Faraco, & Woldorff, 2010).

This notion is consistent with an electroencephalographic (EEG) study, in which we examined the influence of task relevant and task irrelevant visual speech stimuli on audiovisual speech processing in a multiple speaker scenario (Senkowski, Saint-Amour, Gruber, & Foxe, 2008). In this study, participants were instructed to detect an occasional audiovisual target syllable by a speaker (i.e. a speaking face) who was presented centrally and surrounded by two flanking speakers. The study comprised of no interference trials, in which a syllable was produced by the relevant central speaker only, and interference trials, in which different audiovisual syllables were produced by three speakers simultaneously. Using steady-state visual evoked potentials (SSVEP) as a real-time index of deployment of visual attention,

we observed that visual attention towards the task irrelevant flanking speakers interferes with the recognition of task relevant audiovisual signals. The main question raised by our study is whether the interference effect is specific for the processing of naturalistic audiovisual speech or whether similar effects would occur when the flanking speakers produce other distracting stimuli, like moving their lips without a sound or when they produce noise instead of syllables.

Using an extended setup of a previous study (Senkowski, Saint-Amour, Gruber, & Foxe, 2008), we addressed this question by examining behavioral data and SSVEPs in three interference conditions and one control condition. In the interference conditions the flanking speakers produced either naturalistic audiovisual syllables, lip movements alone, or lip movements in combination with acoustic noise.

3.2. Hypotheses

In line with our previous study, we expected distraction effects in behavioral data that are paralleled by enhanced SSVEPs to flanking speakers when these speakers produced naturalistic audiovisual speech. Given the salience of audiovisual speech, we predicted that the interference effects of lip movements alone and lip movements accompanied by auditory noise would be much weaker or even vanished.

3.3. Methods

Participants

Twenty volunteers, who reported no history of neurologic or psychiatric illness, participated in the study. Four participants were excluded from the analysis on the basis of extensive eye movements. Additional 3 participants were excluded because their hit rate was lower than 50% in the 'Speech Interference' condition (see below). The remaining 13 participants (all right handed, mean age 22.92 years, range 21-29 years, 6 females) had normal hearing, as assessed by a hearing test in which 30 dB sinusoidal tones of varying frequencies had to be detected. Participants had normal or corrected-to-normal vision, as ensured by the Landolt test of visual acuity (visus ≥ 0.9). The Institutional Review Board of the Medical Association of Hamburg approved the experimental procedures, and each subject provided written informed consent and was paid for participation.

Procedure and Stimuli

A continuous stream of four stimulation conditions was presented (Fig. 1). Two of the conditions were identical to those used in our previous study. This previous study comprised of a 'No Interference' control condition, in which only the center speaker produced a syllable, and a 'Speech Interference' condition, in which all three speakers produced syllables (a short clip of this experiment is provided at: http://www.sciencedirect.com/science/article/pii/S1053811908007933). In the present study, two conditions were added to examine in further detail how visual attention towards flanking speakers interferes with audiovisual speech processing. In one of these conditions the flanking speakers produced acoustic non-speech noise instead of syllables. Non-speech noise samples were directly derived from the original syllables by phase-scrambling the auditory syllables, thereby maintaining basic properties like stimulus power. We will refer to this condition as 'Auditory Noise Interference'. In the other condition the flanking speakers moved their lips without producing an acoustic syllable. We will refer to this condition as 'Lip Movement Interference' condition. Thus, the study comprised of four conditions: 'No Interference', 'Speech Interference', Auditory Noise Interference', and 'Lip Movement Interference'. The center speaker produced one of the syllables /ta/, /da/, /ga/, or /ba/ in all conditions, whereas the flanking speakers could produce the syllables /ta/, /da/, or /ga/ in the 'Speech Interference' condition. The four conditions and the different syllables were presented in random order. Participants were instructed to focus their attention to the center speaker and to ignore the signals from the flanking speakers. Furthermore, they had to indicate the occasional appearance of the target syllable /ba/ by the center speaker with a button press of their right index finger. The target syllable occurred in 20% of all trials. The three speakers never produced the same syllable in a trial and syllable combinations that could evoke the McGurk illusion (McGurk & MacDonald, 1976), like the combination /ba/ and /ga/ were excluded.

On average 76 targets and 300 non-target stimuli were presented for each condition. One trial consisted of 120 visual frames of 6.67 ms each, resulting in a trial duration of 792 ms. Two fixed cycles of 24 frames were added per trial. Moreover, a variable number of 1-5 cycles (average: 3 cycles) was added, resulting in a total average trial duration of 1592 ms. During the inter-trial interval the faces of the three speakers were presented on the screen without producing any lip movements or speech sounds, but the 19 Hz flicker of the flanking speakers and the 25 Hz flicker of the center speaker continued. An additional number of 645 (about 30 % of all trials) 'omitted trial' periods (Busse & Woldorff, 2003) were randomly inserted into the continuous stream of stimuli, further reducing the predictability of the

experimental stimuli. During omitted trial periods, the faces of the three speakers were presented for a time interval that was identical to the interval of regular experimental events (i.e., 792 ms) but without any lip movements or speech sounds. Each participant underwent 18 experimental blocks with 120 trials each.

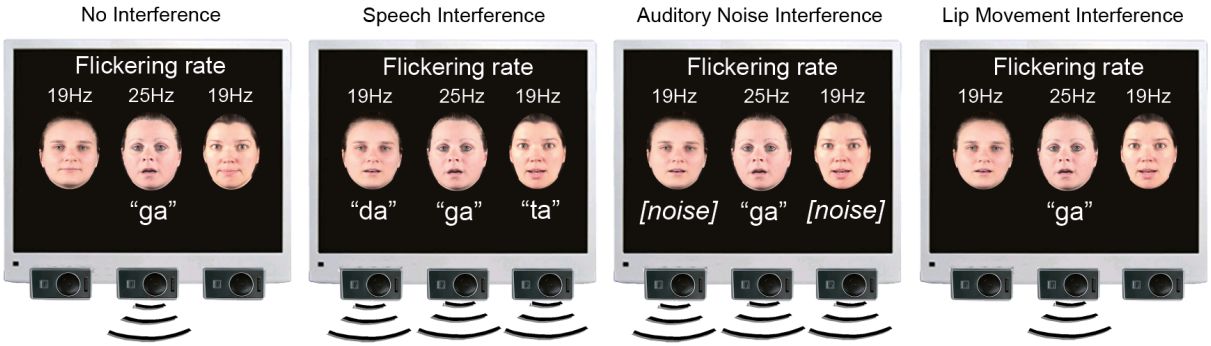


Figure 3.3-1: Stimulus setup. Stimuli consist of three horizontally aligned speakers on a black background. In all experimental conditions, the center face is visually presented in an on-off fashion so that a 25 Hz flicker was elicited. The center speaker produces natural auditory and visible syllables ('ta', 'da', 'ga', 'ba'), whereas the two flanking speakers are always presented with a flicker frequency of 19 Hz. The subject`s task is to detect the syllable 'ba' by the center speaker. In the No Interference condition, the flanking speakers produce neither visual lip movements nor speech sounds, whereas they perform natural speech syllables ('ta', 'da' and 'ga') simultaneous with the syllables of the center speaker in the Speech Interference condition. The Auditory Noise Interference condition consists of phase-scrambled versions of the original syllables 'ta', 'da' and 'ga' produced by the flanking speakers, and in the Lip Movement Interference condition the flanking speakers produce lip movements of the original syllables without any accompanying auditory signal.

Recordings of syllables from the three speakers were obtained at frame rates of 30/s. Each syllable consisted of 20 frames of 33 ms duration, which results in a total duration of 660 ms for each syllable. The visual angle of the speakers subtended 7° between adjacent speakers (from mouth to mouth) and the width of the speakers' faces subtended an angle of 4.8° each. The characters of the flanking speakers switched their location (i.e. left or right of the center speaker) after every block, while the center speaker character remained the same throughout the experiment. The monitor was set to a refresh rate of 150 Hz, i.e., the refresh rate duration for one frame was 6.67 ms. To induce steady-state visual evoked potentials (SSVEPs), the continuous stream of pictures was dissected in an on-off fashion, i.e., pictures of the continuous stream ('on') were presented alternately with blank screens ('off'). Pictures of the continuous stream and blank frames alternated every 20 ms. Thus, the flicker frequency (i.e. on-off cycle) was 25 Hz for the center speaker. For the two flanking speakers, the on-off periods alternated every 26.6 ms simultaneously for both speakers, corresponding to a flicker frequency of about 19 Hz. In the EEG the time-frequency transformed activity of a sustained

visual on-off flicker is reflected in event-related activity that corresponds to the presented flicker frequency (Herrmann, 2001).

Both the 19 Hz flicker and the 25 Hz flicker were presented continuously and all trials started with an 'on' period. The average stimulus duration of the acoustic syllables was 295 ms and the onset of these syllables followed the onset of visual lip movements on average by 230 ms. To eliminate overlapping event-related responses to the sounds, a relative stimulus onset jitter of 110 ms (more than two times the duration of a 19 Hz and a 25 Hz cycle) was used by adding or subtracting a random time interval between ±55 ms to the real acoustic sound onset in each trial (Senkowski, Talsma, Grigutsch, Herrmann, & Woldorff, 2007; Woldorff, 1993). This jitter prevented overlapping event-related 19 and 25 Hz responses to the acoustic inputs. A spline curve FFT filter between 400 to 4000 Hz was applied to all syllables to align the voice characteristics between the three speakers.

Data acquisition

The EEG was recorded from 124 scalp sites using an active electrode system (EASYCAP, Herrsching, Germany). In addition, the electrooculogram was recorded by two electrodes. One of these electrodes was placed below the eye and the other one was placed at the lateral bridge of the nose. The nose tip was used as reference during recording and data were off-line re-referenced to average reference. Data were digitized at a sampling rate of 1000 Hz using BrainAmp amplifiers (BrainProducts, Munich, Germany), filtered from 0.3 to 120 Hz and downsampled to 250 Hz for the off-line analysis. Epochs were cut around the visual motion onset (0 indicates the first frame of the visible movement) from -1000 ms before to 1200 ms after visual motion onset. Trials containing artifacts in EEG data resulting from eyeblinks, horizontal eye movements, or muscle activity were removed from the further analysis. Noisy channels were linearly interpolated. Finally, an automatic threshold was applied, excluding all trials in which the EEG amplitude exceeded 100 μV.

Data Analysis

Reaction times (RTs) to target stimuli were calculated by averaging all trials in which subjects responded between 230 and 1000 ms after visual motion onset and in which the RT did not exceed 2 standard deviations from the mean RT within each participant and condition. For the statistical analysis of RTs, hit rate (HR), and false alarms (FA) an ANOVA or Friedman test (if the assumption of gaussianity was violated) with the factor experimental

condition (No Interference, Speech Interference, Auditory Noise Interference, Lip Movement Interference) was calculated. A Kolmogorov-Smirnov test was computed to test for gaussianity of RT, HR, and FA distributions. Moreover, three planned contrasts were computed: Speech Interference vs. No Interference, Auditory Noise Interference vs. No Interference, and Lip Movement Interference vs. No Interference.

EEG data were analyzed using MATLAB (Version 7.10), EEGLAB 5.03 (http://www.sccn.ucsd.edu/eeglab) and the FIELDTRIP toolbox (Oostenveld, Fries, Maris, & Schoffelen, 2011). For the analysis of SSVEPs, event-related activity was calculated by averaging the epochs of each condition. For the averaged activity, time-frequency (TF) analyses were calculated using wavelet transformation with Morlet wavelets spanning a range of 10 to 30 Hz with a length of 12 cycles. The TF analysis was computed in 0.25 Hz steps. In agreement with our previous study we analyzed SSVEPs for three predefined regions of interest (ROIs): an occipital ROI, comprising of 7 electrodes that were located at midline-occipital scalp, and two symmetric bilateral ROIs that were located at lateral temporal scalp, comprising of 6 electrodes each.

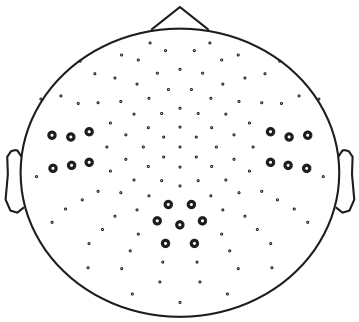


Figure 3.3-1. Left temporal, right temporal and occipital sensors were pooled in three regions of interest and used for the statistical analysis of the SSVEPs.

In line with the observed SSVEP response pattern, the analysis was done for the time window of 230 ms to 550 ms after onset of the visual motion onset. To investigate how visual inputs of the center speaker and the flanking speakers were processed in the different experimental conditions, wavelet transformed data were analyzed for those frequencies that corresponded to the visual stimulation frequencies of the speakers. The length of the wavelet was 480 ms for the analysis of 25 Hz activity and 632 ms for the analysis of 19 Hz activity, with a wavelet length of 12 cycles, respectively. Repeated measures ANOVAs with the within-subject factors Condition (No Interference, Speech Interference, Auditory Noise Interference, and Lip Movement Interference) and ROI (left temporal, right temporal, occipital) were conducted.

Furthermore, planned contrasts between each of the three interference conditions (Speech Interference, Auditory Noise Interference, Lip Movement Interference) and the no-interference condition were computed. In case of non-sphericity, as tested by Mauchly`s sphericity test, the degrees of freedom were adjusted in the ANOVAs.

3.4. Results

Behavioral Data

The ANOVA for RTs with the factor Condition (No Interference, Speech Interference, Auditory Noise Interference, Lip Movement Interference) revealed a significant effect ($F_{(2.07,24.85)}$ = 16,169, $p < 0.0001$; Fig. 2). The analysis of planned contrasts revealed significant longer RTs in Speech Interference Condition (731 ms) compared to the No Interference condition (673 ms; $t_{12} = -6.557$, $p < 0.001$). No other significant effects were observed for RTs.

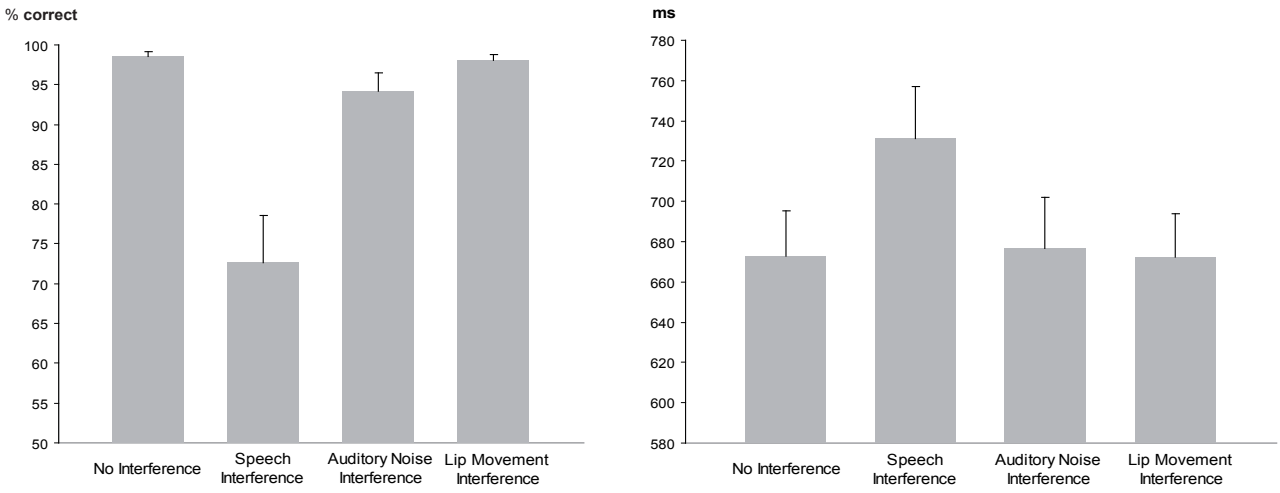


Figure 3.4-1. Behavioral performance. Reaction times (RTs) and hit rates (HRs) for the No Interference control condition as well as for the three Interference conditions.

Since the Kolmogorov-Smirnov tests indicated violations of gaussianity in the distributions of HR and FA data, non-parametric Friedman tests were computed for the analysis of effects in HR and FA rate. For the HR, this test revealed a significant difference between conditions ($p < 0.0001$). The analysis of pair-wise planned contrasts (using non-

parametric Wilcoxon tests) revealed significant differences between the No Interference and the Speech Interference Condition (p = 0.001) and the No Interference and the Auditory Noise Interference Condition (p = 0.003). For both comparisons the HR was higher in the No Interference condition. There was no significant difference between the No Interference and the Lip Movement Interference Condition (p = 0.128). For the three Interference Conditions, a significant difference was found between the Lip Movement Interference and the Auditory Noise Interference Condition (p = 0.011), due to a higher HR in the Lip Movement Interference Condition. Furthermore, there were significant differences between the Lip Movement Interference and the Speech Interference Conditon (p = 0.001) as well as between the Speech Interference and the Auditory Noise Interference Condition (p = 0.001). The HR was higher in the Lip Movement and the Auditory Noise Interference conditions compared to the Speech Interference Condition.

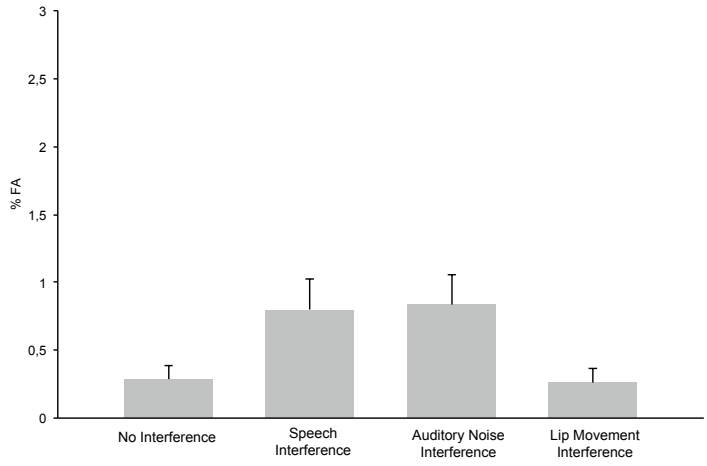


Figure 3.4-2. False alarm (FA) rates for No Interference, Speech Interference, Auditory Noise Interference and Lip Movement Interference Condition.

The Friedman Test for FA rate revealed a significant result (p = 0.019; Fig. 2b). Pairwise Wilcoxon tests revealed significantly larger FA rates in the Speech Interference Condition (0.799 %) compared to the No Interference Condition (0.287 %, p = 0.021). However, the differences between the No Interference compared to the Auditory Noise Interference Condition (0.835 %) and the Lip Movement Interference Condition (0.257 %) were not significant.

Steady-state visual evoked potentials

The spectral analysis revealed occipital SSVEPs that corresponded to the flicker frequency of flanking speakers (19 Hz) and the center speaker (25 Hz, Fig. 3). The two-way ANOVA for flanking speakers' 19 Hz SSVEPs using the factors Condition (No Interference, Speech Interference, Auditory Noise Interference, Lip Movement Interference) and ROI (left temporal, right temporal, occipital) revealed significant main effects of Condition ($F_{(3,12)}$= 4.123, $p < 0.05$) and ROI ($F_{(2,12)} = 12.780$, $p < 0.001$), and a significant interaction between these factors ($F_{(6,72)} = 2.770$, $p < 0.05$). Follow-up analyses were performed separately for the three ROIs. Whereas no significant effects were observed for the bilateral temporal ROIs (all p's > 0.1), a significant main effect of Condition was found for the occipital ROI ($F_{(3,12)}$= 3.777, $p < 0.05$, Fig. 4). The analysis of planned contrasts revealed a significant effect for the contrast between the Speech Interference and the No Interference condition ($F_{(1,12)}$= 5.996, $p < 0.05$), due to larger flanking speaker SSVEPs in the Speech Interference condition. Moreover, a trend towards significance was found for the contrast between the Lip Movement Interference and the No Interference condition ($F_{(1,12)}$=4.488, $p < 0.1$). SSVEPs tended to be larger in the Lip Movement than in the No Interference condition. No other significant effects were found, neither in the 19 Hz nor in the 25 Hz SSVEPs.

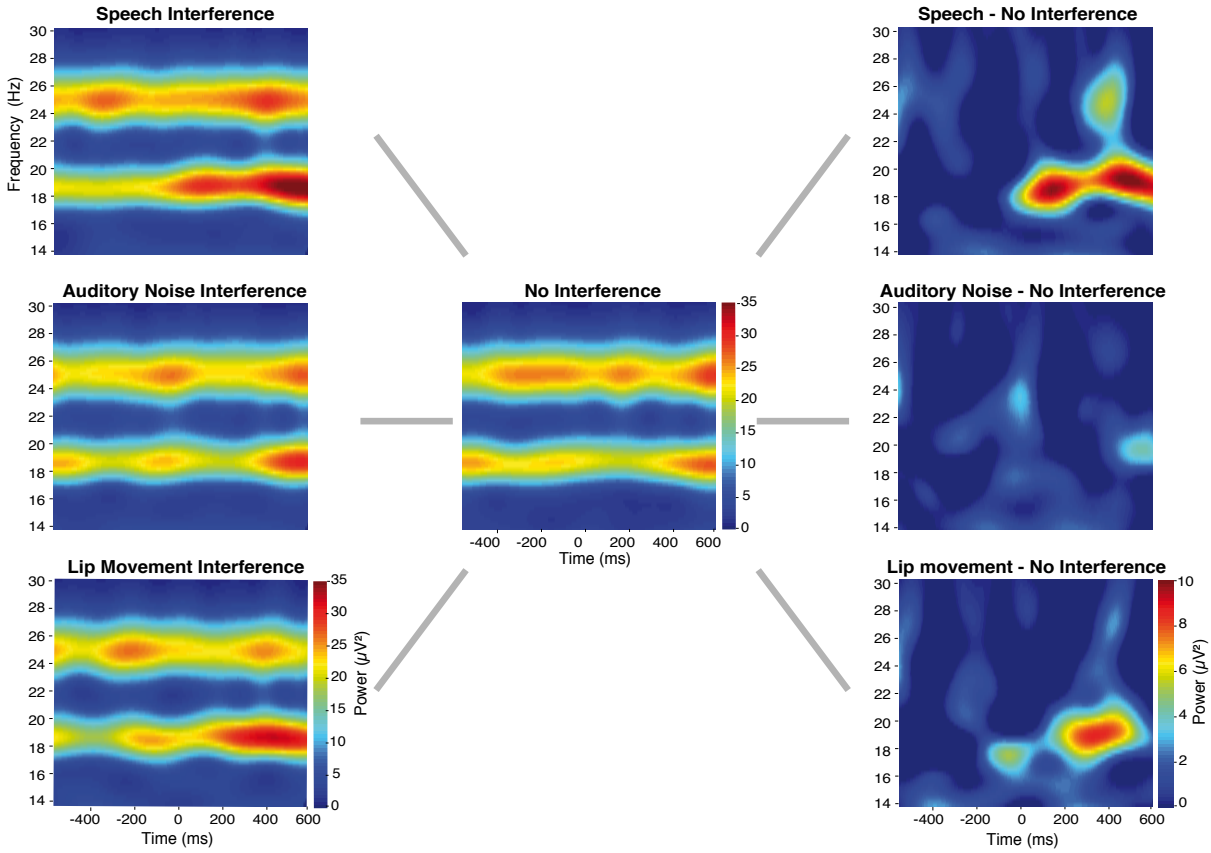


Figure 3.4-3. Time-frequency-plots of SSVEPs for the three Interference conditions (left panel), the No Interference condition (middle panel) as well as for the differences between Interference and No Interference conditions (right panel) for the occipital ROI (see Fig. 4b). For the statistical analysis a time-frequency window of 230-550 ms and 19 Hz was used.

The present finding of a clear occipital modulation of the 19 Hz SSVEPs differs from our previous study, which found relevant effects at a left temporal ROI. To ensure that the differences in the topographic distribution of the maximum SSVEP power between our studies are not due to some technical malfunction, we tested the original stimulation setup as used in our previous study (Senkowski, Saint-Amour, et al., 2008a) as well as the stimulation files which we used in the present study with a photodiode and found no deviations in visual stimulation frequencies.

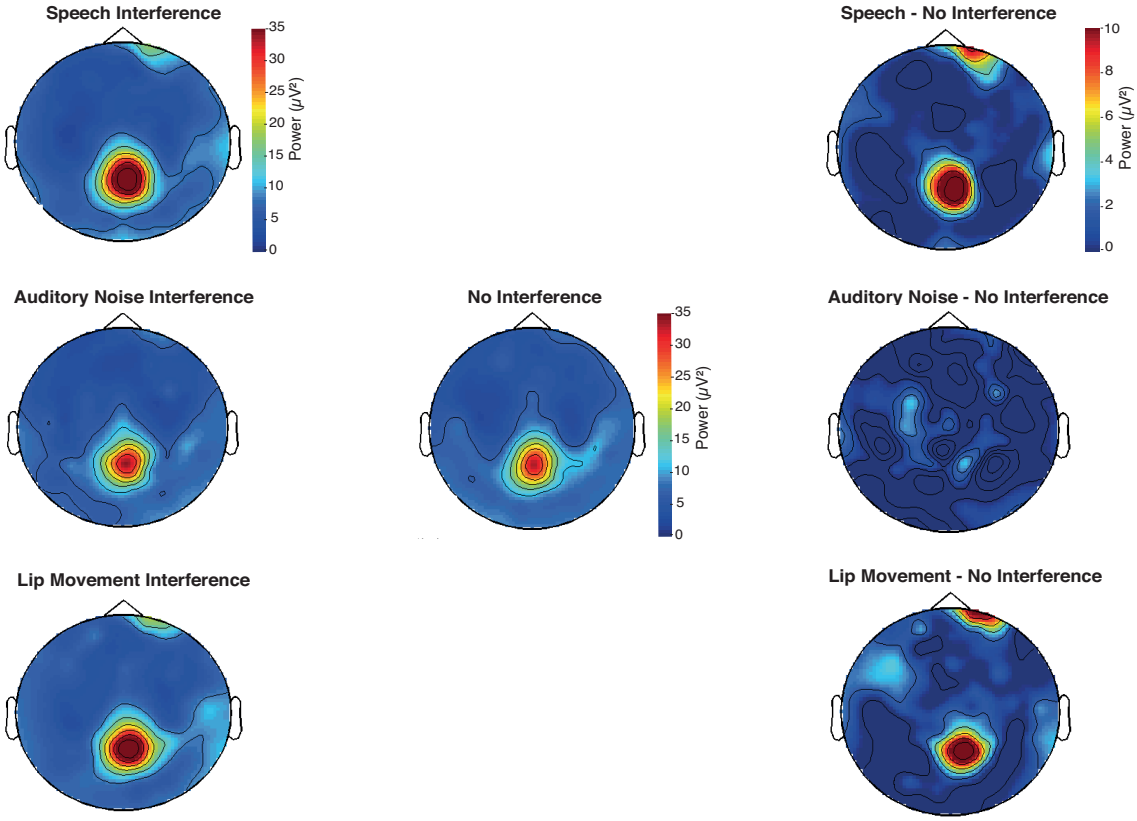


Abbildung 3.4-1. Topographies of flanking speaker's induced SSVEPs (19 Hz) for the time window of 230 to 550 ms after visual motion onset.

3.5. Discussion

In the present study two bimodal audiovisual interference conditions were examined: one consisted of natural audiovisual speech signals and the other of lip movements and auditory noise. In agreement with the above-described studies, this suggests that auditory speech stimuli serve as salient inputs in our environment, even if they are unattended.

Behavioral data

From the three distraction conditions (Figure 1), an interference effect in RT data was found particularly in the naturalistic audiovisual speech condition. Although we also found a significant difference in the HR between the Auditory Noise Interference Condition and the No Interference Condition, the most robust interference effects on RT, FA, and HR were found in the Speech Interference Condition (see Fig. 2a). Previous studies have shown that synchronously presented auditory and visual stimuli can serve as salient distractors, which can, for instance, bias temporal order judgements and simultaneity judgements of visual stimuli (van der Burg et al., 2008). Furthermore, it has been demonstrated that task irrelevant auditory signals can facilitate visual search (Van der Burg, Talsma, Olivers, Hickey, &

Theeuwes, 2011), in particular when the auditory signal is presented synchronously with the visual target (Van der Burg, Olivers, Bronkhorst, & Theeuwes, 2008) and when it is transient (Van der Burg, Cass, Olivers, Theeuwes, & Alais, 2010). Using a spatial cueing paradigm, another study showed a stronger attentional capture for bimodal audiovisual compared to unimodal visual distractors (Matusz & Eimer, 2011). All of these studies have used basic, semantically meaningless, auditory and visual stimuli. A study in which participants were asked to detect or localize a naturalistic face (out of up to four faces) that matches in its lip movements with a simultaneously presented auditory speech, showed a decrease in accuracy and an increase in search times with increasing set size in the localization task (Alsius and Soto Faraco, 2011). This suggests that the faces were processed in a serial fashion (Wolfe, 2003).

Alsius and Soto-Faraco (2011) conducted another experiment, in which the task was to detect or to localize an auditory stream (out of up to four auditory streams) matching the lip movements of a face. In this experiment, RTs and accuracy did not depend on set size in the detection task, supporting the assumption of parallel processing of the auditory streams. Together, these studies show that auditory speech represents a salient input and that auditory stimuli can strongly bias the processing of concurrently presented visual stimuli.

Taken together, our study demonstrates that irrelevant naturalistic audiovisual speech signals have a much stronger interference effect on RTs than visual lip movements alone or lip-movements that are accompanied by acoustic noise. This highlights the unique relevance of speech signals in our environment.

Interference effects in SSVEP

The finding of enhanced flanking speaker induced SSVEPs for naturalistic audiovisual speech stimuli fits with our previous study, which had only two experimental conditions (Audiovisual Speech Interference and No Interference). Importantly, the present observations extend our previous findings by demonstrating that the enhancement of flanking speaker induced SSVEP occurs primarily when the flanking speakers produced naturalistic audiovisual speech but this enhancement is weaker (in the Lip Movement Interference condition) or even vanished (in the Auditory Noise Interference condition) in the other distraction conditions. In contrast to our previous study, the present results allow a more specific interpretation of the interfering effects of naturalistic audiovisual speech signals,

since no interfering effects on RTs were found when auditory noise, which resembled the naturalistic syllables in its basic properties, like stimulus power, was presented. As shown in previous visual attention studies, SSVEP enhancement likely reflects an increased processing of the respective visual flicker stimuli and thus can serve as an electrophysiological measure for the allocation of visual attention (Martens, Trujillo-Barreto, & Gruber, 2011; Morgan, Hansen, & Hillyard, 1996; Müller, Malinowski, Gruber, & Hillyard, 2003). Therefore, we suggest that the enhanced flanking speaker's SSVEPs reflect a capture of visual attention by the non-relevant audiovisual speech signals.

Another interesting observation was the trend towards a significant enhancement of the flanking speaker's SSVEPs in the Lip Movement Interference condition. Since there were no behavioral interference effects of viewing lip movements alone, the enhanced SSVEPs in this condition do not appear to reflect a behaviorally relevant capture of visual attention. An explanation for the observed trend could be that the lip movements of the flanking speakers were not accompanied by an acoustic stimulus, which may have led to a crossmodal mismatch detection (Arnal, Wyart, & Giraud, 2011), that enhanced visual processing of the flanking speakers.

The absence of interference effects on the center speaker's induced SSVEPs is in line with our previous study. It may be that the capture of attention observed in the Speech Interference Condition involves a split of the attentional focus when the flanking speakers produced bimodal audiovisual syllables. Previous studies have shown that the attentional spotlight can be split (McMains & Somers, 2004; Müller et al., 2003). These studies have shown that visual input presented at multiple locations can be monitored in parallel by our attentional system. In the current study, however, such a possible split of visual attention did not substantially affect the processing of the visual input from the attended center speaker.

While the finding that the distraction effects are particularly reflected in flanking speakers SSVEP is in agreement with our previous study, there are also some differences in results. The main difference is that the effects on flanking speakers SSVEPs in our previous study were found at left lateral temporal electrode sites, whereas in the present study we observed modulations at occipital sites. The differences between our previous study and the present work may emerge from differences in experimental setups. The paradigm in the present study consisted of four experimental conditions (including three distraction conditions) compared to two conditions (with only one distraction condition) in our previous study. We cannot role out that these differences contributed to the differences in results (i.e. topography of effects). Notably, however, the effects in both studies were found particularly for flanking speaker

SSVEPs. Interpreting the results in terms of a capture of visual attention, the observation of effects at occipital electrodes in the present study fits well with previous studies showing attention related effects on SSVEPs at postero-occitipal scalp (e.g., Müller et al., 2003). Future studies are necessary to examine in further detail which factors have contributed to the differences in topographic findings between our previous and the present study.

We observed behavioral interference in the reaction times in particular when the flanking speakers produced naturalistic audiovisual speech. These effects were paralleled by enhanced 19 Hz SSVEP induced by the flanking speakers, indicative of a stimulus-driven capture of attention towards these interfering speakers. Thus, our study provides evidence that non-relevant audiovisual speech signals serve as highly salient distractors, which capture attention in a stimulus-driven fashion.

The present study demonstrates that processing of distracting audiovisual speech signals interferes with the recognition of attended audiovisual speech. Comparing speech recognition performance in three interference conditions with a no-interference control condition, we observed a decrease in response speed primarily when the distracting signals comprised of naturalistic audiovisual speech. This finding was paralleled by an enhancement of flanking speakers SSVEPs over the occipital lobe.

Conclusion

Our study demonstrates that non-relevant audiovisual speech stimuli serve as highly salient distractors in the processing of audiovisual speech. The enhanced attentional capture in the naturalistic audiovisual speech interference condition is reflected by a decrease in behavioral performance and an enhancement of flanking speaker induced SSVEPs. The interference effects in the other distraction conditions, comprising of visual lip movements alone and lip movements accompanied by auditory noise, were much weaker or even vanished, respectively. Taken together, our study provides evidence that non-relevant audiovisual speech in particular leads to stronger distraction in speech interference situations as compared to other sensory signals.

4. Experimental Section 2: „SSVEPs as a neurophysiological Correlate of Distractibility under audiovisual Speech interference Conditions in Schizophrenia (EEG)“

4.1. Introduction

Among the diverse positive, negative and cognitive symptoms of SZ, one striking characteristic of this disorder is the feeling of being overwhelmed by sensory information (Freedman, 1974). This becomes apparent in everyday situations, which are usually not characterized by enhanced attentional or cognitive demands for unaffected individuals. These situations can become stressful or even threatening for patients with SZ due to the subjectively overwhelming sensory input. Observations like these led several scientists and clinicians to propose that there may be a malfunction in filtering of sensory information, which might contribute to of the emergence of core symptoms in SZ, such as thought disorder, paranoid thinking, or delusions. Involved in filtering of sensory information are processes of attention and perception, which have been investigated, for instance, with qualitative interviews in patients with early SZ (McGhie & Chapman, 1961). Specifically, among different types of disturbances in attention, distractibility was revealed as a major factor to which many of the patients` statements were related. Furthermore, for the domain of disorders of perception, a disturbance in the perception of speech patterns was discussed. One comment of a participant in the study by McGhie & Chapman (1961) illustrates the subjective view on these disturbances as follows: “(Patient 18) - If there are three or four people talking at one time I can`t take it in. I would not be able to hear what they were saying properly and I would get the one mixed up with the other. To me it`s just like a babble – a noise that goes right through me.” (McGhie & Chapman, 1961, pp. 105–106).

Experimental research on distractibility in speech recognition tasks in SZ has revealed deficits in multisensory stimulation conditions (Ross et al., 2007). Sensitivity to distracting noise has also been investigated in patients with SZ using an auditory attention task and P50 gating ratios (Smucny et al., 2013). The results of this study indicate a stronger distraction effect of noise on reaction times (RTs) and higher P50 auditory gating ratios in patients than in non-clinical control participants. Furthermore, there was a positive correlation between the magnitude of noise-induced RT increase and the P50 gating ratio. Neural abnormalities in language processing have been demonstrated in SZ in an MEG study in which evoked oscillatory responses to speech and non-speech sounds were investigated (S. Hirano et al., 2008b). Results revealed reduced evoked oscillatory power to speech sounds between 0-50

ms and larger power in the time window 100-150 ms in the left hemisphere in the patient group. Moreover, in patients, a delay in the peak latencies of the evoked oscillatory power and phase locking to speech sounds was found in the left hemisphere. A similar effect was observed for nonspeech sounds in the right hemisphere. Taken together, these findings indicate deviations from non-clinical subjects regarding hemispheric lateralization as well as impaired speech identification mechanisms.

The present EEG study aims at investigating if patients with SZ show enhanced behavioural distractibility and impaired electrophysiological brain signals as compared to non-clinical control subjects in an audiovisual speech interference paradigm using naturalistic speech stimuli. Beyond the question if patients with SZ show enhanced distractibility in behavioural performance, an additional goal of my study was to investigate the eligibility of Steady-State Visual Evoked Potentials (SSVEP) as a neurophysiological marker of distractibility in SZ. SSVEPs are a measure of neural entrainment to a repetitive sensory stimulus and appear in the recorded EEG as stimulus-locked neural activity reflecting the frequency of the repetitive sensory stimulus (C S Herrmann, 2001b). A particular strength of SSVEP is that they allow to investigate the continuous deployment of visual attention.

In the original version of the paradigm that was used in the present study participants were instructed to detect an occasional audiovisual target syllable by a speaker (i.e. a speaking face), who was presented centrally and surrounded by two flanking speakers (Senkowski, Saint-Amour, et al., 2008a). In *No Interference* trials, a syllable was produced by the relevant central speaker only. In *Speech Interference trials*, audiovisual syllables were produced by three speakers simultaneously. Steady-state visual evoked potentials (SSVEP) in response to the flickering faces were recorded as a real-time index of the deployment of visual attention. The results obtained by Senkowski et al. (2008) indicated a capture of visual attention towards the task in interference vs no interference trails towards the task-irrelevant flanking speakers in interference vs. no interference trials. In my recent EEG study (Krause, Schneider, Engel, & Senkowski, 2012) which I introduced in the previous chapter, I used a modified version of the paradigm which included two additional distraction conditions. The main question of this recent study was whether the interference effect is specific for the processing of naturalistic audiovisual speech or whether similar effects would occur when the flanking speakers produce other distracting stimuli, like moving their lips without a sound or when they produce noise instead of syllables. Therefore, I added an *Auditory Noise Interference Condition* and a *Lip Movement Interference Condition* in my recent study. The results of my study showed that non-relevant audiovisual natural speech affected behavioural performance

as well as flanking speaker induced SSVEPs significantly stronger than visual lip movements without sounds and visual lip movements that were accompanied by auditory noise. These findings point to an enhanced attentional capture of naturalistic speech as compared to audiovisual non-speech or visual lip movement stimuli in speech interference situations.

To adapt the experimental paradigm to the requirements of a study including patients with SZ, the experimental runtime had to be shortened. Furthermore, reports of healthy participants in my previous study indicated that the experiment was very demanding. For this reason, in order to make the experiment shorter and less demanding for the patient study, one experimental condition was removed. To decide about the conditions that should be included, the findings of my recent (Krause et al., 2012) study as well as relevant findings on differences between patients with SZ and non-clinical control participants in cognitive tasks (see chapter 2) were taken into consideration. Since in earlier studies including healthy participants with similar paradigms significant condition differences were found for 19 Hz SSVEP power in response to flanking speakers producing naturalistic audiovisual speech as compared to a no interference condition (Krause et al., 2012; Senkowski, Saint-Amour, et al., 2008), the No Interference Condition as well as the naturalistic Audiovisual Speech Interference condition were also included in the patient study. From the two additional interference conditions, which were included in my previous study (i.e., the Lip Movement Interference Condition and the Auditory Noise Interference Condition), one was chosen as a second interference condition for the patient study. Empirical findings indicate that patients with SZ have deficits in their ability to benefit from visual information in audiovisual speech situations when they are asked to recognize spoken words embedded in noise as compared to healthy subjects (Ross et al., 2007): in this study, audiovisual and unisensory auditory words were presented with seven different levels of pink noise imposed on the auditory inputs. Noise diminished the performance for patients and healthy control subjects, but in the patient group, a specific deficit in multisensory speech processing was found. Interestingly, this specific deficit which was strongest at an 'intermediate' signal-to-noise ratio for which in healthy subjects the gain of audiovisual stimulation was maximal (Ross et al., 2007).

In contrast to this difference between patients with SZ and non-clinical control subjects in auditory noise conditions, findings on lip reading performance in patients with SZ are inconclusive with some observations pointing to differences (de Gelder et al., 2003), whereas others failed to show differences between the groups (Myslobodsky et al., 1992). Therefore, the Audiovisual Noise Interference Condition and not the Lip Movement Interference Condition was selected as the second distraction condition in the present patient study.

4.2. Hypotheses

Motivated by the findings reported above, we expected to find a stronger behavioural distractibility in patients with SZ. This should be expressed in lower hit rates (HRs) and longer reaction times (RTs) in the speech interference condition in patients as compared to healthy control subjects. Furthermore, we predicted that the distractibility effect in the auditory noise interference condition is larger in patients than in healthy control subjects. In addition, since the strength of the distractibility effect seems to be reflected in the power of the SSVEP, we expected to find impairments in SSVEP power that reflect the behavioural performance deficits in the patient compared to the control group.

4.3. Methods

Participants

Eighteen patients with SZ (as assessed by SCID) and 18 healthy control subjects, matched for age, gender and education participated in the study. One patient with SZ was excluded from the analysis because of Cannabis use, 4 patients were excluded from the analysis because their behavioural performance differed more than 2 standard deviations from the mean. Two additional patients were excluded from the analysis because their diagnoses changed during the course of the study, so the inclusion criteria were not fulfilled anymore. Eight of the remaining 9 patients had a diagnosis of paranoid SZ and one patient had a diagnosis of disorganized SZ.

The remaining patients and nine non-clinical control subjects had normal hearing, as assessed by a hearing test in which 30 dB sinusoidal tones of varying frequencies had to be detected. The mean age of patients with SZ (36.44 years, SD 13.99) did not differ significantly from the mean age of non-clinical control subjects (35.56 years, SD 12.04). Participants had normal or corrected-to-normal vision, as ensured by the Landolt test of visual acuity (visus ≥ 0.9). The Institutional Review Board of the Medical Association of Hamburg approved the experimental procedures, and each subject provided written informed consent and was paid for participation.

Patients (N=9)		Control Subjects (N=9)		
	Mean	Std	Mean	Std
Age	36.44	13.99	35.56	12.04
Sex (male)	6		6	
Handedness (right)	9		9	
CPZ equivalents	475.00	346.05		
PANSS (total)	51.85	16.96		

Table 2. Age, Sex, and Handedness for patients with SZ and non-clinical control subjects, and Chlorpromazine equivalents (for 7 patients) and the total score of the Positive and Negative Syndrome Scale (PANSS) for patients with SZ.

Procedure and Stimuli

A video stream of three stimulation conditions was presented continuously (Fig. 4.3.1), with two of the conditions being identical to those used in a previous study (Senkowski, Saint-Amour, Gruber, & Foxe, 2008). In this previous study a No Interference control condition, in which only the center speaker produced a syllable, and a 'Speech Interference' condition, in which all three speakers produced syllables was presented (a short clip of the experiment from a previous study is provided at: http://www.sciencedirect.com/science/article/pii/S1053811908007933). One experimental condition was added to the original setup which consists of a No Interference and Speech Interference conditon (Senkowski, Saint-Amour, et al., 2008) in the present study to examine not only the Speech Interference Condition, but different kinds of distraction: the Auditory Noise Interference Condition, which comprises of the center speaker which produces speech syllables as in all the other distraction conditions, as well as in the No Interference Condition and the to-be-ignored flanking speakers which produced acoustic non-speech noise instead of syllables. These non-speech noise samples were derived from the original syllables of the Speech Interference Condition by phase-scrambling the auditory syllables, thereby maintaining basic properties like stimulus power. Thus, the paradigm comprised three conditions: No Interference, Speech Interference and Auditory Noise Interference. The center speaker produced one of the syllables /ta/, /da/, /ga/, or /ba/ in all conditions, whereas in the No Interference Condition, the flanking speakers did not produce any auditory or visual speech. In the Speech Interference Condition, the flanking speakers produced the syllables /ta/, /da/, or /ga/, and in the 'Auditory Noise Interference' condition, the flanking speakers produced auditory noise. Syllables as well as conditions were presented in random order.

The task required the detection of the occasionally produced target syllable /ba/ by the center speaker to which participants were required to respond with a button press of their right index finger. Participants were instructed to focus their attention to the center speaker and to ignore the signals from the flanking speakers. Furthermore, The target syllable occurred in 20% of all trials. The three speakers never produced the same syllable in a trial and syllable combinations that could evoke the McGurk illusion (McGurk & MacDonald, 1976), like the combination /ba/ and /ga/ were excluded.

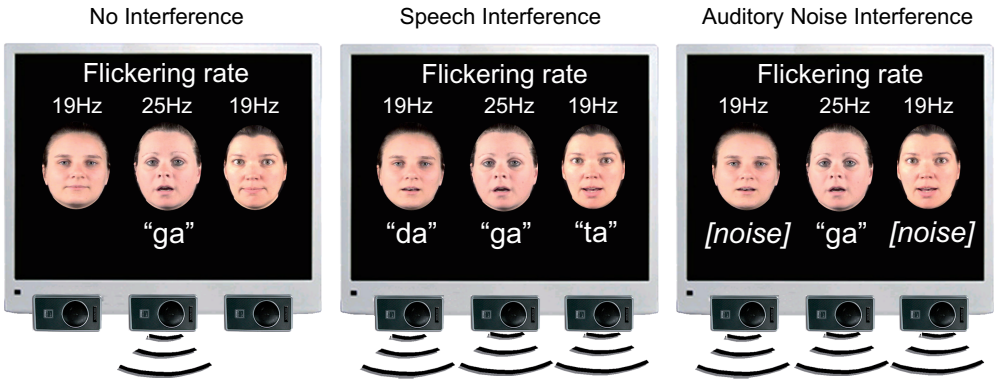


Figure 4.3-1. Stimulus setup. Stimuli consist of three horizontally aligned speakers on a black background. In all experimental conditions, the center face is visually presented in an on-off fashion so that a 25 Hz flicker was elicited. The flanking speakers were presented with a 19 Hz on-off flicker. The center speaker produced natural auditory and visible syllables (/ta/, /da/, /ga/, /ba/) in the No Interference, Speech Interference and Auditory Noise Interference Condition. The subject`s task was to detect the syllable /ba/ by the center speaker. In the No Interference condition, the flanking speakers produced neither visual lip movements nor speech sounds, whereas in the Speech Interference condition, they produced audiovisual syllables (/ta/, /da/ and /ga/) simultaneously with the center speaker. The Auditory Noise Interference condition consisted of phase-scrambled versions of the original syllables /ta/, /da/ and /ga/ produced by the flanking speakers.

On average 55 targets and 225 non-target stimuli were presented for each condition. One trial consisted of 120 visual frames. Each frame was presented for 6.67 ms each, resulting in a total trial duration of 792 ms. Two fixed cycles of 24 frames were added per trial. Moreover, a variable number of 1-5 cycles (average: 3 cycles) was added, resulting in a total average trial duration of 1592 ms. During the inter-trial interval the faces of the three speakers were presented on the screen without producing any lip movements or speech sounds, but the 19 Hz flicker of the flanking speakers and the 25 Hz flicker of the center speaker continued. An additional number of 360 (about 30 % of all trials) 'omitted trial' periods (Busse & Woldorff, 2003) were randomly inserted into the continuous stream of stimuli, further reducing the predictability of the experimental stimuli. During omitted trial periods, the faces of the three speakers were presented for a time interval that was identical to the interval of regular

experimental events (i.e., 792 ms) but without any lip movements or speech sounds. Each participant underwent 10 experimental blocks with 120 trials each.

Recordings of syllables from the three speakers were obtained at frame rates of 30/s. Each syllable consisted of 20 frames of 33 ms duration, which results in a total duration of 660 ms for each syllable. The visual angle of the speakers subtended 7° between adjacent speakers (from mouth to mouth) and the width of the speakers' faces subtended an angle of 4.8° each. The characters of the flanking speakers switched their location (i.e. left or right of the center speaker) after every block, while the center speaker character remained the same throughout the experiment. The monitor was set to a refresh rate of 150 Hz, i.e., the refresh rate duration for one frame was 6.67 ms. To induce steady-state visual evoked potentials (SSVEPs), the continuous stream of pictures was dissected in an on-off fashion, i.e., pictures of the continuous stream ('on') were presented alternately with blank screens ('off'). Pictures of the continuous stream and blank frames alternated every 20 ms. Thus, the flicker frequency (i.e. on-off cycle) was 25 Hz for the center speaker. For the two flanking speakers, the on-off periods alternated every 26.6 ms simultaneously for both speakers, corresponding to a flicker frequency of about 19 Hz. In the EEG the time-frequency transformed activity of a sustained visual on-off flicker is reflected in event-related activity that corresponds to the presented flicker frequency (C S Herrmann, 2001b). Both the 19 Hz flicker and the 25 Hz flicker were presented continuously and all trials started with an 'on' period. The average stimulus duration of the acoustic syllables was 295 ms and the onset of these syllables followed the onset of visual lip movements on average by 230 ms. To eliminate overlapping event-related responses to the sounds, a relative stimulus onset jitter of 110 ms (more than two times the duration of a 19 Hz and a 25 Hz cycle) was used by adding or subtracting a random time interval between ±55 ms to the real acoustic sound onset in each trial (Senkowski, Talsma, Grigutsch, Herrmann, & Woldorff, 2007; Woldorff, 1993). This jitter prevented overlapping event-related 19 and 25 Hz responses to the acoustic inputs. A spline curve FFT filter between 400 to 4000 Hz was applied to all syllables to align the voice characteristics between the three speakers.

Data acquisition

The EEG was recorded from 124 scalp sites using an active electrode system (EASYCAP, Herrsching, Germany). In addition, the electrooculogram was recorded by two electrodes. One of these electrodes was placed below the eye and the other one was placed at the lateral bridge of the nose. The nose tip was used as reference during recording and data were off-line

re-referenced to average reference. Data were digitized at a sampling rate of 1000 Hz using BrainAmp amplifiers (BrainProducts, Munich, Germany), filtered from 0.3 to 120 Hz and downsampled to 250 Hz for the off-line analysis. Epochs were cut around the visual motion onset (0 indicates the first frame of the visible movement) from -1000 ms before to 1200 ms after visual motion onset. Trials containing artifacts in EEG data resulting from eyeblinks, horizontal eye movements, or muscle activity were removed from the further analysis. Noisy channels were linearly interpolated. Finally, an automatic threshold was applied, excluding all trials in which the EEG amplitude exceeded 100 μV.

Data Analysis

Reaction times (RTs) to target stimuli were calculated by averaging all trials in which subjects responded between 230 and 1000 ms after visual motion onset and in which the RT did not exceed 2 standard deviations from the mean RT within each participant and condition. For the statistical analysis of RTs, hit rate (HR), and false alarms (FA) an ANOVA or Friedman test (if the assumption of Gaussianity was violated) with the factors experimental condition (No Interference, Speech Interference, Auditory Noise Interference) and group (patient with SZ, non-clinical control subject) was calculated. A Kolmogorov-Smirnov test was computed to test for Gaussianity of the RT, HR, and FA distributions. Moreover, three planned contrasts were computed: Speech Interference vs. No Interference; Auditory Noise Interference vs. No Interference; and Lip Movement Interference vs. No Interference.

EEG data were analyzed using MATLAB (Version 7.11.0, R2010b), EEGLAB 5.03 (http://www.sccn.ucsd.edu/eeglab) and the FIELDTRIP toolbox (Oostenveld, Fries, Maris, & Schoffelen, 2011). For the analysis of SSVEPs, event-related activity was calculated by averaging the epochs of each condition. For the averaged activity, time-frequency (TF) analyses were calculated using wavelet transformation with Morlet wavelets spanning a range of 10 to 30 Hz with a length of 12 cycles. The TF analysis was computed in 0.25 Hz steps. In agreement with a previous study (Senkowski, Saint-Amour, et al., 2008b). SSVEPs were analyzed for three predefined regions of interest (ROIs): an occipital ROI, comprising of 7 electrodes that were located at midline-occipital scalp, and two symmetric bilateral ROIs that were located at lateral temporal scalp, comprising of 6 electrodes each (see 3.3-1, p. 45). In line with the observed SSVEP response pattern, the analysis was done for the time window of 230 ms to 550 ms after onset of the visual motion onset. To investigate how visual inputs of the center speaker and the flanking speakers were processed in the different experimental conditions, wavelet transformed data were analyzed for those frequencies that corresponded

to the visual stimulation frequencies of the speakers. The length of the wavelet was 480 ms for the analysis of 25 Hz activity and 632 ms for the analysis of 19 Hz activity, with a wavelet length of 12 cycles, respectively. Repeated measures ANOVAs with the within-subject factors Condition (No Interference, Speech Interference, Auditory Noise Interference, and Lip Movement Interference) and ROI (left temporal, right temporal, occipital) were conducted. Furthermore, planned contrasts between each of the three interference conditions (Speech Interference, Auditory Noise Interference, Lip Movement Interference) and the no-interference condition were computed. In case of non-sphericity, as tested by Mauchly`s sphericity test, the degrees of freedom were adjusted in the ANOVAs.

4.4. Results

Behavioral Data

An ANOVA for hit rate with the factors Group (patient with SZ, non-clinical control subject) and Condition (No Interference, Speech Interference, Auditory Noise Interference) yielded a significant effect of the factor Condition ($F_{(2,32)}$= 32.358, $p < .001$), with significantly larger hit rates in the No Interference vs. Speech Interference Condition (< .001), with a mean HR of 98.51 for the non-clinical control subjects and 90.66 for the patients with SZ in the No Interference Condition and mean RTs of 62.27 for the non-clinical control subjects and 41.70 for the patients with SZ in the Speech Interference Condition. Furthermore, the Speech Interference vs. Auditory Noise Interference differed significantly ($p < .001$). For the Noise Interference Condition, the non-clinical control subject´s mean HR was 88.02 and for the patients with SZ 82.71.

There was no significant effect for the factor group and no interaction with the factor group. Thus, there were no substantial differences in the hit rate between patients and control subjects.

For the analysis of reaction times (RT), a significant effect of the factor Condition was found ($F_{(1,435,\ 22,958)}$ = 5.084, $p = .012$). Follow-up tests revealed shorter reaction times for the No Interference (mean = 728 in non-clinical control subjects and 778 in patients with SZ) vs. Speech Interference condition (mean = 772 for non-clinical control subjects and 811 for patients with SZ) ($p = .036$). The mean RTs in the Noise Interference Condition were 746 for the non-clinical control subjects and 797 for the patients with SZ.

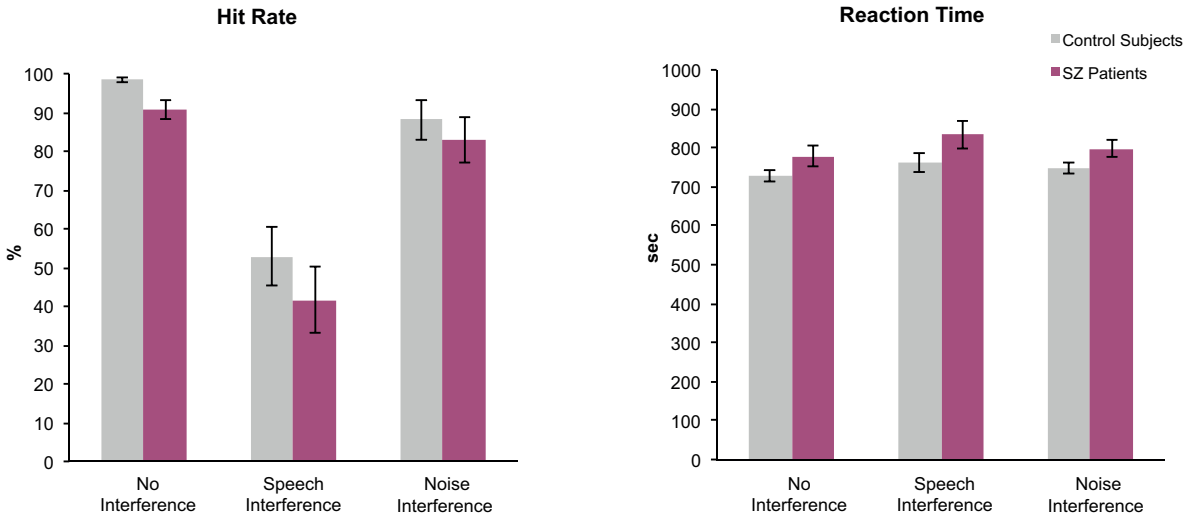


Figure 4.4-1. Behavioral performance. Reaction times (RTs) and hit rates (HRs) for the No Interference control condition as well as for the Speech Interference and Noise Interference conditions in control subjects (grey) and patients with SZ (magenta).

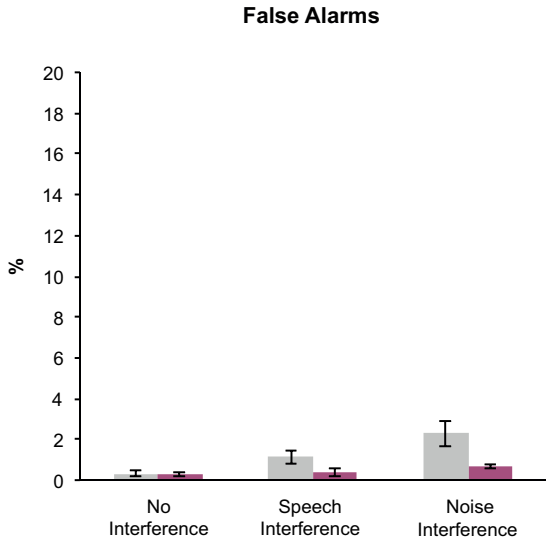


Figure 4.4-2. False Alarm rate for No Interference, Speech Interference and Noise Interference condition in Patients and non-clinical control subjects.

The repeated measures ANOVA for the false alarm rate revealed a significant effect of the factor Condition ($F_{(2,32)}$=4.758; p = .016). Follow-up tests revealed a significantly higher false alarm rate in the Auditory Noise Interference compared to the No Interference condition (p = .050). No significant effects were observed for the factor Group.

Steady-state visual evoked potentials

In the Time-frequency representations of event-related SSVEP of the occipital ROI, a band of enhanced spectral activity at around 19 Hz was found for the No Interference, Speech Interference and Auditory Noise Interference Condition in patients with SZ and non-clinical control subjects (Figure 4.4-3 for patients and Figure 4.4-4 for the non-clinical control subjects). In the non-clinical control subjects, a second band of enhanced spectral activity with a smaller amplitude enhancement was visible at 25 Hz in the No Interference, Speech Interference and Auditory Noise Interference Condition. The ranges of these enhancements correspond to the frequencies of stimulation, i.e., 19 Hz for the distracting flanking speakers and 25 Hz for the to-be-attended center speaker, and reflect the expected neural entrainment towards the stimulation frequencies.

Source		Type III Sum of Squares	Df	Mean Square	F	Sig.
Condition	Sphericity Assumed	26.520	2	13.260	.750	.480
	Greenhouse-Geisser	26.520	1.595	16.623	.750	.454
	Huynh-Feldt	26.520	1.855	14.299	.750	.472
	Lower-bound	26.520	1.000	26.520	.750	.399
Condition * Group	Sphericity Assumed	34.257	2	17.128	.969	.390
	Greenhouse-Geisser	34.257	1.595	21.473	.969	.375
	Huynh-Feldt	34.257	1.855	18.470	.969	.385
	Lower-bound	34.257	1.000	34.257	.969	.340
Error(Condition)	Sphericity Assumed	565.597	32	17.675		
	Greenhouse-Geisser	565.597	25.526	22.158		
	Huynh-Feldt	565.597	29.675	19.060		
	Lower-bound	565.597	16.000	35.350		

Table 3. Results of the Repeated Measures ANOVA for the 19 Hz SSVEP Power as dependent variable and Condition as a within-subject factor and Group as a between-subjects factor.

The repeated measures ANOVA, with 19 Hz (i.e., the stimulation frequency of the flanking speakers) SSVEPs between 230-550 ms after visual motion onset as dependent measure and the factors Group as between-subject factor and Condition as within-subject factor, revealed no significant main effects or interactions (Table 2). For this reason, no follow-up tests were calculated. In a similar vein, the analysis of 25 Hz SSVEPs did also not reveal any significant main effects or interactions.

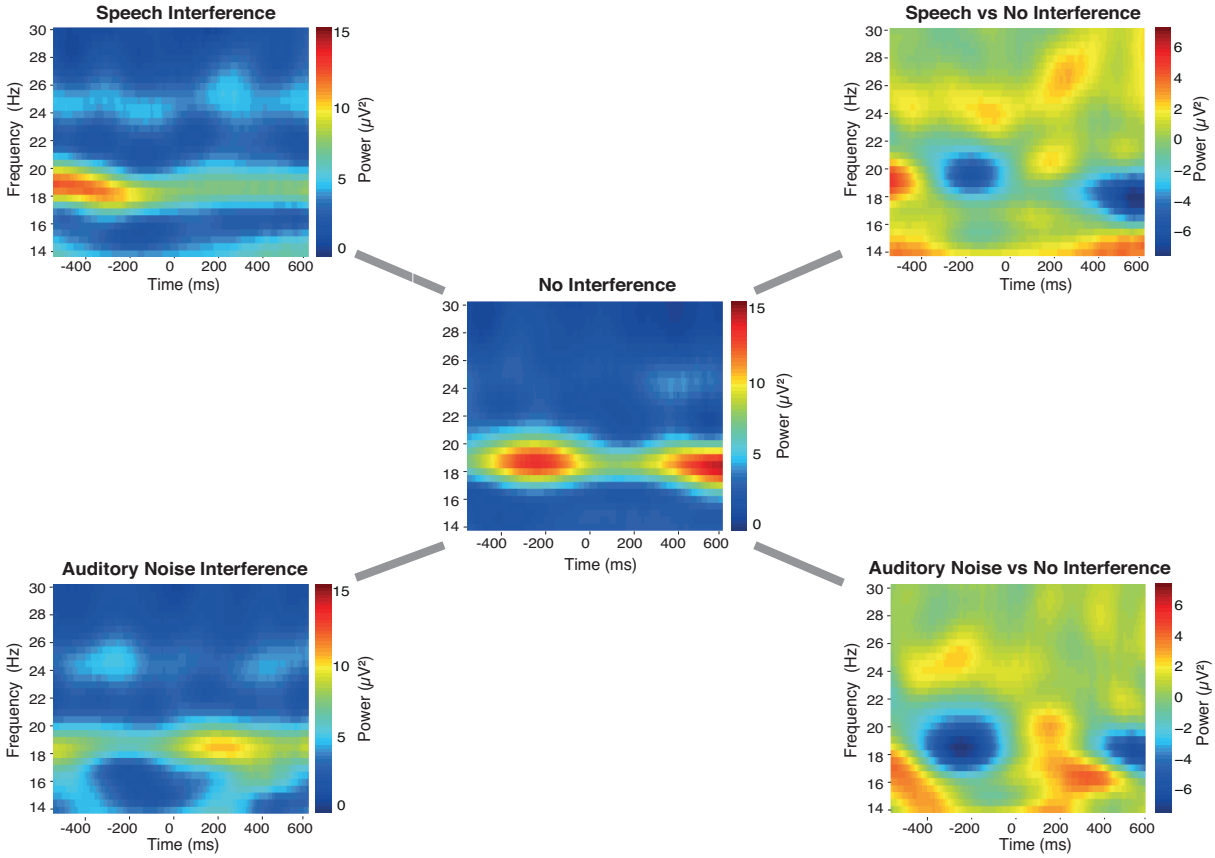


Figure 4.4-3. Time-frequency-plots of SSVEPs for the two Interference conditions (left panel), the No Interference condition (middle panel) as well as for the differences between Interference and No Interference conditions (right panel) for the occipital ROI for the patient sample. For the statistical analysis the same time-frequency window as in the first study was used (230-550 ms and 19 Hz).

4.1. Discussion

The goal of the present study was to investigate if patients with SZ show differences from non-clinical control participants in task performance in an audiovisual speech interference task as well as in attention-related modulations of SSVEP power in the EEG. The paradigm consisted of a No Interference Condition and two bimodal audiovisual interference conditions: the Speech Interference Condition, which comprised natural audiovisual speech signals and the Auditory Noise Interference Condition, with visual lip movements combined with auditory noise. Previous work has shown a stronger interference effect, as indicated by an enhanced 19 Hz SSVEP power as well as diminished task performance for the Speech Interference Condition as compared to other interference conditions in similar paradigms (see previous chapter and (Senkowski, Saint-Amour, et al., 2008). In the present study, the behavioural results are widely in line with our previous findings. However, no significant differences between conditions were found in the SSVEP evoked power and no significant differences were found between the patient group and the healthy control group.

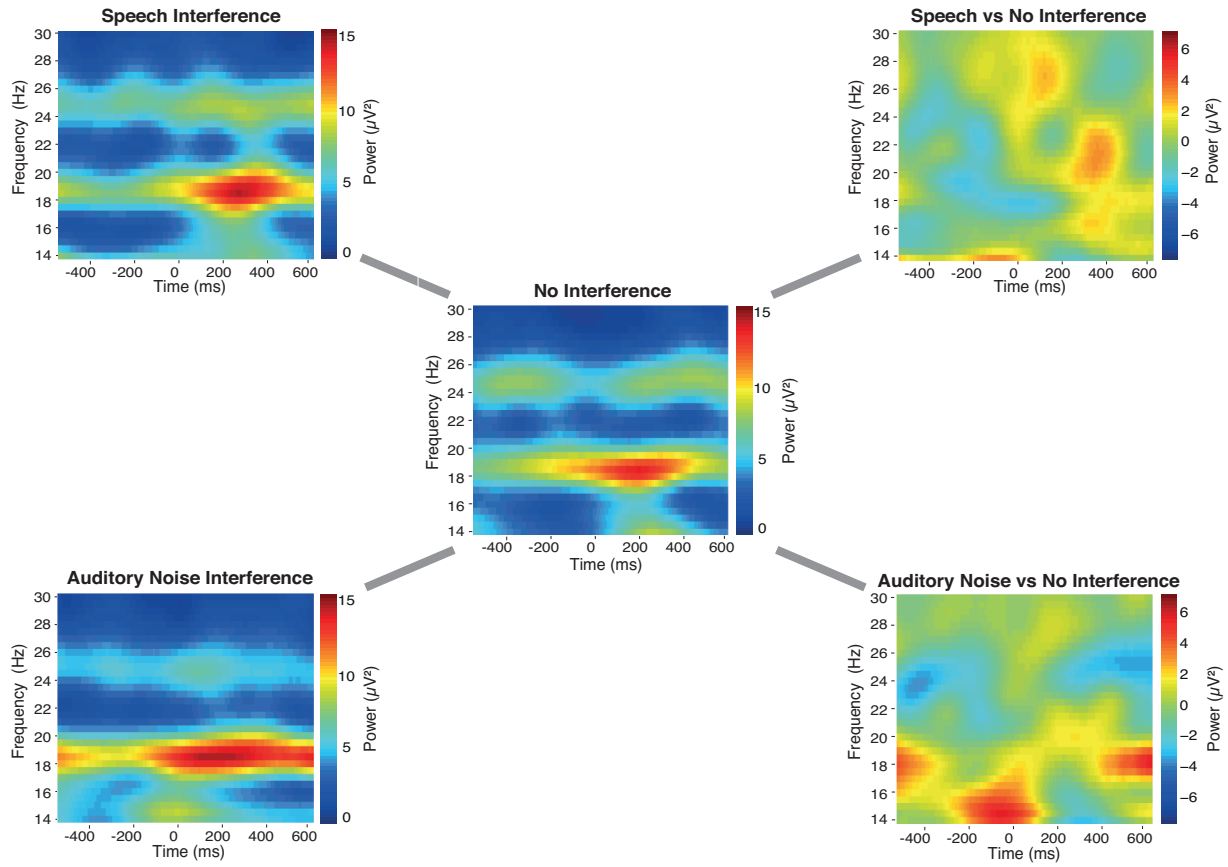


Figure 4.1-1. Time-frequency-plots of SSVEPs for the two Interference conditions (left panel), the No Interference condition (middle panel) as well as for the differences between Interference and No Interference conditions (right panel) for the occipital ROI for the control subject sample. For the statistical analysis the same time-frequency window as in the first study was used (230-550 ms and 19 Hz).

Behavioral data

For the hit rate, a significant condition effect was found with higher hit rates in the No Interference as compared to the Speech Interference condition as well as significantly higher hit rates in the Auditory Noise Interference Condition as compared to the Speech Interference Condition. In all conditions, hit rates in the patient group were numerically lower as compared to non-clinical control group, but these differences were statistically not significant. The reaction times also differed significantly between experimental conditions. In the No Interference condition reaction times were significantly shorter as compared to the Speech Interference condition. Again, no differences in RTs were found between the patient and the control group. Significant differences were also found between the experimental conditions in the FA rates. The false alarm rate was higher in the Auditory Noise Interference Condition than in the No Interference Condition. However, there were no significant differences in the false alarm rates between patients and control subjects.

The behavioural results of the present study differ substantially from those of the previous study (Krause et al., 2012), especially regarding the control subjects` RTs for those conditions which have been used in both studies. The mean RT of 673 ms in the No Interference Condition in the previous study is much lower than the mean of 728 ms for the non-clinical control subjects in the present study. Similarly, the mean RTs for the Speech Interference Condition differ: 731 ms in the previous study vs. 773 ms for the non-clinical control participants in the present study. This comparison was not tested statistically because participants of these two samples took part in different studies, but taking into consideration these differences in mean RTs reveals an interesting aspect about the present study. Specifically, healthy participants in the previous study and matched non-clinical control subjects in the present study, which are expected to perform equally well, seem to strongly differ a in their behavioural performance. By contrast, patients with SZ and their matched non-clinical control subjects in the present study did not differ significantly. The fact that for the behavioural data of the present study, no significant group differences were found, as well as the substantial difference between the behavioural performance of healthy subjects of the present and the previous study point to larger similarities between patients with SZ and their non-clinical matched controls than between the two samples of healthy subjects when comparing the previous (Krause et al., 2012) and the present studies. Taking this into account, it can not be ruled out that a close matching regarding several important variables (such as age, education, gender) as it was done for the present study may account for more variance than the group separation patient with SZ vs non-clinical control subject.

Interference effects in SSVEP

No statistically significant group or condition effect was found for the 19 Hz SSVEP power. One reason for the fact that the results in the SSVEPs did not replicate our previous study is probably a large variance within each of the groups regarding several variables, for instance the age range. When independent sample ANOVAs are calculated, significant differences emerge when the variance between groups is large but the difference within groups is small. This was probably not the case in the present study, since for example age and education show much larger variance than comparable studies with healthy subjects, such as our previous studies with similar experimental setups (Krause et al., 2012; Senkowski, Saint-Amour, et al., 2008). It is likely that the low sample size, which was probably not sufficient for the investigation of EEG signals with a considerable variation across subjects regarding the absolute values contributed to the lack of statistically significant effects. Within the

sample of SZ patients, a large heterogeneity regarding duration of illness as well as type of diagnosis may have also contributed to the large variance in SSVEPs across subjects.

Another aspect is related to the type of stimulation. The experimental setup itself was very demanding and the visual flicker was perceived by many participants as being very tiring for the eyes. A long EEG recording session with a difficult task in combination with the flickering visual stimuli might have been very demanding for some of the subjects in the present study. Participants in the previous study (Krause et al., 2012) were mostly medical students. The mean age of this sample of healthy subjects was 22.92 years, whereas in the present study, the mean age for patients and matched controls was about 36 years.

An aspect that holds true for the previous as well as for the present study is the question if participants were consistently following the instruction to keep the visual focus on the center speaker. In the present as well as related previous studies, the eye-position was not recorded, e.g., using an eye-tracker. For this reason, it cannot be excluded that participants failed to focus on the center speaker continuously. It might be that subjects who suffered from the flickering stimulation still managed to perform the behavioural task, but were not able to keep the visual focus on the strongly flickering stimuli. This could explain or contribute to the fact that the findings of the present study show significant condition effects in the behavioural data but non-significant SSVEP findings.

Finally, the general quality of the data should be considered in the interpretation of the results. The experimental runtime was shortened to make it more appropriate for a patient study and to decrease the risk of patients and non-clinical control subjects to cancel the participation before the end of the experiment. Not only was one experimental condition removed as compared to my previous study (Krause et al., 2012), but also for each of the remaining conditions, fewer trials were presented. Furthermore, as compared to the previous study, more eye-blinks and muscle artifacts were present in the data, which also diminished the number of remaining trials. Therefore, the averages were calculated on fewer trials, which has probably led to a higher noise level and is probably at the expense of the quality of the averaged SSVEPs.

Conclusion

The behavioural data in the present study suggest that natural audiovisual speech exerts stronger interference on speech recognition as compared to auditory noise alone. This finding supports the results of my previous study, which yielded a similarly high task difficulty for the Speech Interference Condition as compared to the other interference conditions. The

electrophysiological data of the present study are challenging to interpret, since no statistic differences were found between groups and conditions. The lack of significant differences between groups and conditions in the SSVEPs points to possible pitfalls in experiments with SZ patients: the appropriateness of the paradigm for participants with a partly diminished attentional capacity should have been explored before the electrophysiological data recordings and an appropriate sample size would have to be achieved to deal with enhanced variance within the groups. However, while the interpretation of EEG data remains difficult, the observation that patients did not substantially differ from healthy controls in their behavioural performance could indicate that patients with SZ do not have a severe deficit in multisensory speech interference, at least in the presented experimental setup. Whether this assumption is correct needs to be investigated in future studies.

5. Experimental Section 3: „Neural Oscillations during visual-to-auditory Semantic Priming in Schizophrenia (MEG)

5.1. Introduction

Hallucinations, delusions and thought disorders are core features of schizophrenia. Patients with SZ frequently report to suffer from symptoms belonging to the group of formal thought disorders (FTD), which comprises frequent derailment, incoherence of speech, disorganized speech or loosening of associations and tangentiality. Pronounced disorders of associations were regarded as a criterion for the diagnosis already early in the history of schizophrenia research (Bleuler, 1911). According to the DSM-IV, "… Disorganized thinking ("formal thought disorder", "loosening of associations") has been argued by some (Bleuler, in particular) to be the single most important feature of schizophrenia … The person may "slip off the track" from one topic to another ("derailment" or "loose associations"); answers to questions may be obliquely related or completely unrelated ("tangentiality")." (*Diagnostic and statistical manual of mental disorders*, 1994, p. 276). The symptoms of FTD are of particular interest for several reasons: on the one hand, patients with schizophrenia often report thought disorder to be the most devastating of all the symptoms of the disease, and furthermore, they affect almost every domain of everyday life, from social and personal to occupational contexts, affecting relationships, communication with others, and self-esteem in a derogatory way.

An influential theory addressing FTD is the spreading activation hypothesis of thought disorder (Maher, Manschreck, Hoover, & Weisstein, 1987) which states that an abnormal increase in the spread of activation in semantic memory could lead to more flexible or loose associations. For experimental investigations of the spread of activation in semantic memory, semantic priming paradigms are suitable. Thereby, loosening of associations can be quantified via reaction times to semantically related versus unrelated items. Semantic priming has been investigated extensively in patients with schizophrenia, most studies applying one of two frequently used experimental paradigms to assess semantic priming: lexical decision (LD) or word pronunciation (WP) tasks. In LD tasks, subjects are asked to decide whether a probe string is a real word or not, whereas in WP tasks the subjects are asked to read the second word. Taken together, results of priming studies in schizophrenia are inconclusive as reported by a meta-analysis (Minzenberg, Ober, & Vinogradov, 2002): normal, increased and reduced priming effects in patients with SZ as compared to healthy controls have been found across studies.

Enhanced semantic priming was found in patients with high FTD scores compared to patients with low FTD scores and to healthy control participants in a masked priming paradigm requiring LDs on target words (Kiefer, Martens, Weisbrod, Hermle, & Spitzer, 2009). In this study, FTD was assessed with the item "conceptual disorganization" of the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987) and a median split of scores for this item was used to divide the patients with SZ into the FTD and non FTD groups. Enhanced indirect semantic priming in patients with SZ with high FTD scores as compared to non FTD patients and healthy controls was also found using a WP task with a paradigm that consisted of a neutral as well as an unrelated condition, thereby showing that the enhancement in priming did not depend on the baseline condition (Moritz, Woodward, Küppers, Lausen, & Schickel, 2003). However, in some studies the priming effect did not differ between patients with SZ and healthy controls (Froud, Titone, Marantz, & Levy, 2010) or no priming effect was found in patients with SZ (Sass et al., 2014).

Behavioural measures of semantic priming are appropriate to test theories of semantic memory in general, but leave the question unanswered how and where in the brain semantic access, storage and memory work. To investigate the proposed spread of activation on the neural level, several imaging studies showed anatomic and functional changes correlated with FTD in schizophrenia: for example, gray matter volume reductions in posterior superior temporal gyrus have been found to be associated with FTD in schizophrenic patients (Shenton, 1992a). An inverse correlation between the severity of positive FTD, which is characterized by features of speech such as incoherence, derailment, tangentiality, pressure of speech, and activity in Wernicke area has been shown by Kircher (2001). Additionally, electrophysiological studies assessing event-related potentials in priming experiments found N400 differences in semantic priming tasks between FTD and Non-FTD schizophrenic patients (Kreher, 2008).

In many behavioural, imaging and electrophysiological studies on semantic priming in SZ, different priming tasks have been used, but in the majority of studies stimuli were presented in a single sensory modality. Since multisensory processing is regarded as one of the functions requiring the coordination of distributed brain areas, its investigation in patients with SZ can reveal insights into neural functioning on the level of broader networks comprising multiple sensory systems. This approach offers links to current theories on the pathophysiology of SZ (Friston, 1998), emphasizing dysfunctional coordination of distant brain areas as a core mechanism for the emergence of symptoms and a range of impairments in cognitive functions. In healthy participants, a crossmodal priming study yielded an

enhanced object recognition of the auditory stimulus for congruent visual-auditory stimulus pairs (Schneider et al., 2008). This behavioural effect was accompanied by an increased gamma-band activity in the EEG for congruent compared to incongruent pairs in the left temporal lobe.

High-frequency neural activity is a major aspect in recent models on the pathophysiology of SZ (Lisman et al., 2008) and has also been investigated in SZ in a range of experiments which revealed substantial deviations from healthy subjects during different sensory and cognitive taks (Hirano et al., 2008; Leicht et al., 2010; Minzenberg et al., 2010; Rutter et al., 2009; Spencer, 2011; Taylor, McCarley, & Salisbury, 2013), but primarily using unisensory setups.

The present study aims at investigating frequency-specific neuronal activity as measured with MEG in a visual-to-auditory semantic priming paradigm in patients with SZ and non-clinical control subjects matched to the patients with regard to age, sex, handedness and education. To explore wether FTD is a relevant variable for semantic priming, patients with high scores of FTD severity as well as patients with low to normal scores of FTD severity were tested. For the present experiment the crossmodal paradigm as described above (Schneider et al., 2008) was modified by adding a control condition consisting of visual primes which were not identifiable (phase-scrambled versions of the images).

5.2. Hypotheses

Based on previous findings, a crossmodal behavioural priming effect with shorter reaction times and higher accuracies for the congruent condition in healthy subjects and patients with SZ is expected. On the neural level, an overall diminished gamma-band response in patients with SZ as compared to non-clinical control subjects is hypothesized, as well as an enhanced gamma-band response for the congruent as compared to the incongruent condition in non-clincical control subjects and patients with SZ. Within the group of patients with SZ, a hyperpriming (enhanced priming) effect is expected in FTD compared to non-FTD patients. On the behavioural level, a correlation between the severity of FTD (as assessed with the PANSS item “conceptual disorganization”) and the behavioural priming effect is hypothesized.

5.3. Methods

Participants

Inclusion criteria for the patient sample comprised an age range of 18-59 years and different schizophrenia subtypes (paranoid schizophrenia (F20.0/295.30), disorganized schizophrenia (295.1), schizophrenia simplex (F20.6), undifferentiated schizophrenia (F20.3/295.50), according to ICD-10 or DSM-IV) were included, as well as different durations of illness. Exclusion criteria subtended other psychiatric disorders than schizophrenia, neurologic symptoms or diseases, head injury in the past, pain symptoms, medication with clozapine or anticonvulsants, current drug or alcohol abuse or a history of drug or alcohol abuse. If patients received benzodiazepines in addition to their neuroleptic medication, a washout since the last benzodiazepine intake of at least 7 days was required before patients could participate in the experiment. In case of a history of drug consumption, patients were only included in the study if the period since the last drug consumption was at least one year long. Since all of the patients with SZ who participated in the study were medicated, chlorpromazine equivalents were calculated (see table 3).

Twenty-one patients with schizophrenia (see table 6) participated in the experiment. Diagnoses were confirmed by DSM-IV procedures (Wittchen, Zaudig, & Fydrich, 1997) by clinicians at the Department of Psychiatry and Psychotherapy of the University Medical Center Hamburg-Eppendorf). Twenty-one non-clinical control subjects who were matched to the patients with regard to age, handedness, education and gender participated in the experiment. Control subjects were screened with the short screening questionnaire of the SCID interview (Wittchen et al., 1997) and included if they had no history of neurological or psychiatric disorders. All participants underwent a Landolt test of visual acuity to ensure sufficient vision (visual acuity ≥ 0.9) and a hearing test in which sinusoidal tones at 30 dB HL with varying frequencies (250, 500, 1000, 1500, 2000, 3000, 4000, 6000, 8000 Hz) had to be detected (hearing loss < 30 dB).

The Institutional Review Board of the Medical Association of Hamburg approved the experimental procedures and each subject provided written informed consent. All participants were paid for participation.

Table 4. Basic variables for Patients with SZ and non-clinical control subjects.

	Patients (N= 18)		Control Subjects (N= 20)	
Age	32,56	12,21	33,94	11,16
Sex (male)	14		14	
Handedness (right)	17		19	
MWT-B	26,56	5,85	28,53	5,45
CPZ equivalents	425,00	275,07		
PANSS (total)	55,24	12,38		
Age at onset	23,61	10,11		
Duration of illness	8,97	11,87		

Diagnostic Procedures

Patients as well as non-clinical control subjects were screened with interviews and questionnaires including age, education, handedness as assessed with the Edinburgh Handedness Inventory (Oldfield, 1971), health status and physical as well as mental well-being assessed with SCL-90-R (Franke, 1995), questions regarding medication, injuries and diseases in the past, alcohol, drug use and smoking habits. Furthermore, all participants participated in extensive neuropsychological testing, including five tests on attention from the Testbatterie zur Aufmerksamkeitsprüfung (TAP) (Zimmermann & Fimm, 2002), the digit span test from the Hamburg-Wechsler-Intelligenztest für Erwachsene (HAWIE-R) (Tewes, 1994) for the assessment of short term memory and working memory, the Trail-Making Test part A and B (Reitan, 1986) for the assessment of visual attention and task switching, the d2 test (Brickenkamp, 2002) for processing speed and attention, and the Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B) (Lehrl, 1989) as a brief measure of verbal intelligence. Patients with SZ took part in additional interviews and completed questionnaires for a detailed symptom rating of schizophrenia symptoms (PANSS) (Kay et al., 1987), rating of social, occupational and psychological functioning (GAF) (Tinger, 1986) and severity of illness (CGI) (Guy & National Institute of Mental Health (U. S.). Psychopharmacology Research Branch. Division of Extramural Research Programs, 1976), as well as symptoms of depression in schizophrenia (CDSS-G) (M. J. Müller et al., 1999).

Patients with schizophrenia	**Non-clinical control subjects**
EHI (Edinburgh Handedness Inventory)	EHI (Edinburgh Handedness Inventory)
Digit Span forward & Digit Span backward (from HAWIE-R)	Digit Span forward & Digit Span backward (from HAWIE-R)
SCL-90-R (symptom checklist)	SCL-90-R (symptom checklist)
TAP (Testbatterie zur Aufmerksamkeitsprüfung) • Alertness • Covert Attention Shifts • Crossmodal Integration • Flexibility (komplexe Bedingung) • Incompatibility	TAP (Testbatterie zur Aufmerksamkeitsprüfung) • Alertness • Covert Attention Shifts • Crossmodal Integration • Flexibility (komplexe Bedingung) • Incompatibility
d2 (d2 Aufmerksamkeits-Belastungs-Test)	d2 (d2 Aufmerksamkeits-Belastungs-Test)
MWT-B (Mehrfachwahl-Wortschatz-Intelligenz-Test)	MWT-B (Mehrfachwahl-Wortschatz-Intelligenz-Test)
TMT-A (Trail-Making-Test A) TMT-B (Trail-Making-Test B)	TMT-A (Trail-Making-Test A) TMT-B (Trail-Making-Test B)
PANSS (Positive and Negative Syndrome Scale)	
CGI (Clinical Global Impression Scale)	
GAF (Global Assessment of Functioning Scale)	
CDSS-G (Calgary Depressions-Skala für Schizophrenie-Patienten, german version)	

Table 5. Applied diagnostic tests in patients with SZ (left) and non-clinical control subjects (right).

Stimulation and behavioural task

This experiment aimed at investigating visual-to-auditory semantic matching in schizophrenia, therefore an S1-S2 paradigm with visual primes (S1) followed by auditory targets (S2) was used. The experimental design was comparable to previous crossmodal priming experiments(Schneider et al., 2008a; Schneider, 2008b). The same visual and auditory stimuli as in the previous experiments were chosen. Stimuli were matched according to previously obtained norms regarding familiarity and identification accuracy (Schneider, T.R. & Engel, 2008). Additionally a control condition (in which non-identifiable visual stimuli were presented as S1) was added in order to disentangle facilitatory from inhibitory behavioural effects. Therefore original images were Fourier transformed and the phase angles were randomly shuffled. The participant`s task was to indicate whether the object that is represented with the auditory S2 would fit into a shoe box.

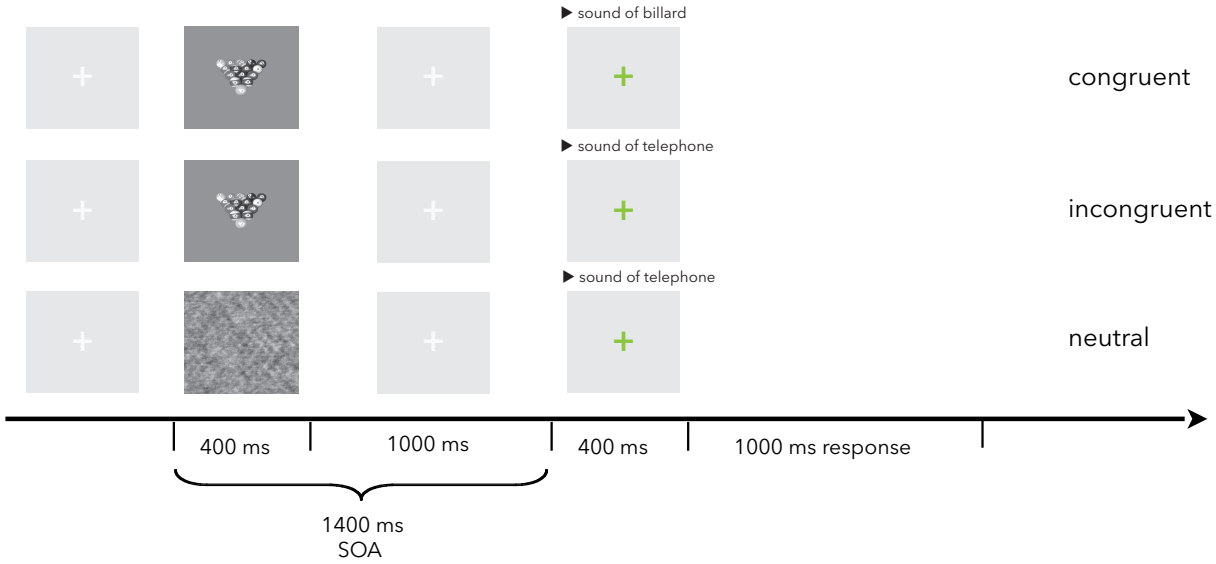


Figure 5.3-1. Experimental Design of the visual-to-auditory semantic priming paradigm. Semantically congruent, incongruent and neutral visual-auditory stimulus pairs were presented in three experimental conditions. For all three conditions, the visual S1 preceded the auditory S2 by 1400 ms. Participants performed in an object classification task, following the auditory S2. A green fixation cross indicated that an immediate response was required.

MEG recording and processing

During the experiment, the MEG was recorded continuously with a 275-channel whole-head system (CTF275, VSM MedTech) in a magnetically shielded room with a sampling frequency of 1200 Hz and an online filter of 300 Hz. A bipolar electrooculogram (EOG) and an electrocardiogram (ECG) were recorded continuously during the experiment. Participants were sitting in the MEG chair fixating a back-projected screen in front of them with a resolution of 1024x768 pixel and a distance of 52 cm. The light was switched on in the MEG chamber throughout the recording. The sounds representing the naturalistic objects were presented with in-ear-phones and before the experiment started, the sound pressure level was adjusted in the MEG individually for each participant according to the individual hearing level.

In the off-line analysis, MEG data were downsampled to 400 Hz, band-pass filtered (1-170 Hz). Line-noise was removed with notch-filters at 50 Hz, 100 Hz, and 150 Hz. Large artifacts related to signal jumps, eye blinks, muscle artifacts passing cars by were rejected with semi-automated procedures. Subsequently, an Independent Component Analysis (ICA) using the extended infomax algorithm was computed with MEG, EOG and ECG data, to identify and remove independent components in the data which reflect saccades, eye blinks and heartbeat artifacts for each subject.

Data Analysis

Reaction Times (RT) in response to the auditory S2 were recorded and all correct responses in the range between 400 ms and 2400 ms after the onset of the auditory S2 were included in further analyses. For the behavioural data, group (non-clinical control subjects vs patients with SZ) x condition (congruent vs incongruent) repeated measures ANOVAs were calculated. Whenever within the group of patients with SZ differences between the FTD and non-FTD patients were tested, the factor group consisted of the groups FTD, non-FTD and non-clinical control subjects.

For the MEG data, the region of interest for subsequent analyses was identified with the calculation of zscores as a statistic for the difference between activation and baseline. Further contrasts were investigated with t-tests. Subsequently, source estimates for the evoked power were calculated using the eLORETA method in the FieldTrip open source toolbox (http://fieldtrip.fcdonders.nl/). The source estimates were determined based on visual inspection of the maxima and labeled according to the Automated Anatomical Labeling software.

5.4. Results

Behavioural Data

A repeated measures ANOVA for Group (patients with SZ vs non-clinical control subject) x Condition (congruent, incongruent, neutral) indicated a significant Condition effect ($F(2,72)= 15.978$, $p > 0.001$). A test of between-subjects effects revealed a significant effect of group ($F(1,36) =5.023$, $p = 0.020$). The condition x group interaction was not significant.

Patients` RTs were longer in all conditions (mean congruent: 824 ms, incongruent: 887 ms, control: 956 ms) as compared to non-clinical control subjects (mean congruent: 640 ms, incongruent: 707 ms, control: 715 ms). Patients as well as control subjects showed shorter RTs for congruent as compared to incongruent visual-to-auditory pairs. The Condition x group interaction was not significant.

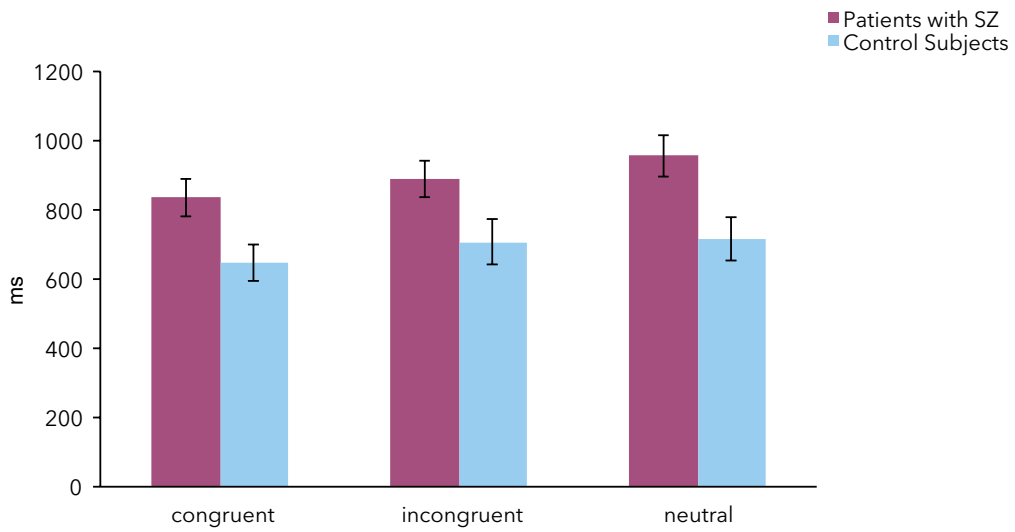


Figure 5.4-1. Reaction Times (RT) for patients with SZ (n = 18) and matched control subjects (n=20) in the congruent, incongruent and neutral condition.

To test the hypothesis of hyper-priming, i.e. enhanced auditory object recognition in patients with Formal Thought Disorder, the group of patients with SZ was divided into FTD patients (patients with PANSS scores ≥ 3 for item P2 "conceptual disorganization"), and non FTD patients (patients with PANSS scores ≤ 3 for item P2 "conceptual disorganization"). The differences between the congruent and incongruent condition did not differ significantly between FTD patients and non FTD patients ($F(4,74) = 0.704$, $p = 0.592$) (see Figure 5.4-3). On average RTs were larger in the sample of FTD patients as compared to non-FTD patients as illustrated in Figure 5.4-2.

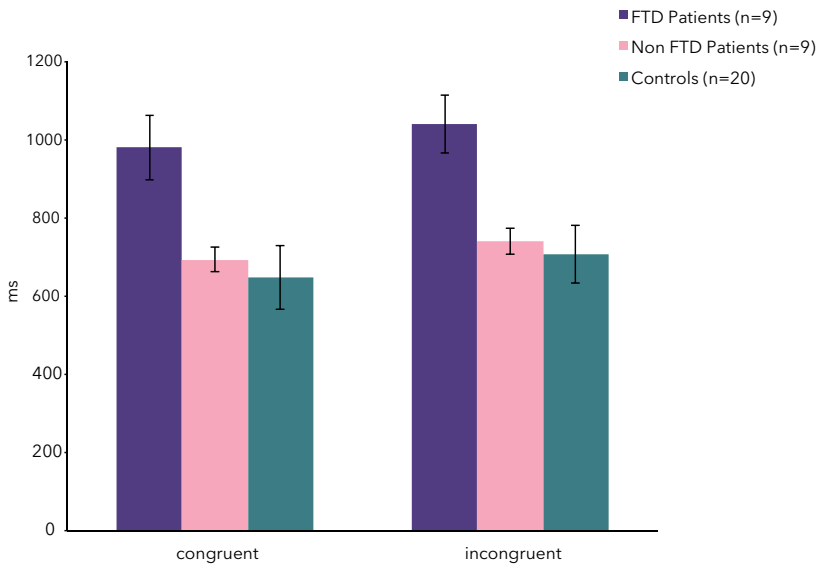


Figure 5.4-2. RTs for FTD patients (with PANSS scores ≥ 3 for item P2 "conceptual disorganization"), non FTD patients and control subjects.

To illustrate the magnitude of the differences between the priming difference congruent minus incongruent between the groups in detail, Figure 5.4-3 depicts the differences as bars, indicating that differences are evident, but that standard errors of the mean are quite large. Furthermore, the difference in RT between the congruent and incongruent condition did not correlate with the scores of the PANSS item P2 (conceptual disorganization).

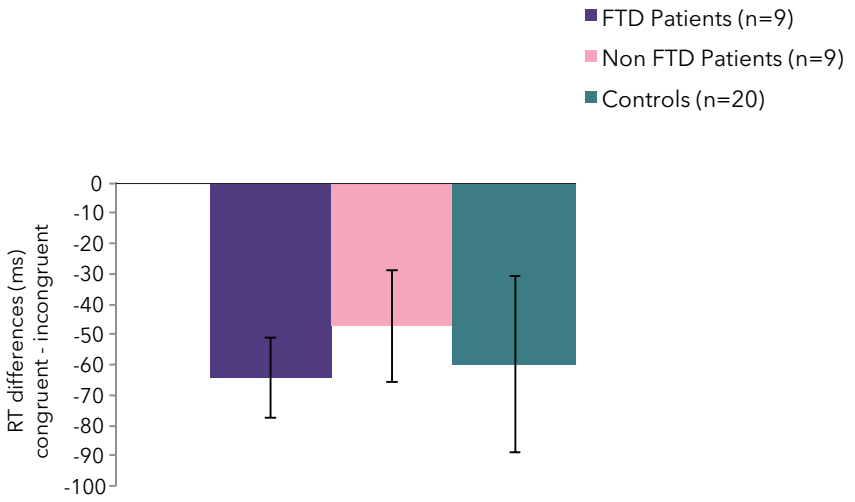


Figure 5.4-3. Differences between RTs in the congruent and incongruent condition (in ms) for the group of FTD patients, non-FTD patients and control subjects.

Evoked Power Response

For patients with SZ as well as non-clinical control subjects, an enhancement in evoked power was primarily found in the frequency range of 30-40 Hz.

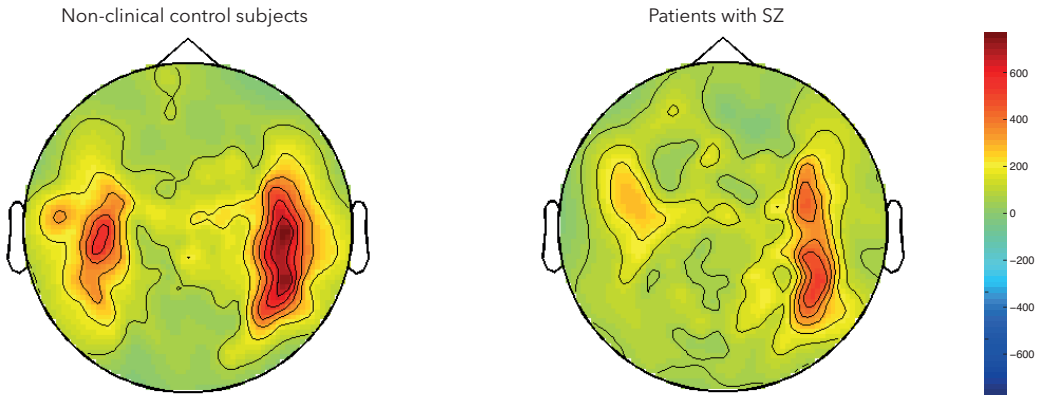


Figure 5.4-4. Topographies of the evoked 30-40 Hz activity for non-clinical control subjects (left) and patients with SZ (right) 20-80 ms after presentation of the auditory S2.

As expected, topographies for the 30-40 Hz auditory evoked response for patients with SZ and non-clinical control subjects showed an enhancement of power over bilateral temporal areas (see Figure 5.4-4), whereas the enhancement was for both groups more pronounced over right temporal areas. The enhancement was generally lower for patients with SZ, specifically over the left temporal area.

To detect the time and frequency range of maximal activation in the data, a contrast between the stimulus interval and a baseline interval of equal length was calculated as a first step. As a baseline period, the time window of -160 ms until -100 ms before auditory S2 onset was chosen, and as stimulus interval, 20-80 ms after the auditory S2 onset. The statistical result of this stimulation vs. baseline contrast is illustrated in the topography (Figure 5.4-5), with statistically significant clusters colour-coded as z-scores.

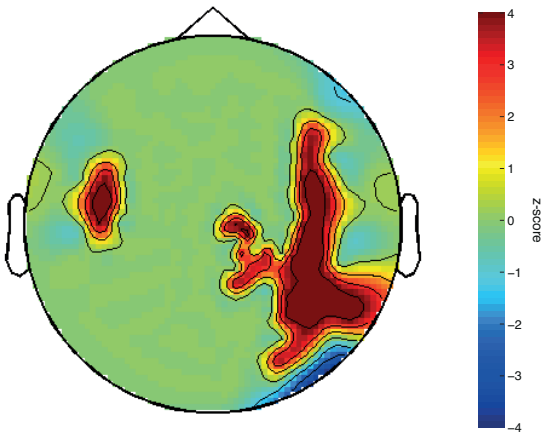


Figure 5.4-5. Topography of evoked power (30-40 Hz) for the difference between an activation period (20-80 ms after auditory S2 onset) and a baseline of equal length (ranging from -100 until -160 ms). Data from non-clinical control subjects and patients with SZ as well as experimental conditions were collapsed. This contrast was used to determine the region of interest (ROI) for subsequent analyses.

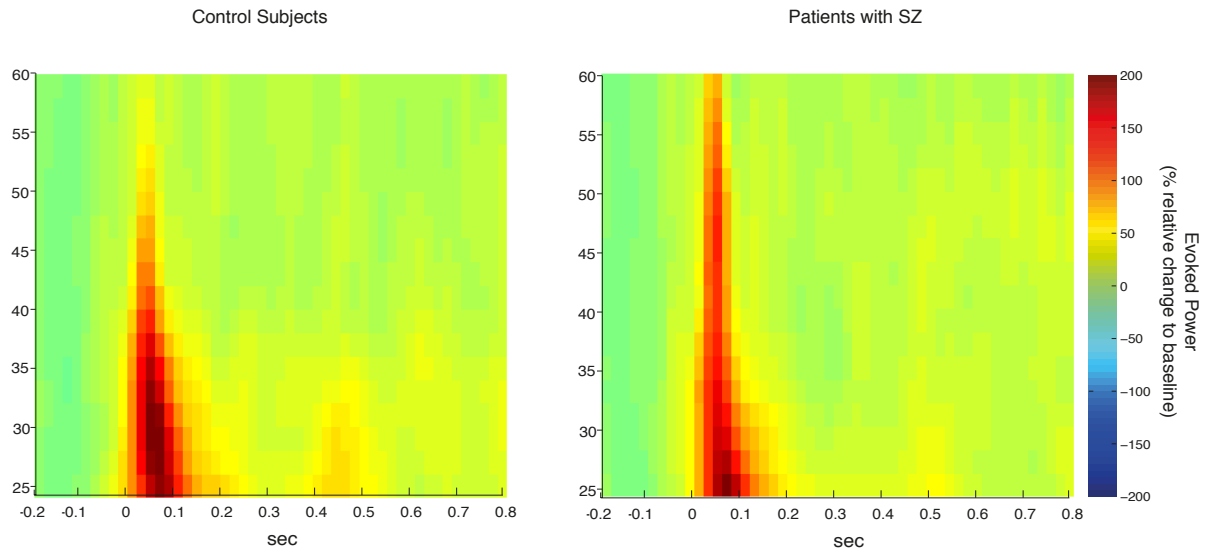


Figure 5.4-6. Time-frequency plots of evoked gamma-band activity in response to the auditory S2 for the grand average over all sensors. The evoked activity is expressed as percent change relative to baseline for patients with SZ (right) and matched control subjects (left).

Differences in evoked 30-40 Hz power for both conditions between patients with SZ and non-clinical control subjects are represented in Figure 5.4-6, corresponding to the significant group difference between patients with SZ and non-clinical control subjects in the 30-40 Hz evoked power in the time range of 20-80 ms after auditory onset (t(36) = -2.1647, p = 0.0186).

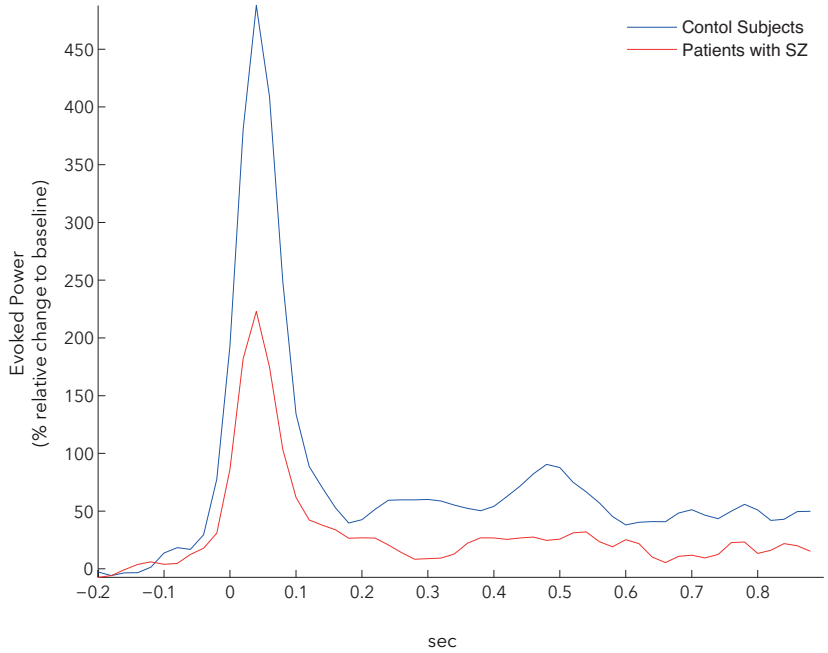


Figure 5.4-5. Evoked power 30-40 Hz for patients with SZ (red) and non-clinical control subjects (blue) for both conditions.

To investigate if a semantic priming effect within the two groups is reflected in neural activity, t-tests for the differences between the 30-40 Hz evoked power in the congruent and incongruent condition from 20 to 80 ms after auditory onset were calculated. The results indicate a significant difference within the patients with SZ (t(17)= -1.8792, p = 0.0387), whereas the two conditions did not differ significantly within the non-clinical control subjects (t(19) = 0.414, p = 0.6583). The direction of the difference in the MEG for patients with SZ and non-clinical control subjects is illustrated in Figure 5.4-8, showing the differences in evoked 30-40 Hz power between the congruent and incongruent condition for the two groups.

Figure 5.4-8 depicts the direction of the evoked gamma-band effect, showing negative values for the patients with SZ and positive values for the non-clinical control subjects. This difference in the direction reveals for the controls enhanced 30-40 Hz power between 20 and 80 ms after auditory onset for the congruent as opposed to the incongruent condition. For patients with SZ the difference points in the opposite direction, i.e. higher power in the congruent as compared to the incongruent condition.

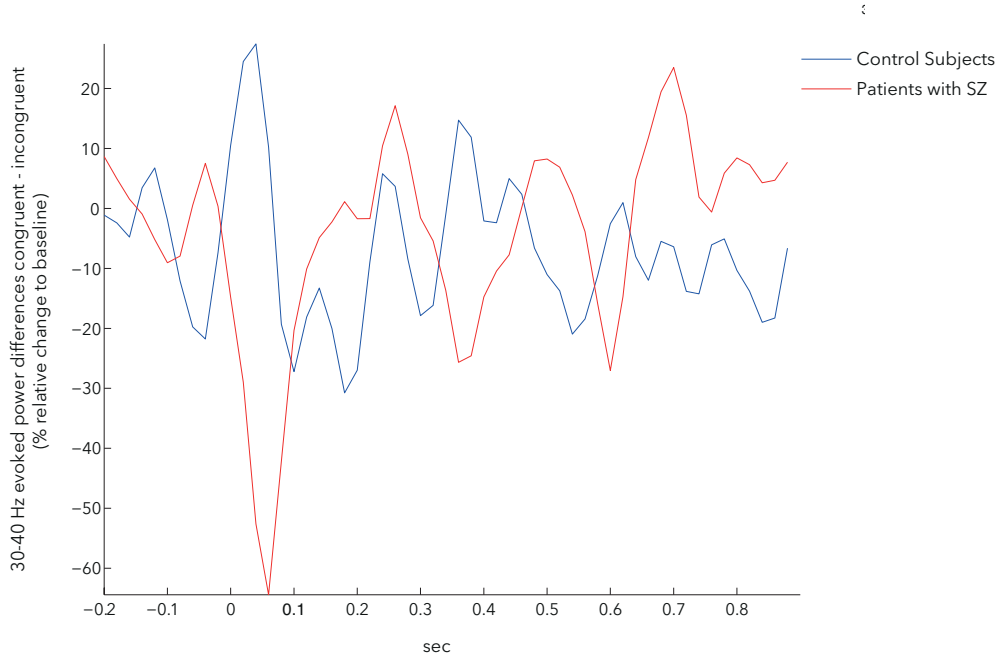


Figure 5.4-6. Evoked 30-40 Hz power (difference between the congruent and incongruent condition) in patients (red) and non-clinical control subjects (blue) expressed as percent change to baseline (0 indicates the onset of the auditory S2).

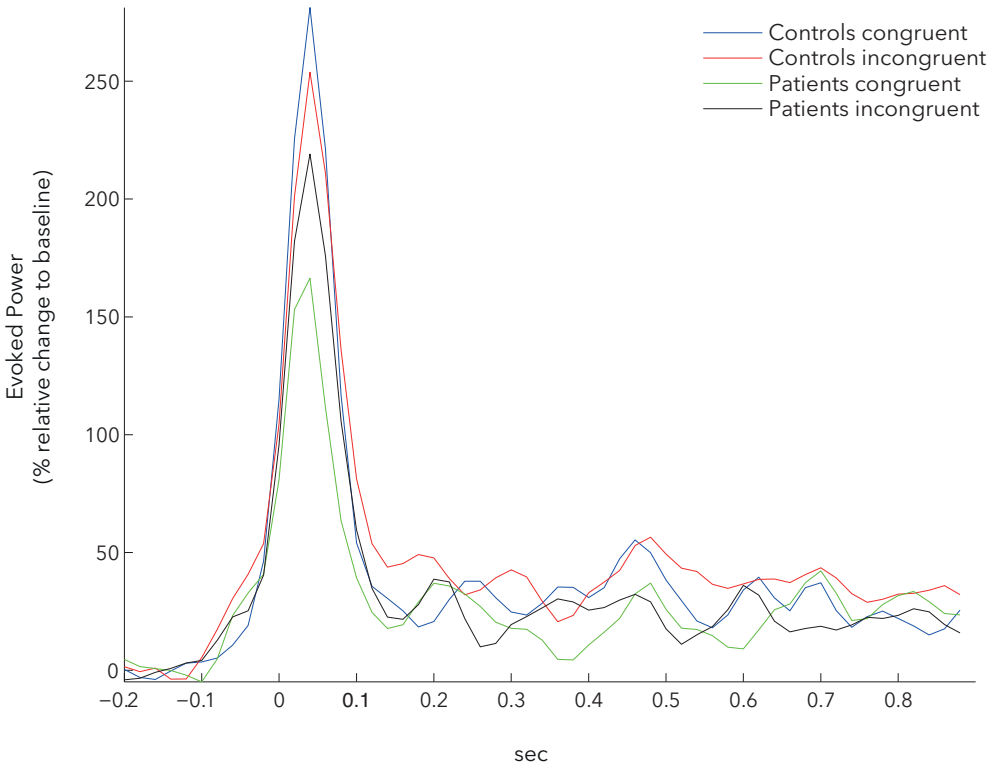


Figure 5.4-7. Evoked 30-40 Hz power for patients and control subjects expressed as percent change relative to baseline for patients with SZ and non-clinical control subject the congruent and incongruent condition.

This is illustrated in more detail in Figure 5.4-9, showing the evoked power for the congruent and the incongruent condition for the two groups. The result of the t-test for the difference between the priming difference within the control subjects and within the patients with SZ, i.e. for the group x condition interaction, yields a probability of t(36)= -1.5968, p = 0.0595, which is marginally significant. Figure 5.4-9 illustrates the group x condition interaction: Control subjects show a higher power relative to baseline in the congruent as compared to the incongruent condition whereas in the patients, the power is higher in the incongruent as compared to the congruent condition.

Symptom Severity and evoked power responses

Correlations between evoked power and measures of symptom severity were found for different items of the three scales of the PANSS, as depicted in the following correlation plots in which a least squares line is inserted to represent an estimation of the best fit to the data: A significant correlation was found between the PANSS item P6 on the positive scale, 'Suspiciousness', and evoked power (30-40 Hz, 20-80 ms) in the congruent condition (rho = 0.5454, p = .0236) as well as for congruent and incongruent conditions collapsed (rho = 0.5063, p = .0381) (see Figure 5.4-8).

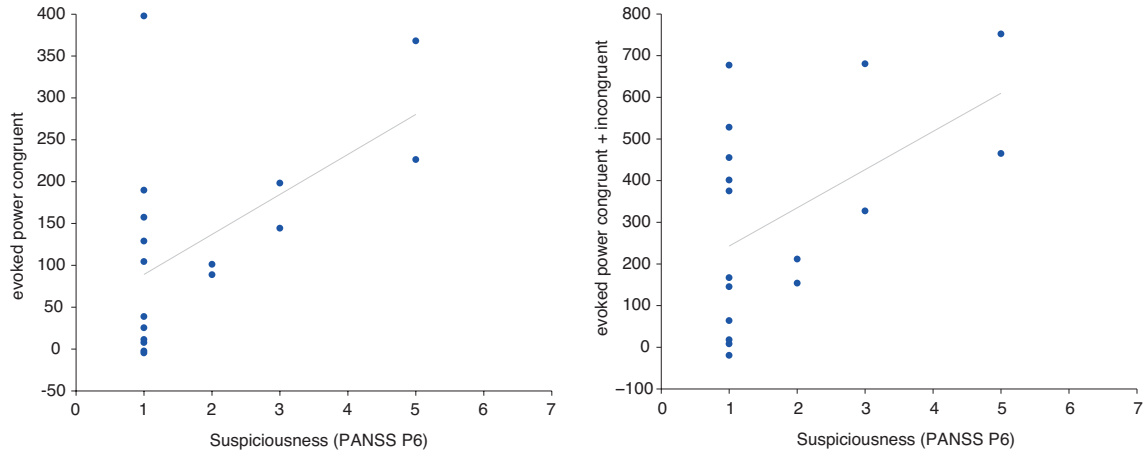


Figure 5.4-8. Correlation between evoked power difference (left panel, congruent minus incongruent condition) in the congruent condition (left) and in the congruent and incongruent condition (right) and symptom severity as assessed with the PANSS item Suspiciousness (P6).

For items on the negative scale, significant correlations between evoked power in both conditions collapsed and Blunted affect (N1) (rho = 0.5853, p = .0136) (see Figure 5.4-9, left) were found as well as a significant correlation between the passive-apathetic social

withdrawal (N4) and evoked power in the congruent condition (rho = 0.5098, p = .0366) (see Figure 5.4-9, right).

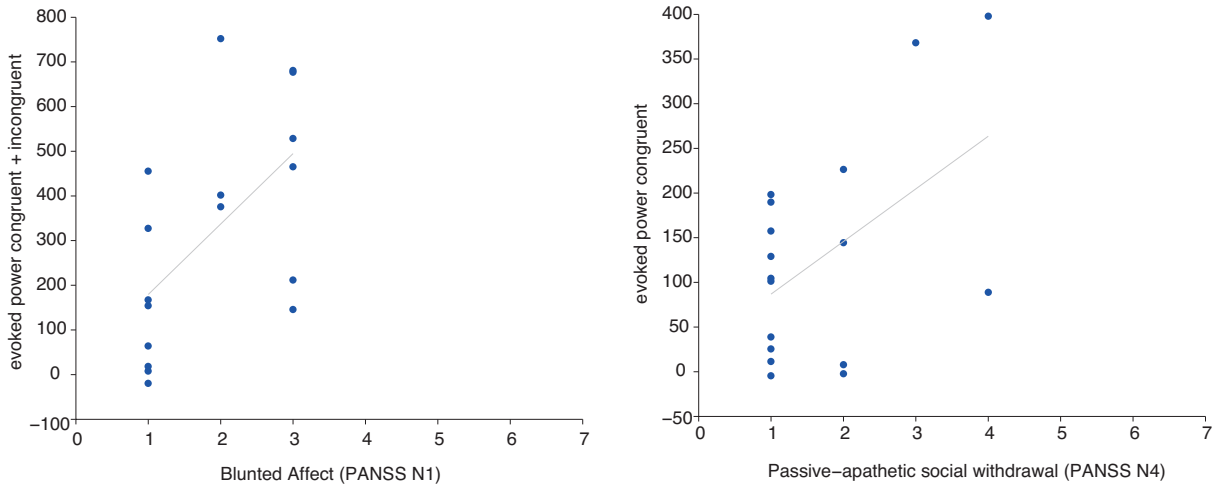


Figure 5.4-9. Correlation between evoked power in the congruent and incongruent condition (left) and symptom severity as assessed with the PANSS item Blunted Affect (N1) (left panel) and between evoked power in the congruent condition and the PANSS item Passive-apathetic social withdrawal (N4) (right panel).

Significant correlations were also found between evoked power in the congruent (rho = 0.5730, p = .0162), incongruent (rho = 0.7298, p = 0.0008) as well as for both conditions collapsed (rho = 0.6689, p = .0033) with N7, 'stereotyped thinking' (see Figure 5.4-10).

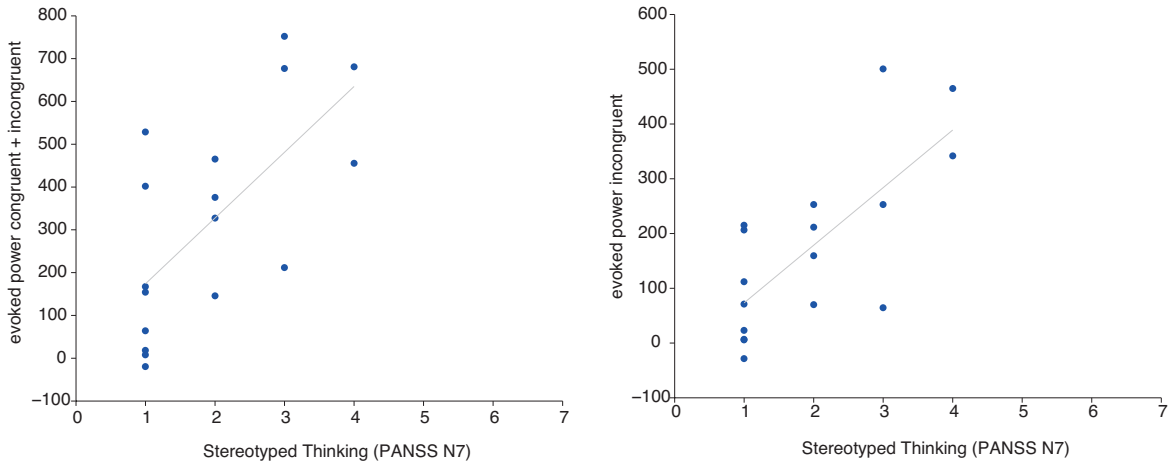
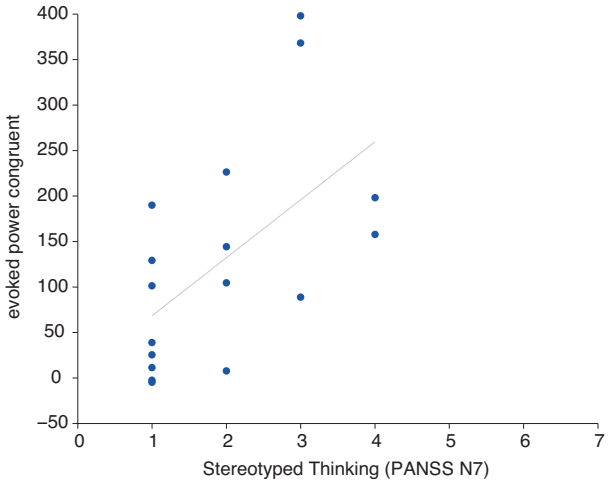


Figure 5.4-10. Correlation between evoked power in the congruent (upper left panel) and incongruent condition (upper right panel) and symptom severity as assessed with the PANSS item Stereotyped Thinking (N7) and between evoked power in the congruent and incongruent condition collapsed and the symptom severity as assessed with the PANSS item Stereotyped Thinking (N7) (lower left panel).



Among items of the general scale, symptom severity for the item ‘anxiety’ (G2) correlated with the difference in evoked power between the congruent and incongruent condition (rho = 0.5089, p = 0.0369) (see Figure 5.4-11), and ‘motor retardation’ (G7) correlated significantly with evoked power in the congruent condition (rho = 0.5380, p = .0259) (see Figure 5.4-12). Since motor retardation is sometimes related to a general slowing factor in patients, which can also be reflected in RTs and is therefore relevant with regard to the priming effect, a correlation between ‘motor retardation’ and the difference between RTs for the congruent and incongruent condition was calculated. There was no significant correlation between ‘motor retardation’ and the RT difference between the congruent and incongruent condition (rho = 0.1981, p = 0.4461).

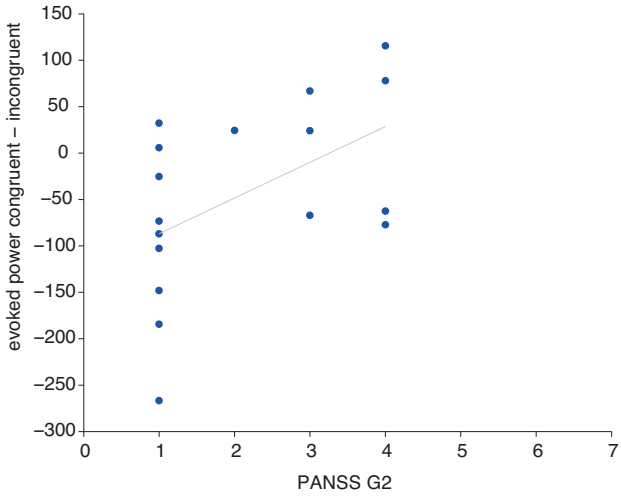


Figure 5.4-11. Correlation between symptom severity for the item ‘anxiety’ (G2) and the difference between the evoked power in the congruent and incongruent condition.

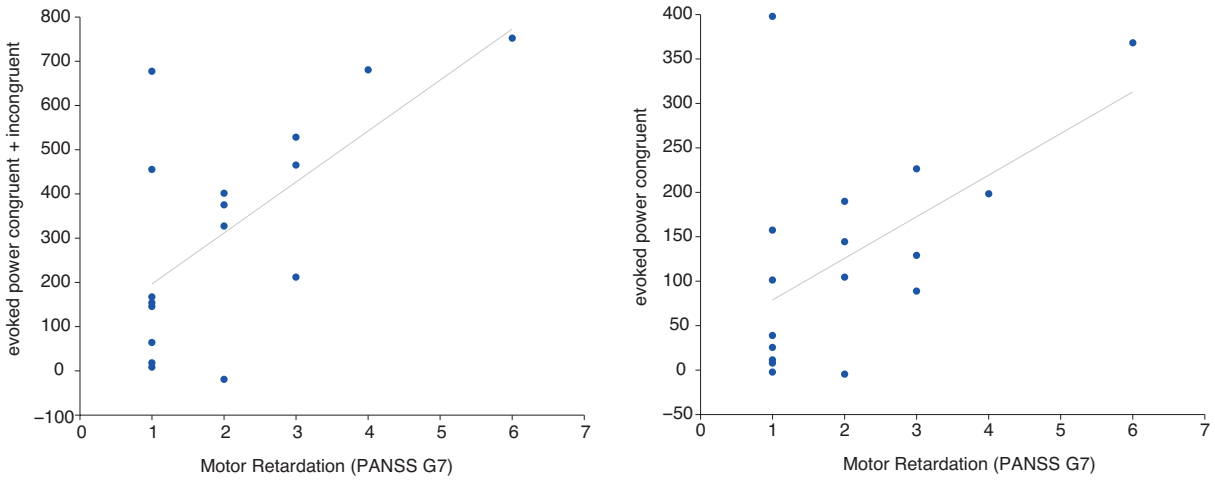


Figure 5.4-12. Correlation between the evoked power in the congruent condition and symptom severity as assessed with the PANSS item Motor retardation (G7) (left panel) and between the evoked power in the congruent and incongruent condition collapsed and Motor retardation item (right panel).

The PANSS item disturbance of volition (G13) correlated significantly with the difference of the evoked power (see Figure 5.4-14, left panel) between the congruent and incongruent condition (rho = 0.5616, p = 0.0190).

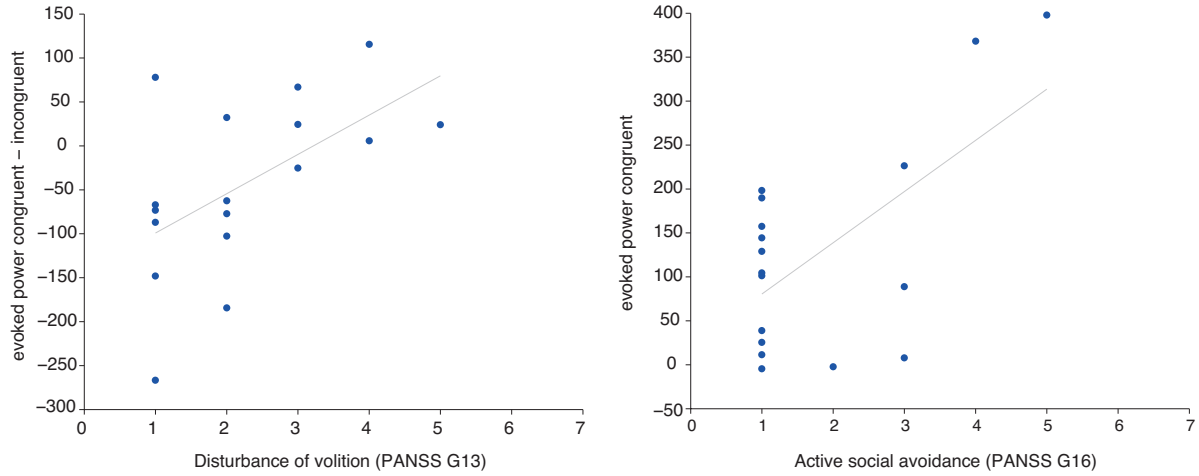


Figure 5.4-13. Correlation between the difference between evoked power in the congruent and incongruent condition and symptom severity as assessed by the PANSS item 'Disturbance of volition' (G13) (left panel) and correlation between evoked power in the congruent condition and PANSS item 'Active social avoidance' (G16) (right panel).

Finally, the PANSS item 'active social avoidance' (G16) correlated significantly with evoked power in the congruent condition (rho = 0.6198, p = .0080) (see Figure 5.4-14, right panel).

RTs and evoked power

Interestingly, a significant correlation (rho = .4746, p = .0466) between the evoked power difference between congruent and incongruent condition in the 30-40 Hz from 20-80 ms and the RT difference between the congruent and incongruent condition was found for the patient group (see Figure 5.4-15). The same contrast did not yield a significant difference for the control subjects.

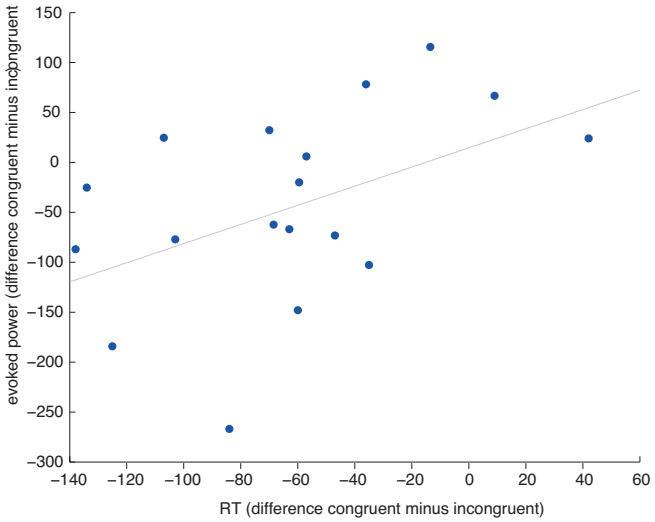


Figure 5.4-14. Correlation between the difference in evoked power between the congruent and incongruent condition and the difference in RTs between the congruent and incongruent condition.

Source estimations of evoked activity

For the calculation of source estimates for the 30-40 Hz power between 20 and 80 ms after auditory stimulus onset, a principal component analysis (PCA) was calculated as a first step with the preprocessed MEG data. For this procedure, experimental conditions were collapsed so that the PCA could be calculated on a larger number of trials for each subject. Components of the PCA for each subject were selected based on the criterion of a maximal similarity to the topography of an auditory response, in order to capture the components that represent the significant 30-40 Hz effect most accurately. Subsequently, these selected components were used for the eLORETA source estimation. For 18 SZ patients, the source estimates for the auditory responses revealed maxima at regions in the right hemisphere including the triangular part of the inferior frontal gyrus (spm coordinates: 54.0 26.0 18.0), the opercular part of the inferior frontal gyrus (spm coordinates: 56.0 12.0 18.0), the rolandic operculum, heschl gyrus and superior temporal gyrus (spm coordinates: 60.0 -16.0 6.0) (see Figure 5.4-15).

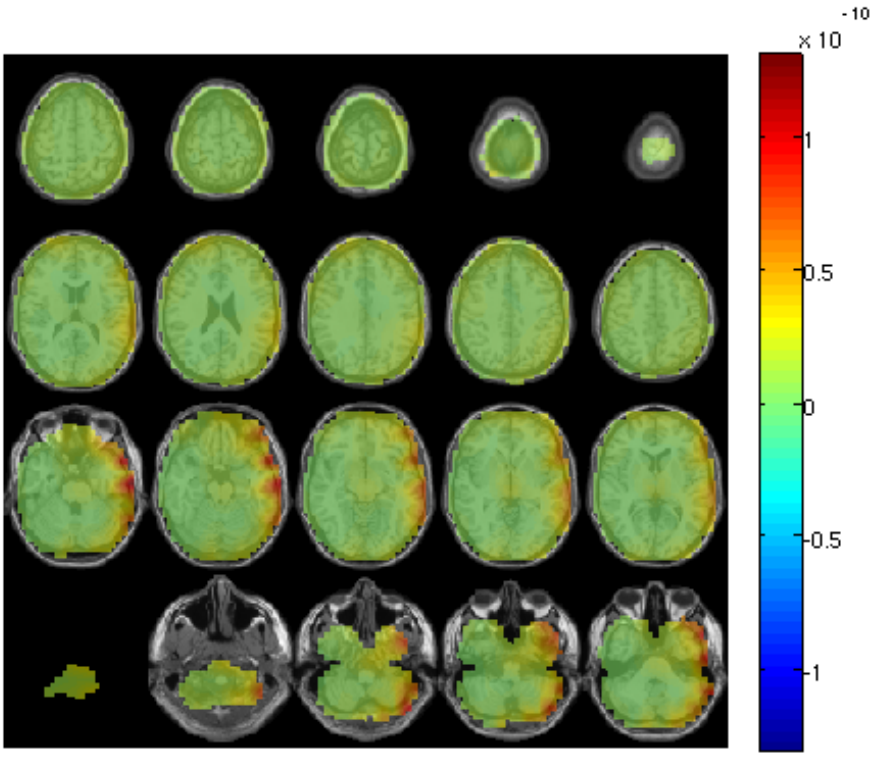


Figure 5.4-15. Source reconstruction for the components reflecting the 30-40 Hz evoked activity in response to the auditory stimulus for the SZ patients.

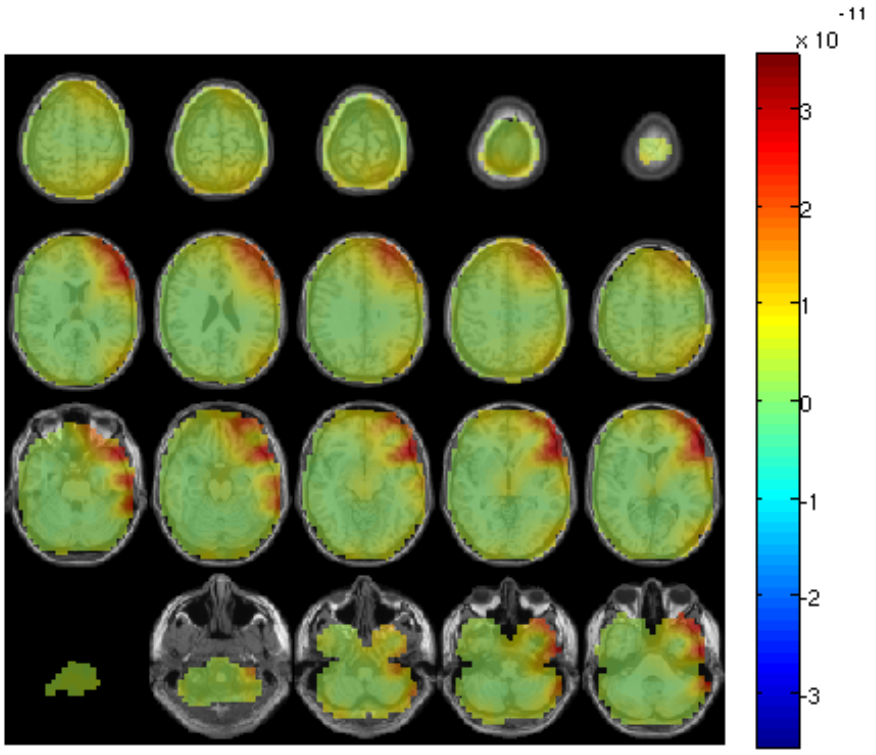


Figure 5.4-16. Source reconstruction for the components reflecting the 30-40 Hz evoked activity in response to the auditory stimulus for the non-clinical control participants.

For 17 non-clinical control participants, the strongest activity was localized in regions including the right middle frontal gyrus (spm coordinates: 40.0 48.0 12.0), the right middle frontal gyrus and triangular part of the right inferior frontal gyrus (spm coordinates: 46.0 42.0 12.0), and the right superior temporal gyrus, as well as right middle temporal gyrus (spm coordinates: 56.0 -4.0 -12.0) (see Figure 5.4-16).

5.5. Discussion

The visual-to-auditory semantic priming paradigm applied in the present study revealed a crossmodal behavioural priming effect for patients with SZ and for non-clinical control participants. Facilitated auditory object recognition as indicated by shorter RTs was found for the congruent as compared to the incongruent condition. In line with the literature (for a review, see Minzenberg et al., 2002), patients with SZ had overall longer RTs as compared to HC in all experimental conditions. The auditory evoked gamma-band response (eGBR) was found to be reduced in patients with SZ compared to non-clinical control participants across conditions, which replicates earlier findings (Ballesteros et al., 2013; Leicht et al., 2010, 2011; Mulert et al., 2007; Popov et al., 2011; Spencer, Salisbury, Shenton, & McCarley, 2008; Tsuchimoto et al., 2011). Additionally, a marginally significant interaction between groups and conditions was found: the two groups showed the reverse pattern for the cross-modal priming conditions in the eGBR. Significant correlations between symptom severity for positive, negative and general symptoms of SZ with the auditory eGBR were found within the group of patients. Furthermore, the strength of the behavioural priming effect was correlated with the strength of the eGBR modulation in SZ.

Behavioural Results

RTs analysis revealed the expected facilitated auditory object recognition for congruent as compared to incongruent visual-to-auditory objects pairs. In line with the hypothesis, patients with SZ showed longer RTs in all conditions as compared to non-clinical control participants, which might reflect a delayed spreading activation peak. Contrary to the hypothesis, no enhanced facilitation of auditory object recognition, i.e. ‚hyper-priming', was not found for patients with FTD compared to non-FTD and healthy control participants. FTD patients showed substantially longer RTs as compared to non-FTD patients and non-clinical control

subjects in all conditions, but priming effects did not differ significantly between the two patients groups. One condition that might have contributed tot he lack of a significant difference might be the small sample size when the group of patients is divided into FTD and non-FTD, each of which comprised only 9 patients.
In line with previous work, priming effects in patients with SZ were found in a crossmodal priming task. Behavioural studies on crossmodal priming in schizophrenia using an LD task comparing unimodal visual-visual and auditory-visual priming (S. Surguladze, Rossell, Rabe-Hesketh, & David, 2002) showed a larger priming effect in the crossmodal version.

For the interpretation of the behavioural results one feature of the paradigm is of importance: as compared to many other priming studies, the paradigm of the present study features a longer SOA, which allows controlled processing. Specifically, for the hyper-priming hypothesis, the duration of the SOA may influence the results, since recent experiments found larger priming effects for FTD patients primarily when short SOAs were used (Safadi, Lichtenstein-Vidne, Dobrusin, & Henik, 2013). Therefore, in the current experiment hyper-priming effects might have been obscured by controlled processing.

Evoked Power

The finding of an enhanced eGBA in response to semantically congruent auditory stimuli in HC is in line with previous findings of a haptic-to-auditory priming EEG study, which demonstrated effects of semantic congruency on the eGBR from 50 to100 ms after presentation oft he auditory S2 (Schneider et al., 2011). The difference between early auditory evoked power in patients with SZ and control subjects replicates previous findings (Leicht et al., 2010) demonstrated a reduction of power in the early auditory eGBA in SZ using EEG in an auditory reaction task.
A new and unexpected finding of the present experiment is the reverse direction of evoked power effects between the two groups for the condition contrast, i.e., enhanced eGBR for the congruent compared to the incongruent condition in HC and reduced eGBR for the same contrast in SZ. The enhanced eGBR in response tot he congruent condition may be explained by the ‘match-and-utilization model’ (Herrmann, Munk, & Engel, 2004). According to the model, a match of information held in working memory with incoming sensory bottom-up information is associated with enhanced gamma-band responses (Herrmann et al., 2004). Findings in line with this hypothesis in healthy subjects were obtained with similar versions

of the paradigm as used in the present study (Schneider et al., 2008, 2011) and such as in a haptic-auditory version (Schneider et al., 2008, 2011; Schneider, T.R. & Engel, 2008) (Senkowski, Schneider, Tandler, & Engel, 2009). For the patients with SZ, additional assumptions are neccessary to explain the finding with the match-and-utilization model: If enhanced GBA is not only likely, as stated in the model, but also necessary for the matching of bottom-up input and preexisting WM templates, the findings for SZ in the present study could be interpreted as a compensatory mechanism: If processing of bottom-up information is dysfunctional, delayed or compromised, the matching of WM templates could be severely impaired. A compensatory up-regulation of GBA in case of dysfunctional bottom-up processing, specifically when incongruent input is presented, could explain the current findings, but has to be regarded as highly speculative. Furthermore, the present findings could question whether the match-and-utilization model is generalizable to neuronal activity in psychiatric diseases: the processing of incoming bottom-up information may have to fulfill certain criteria to initiate a proper matching process, which might be disrupted in SZ on very early processing stages.

A dissociation between behavioural and MEG data is obvious in the findings of the present study. The direction of the priming difference is the same for both groups in the behavioural data, i.e., in both groups, longer RTs to incongruent as compared to congruent object pairs were found. The MEG data, on the other hand, show the interaction between group and condition as discussed above with a reversed pattern of the condition effect. A correspondence between the direction of behavioural and MEG data was only found for the non-clinical control participants.

Contrary to the hypothesis, the present experiment revealed effects in evoked, but not in total power between conditions and groups. This lacking of effects in total power might be related to larger individual differences between participants in the current sample. The patients` sample as well as their matched control participants are both characterized by a larger heterogeneity than, for example, the healthy subjects in the original version oft he visual-to-auditory semantic priming paradigm (Schneider et al., 2008). Even basic variables such as age and education could contribute to the lack of significant total power differences.

Symptom Severity and oscillatory evoked power

An interesting finding is the correlation between evoked power and symptom severity in different PANSS items. First of all, it is striking that symptom severities of all three domains

(positive, negative and as general symptoms) are correlated with evoked power. Second, the direction of these correlations is contrary to the expectation. In general, patients with SZ show decreased evoked power as compared to non-clinical control participants. The correlations between evoked power and sympom severity, however, are positive, i.e. they indicate an association of higher evoked power with higher symptom scores. Based on the direction of the general group effect, one would expect an eGBR decrease to be related to symptom severity. It should be noted, that correlations between symptom severity and oscillatory activity have been reported before, although for visual stimuli (Spencer, et al., 2004). In a recent study, the same group found a reversal of a condition difference in response-locked gamma oscillations in a visual Gestalt perception task in response to illusory Kanisza squares as compared to No-square control stimuli between healthy subjects and patients with SZ (Spencer & Ghorashi, 2014). Interestingly, as in the earlier study of the authors, thought disorder correlated with the condition effect.

The experimental paradigm in the present study featured a long SOA, allowing for controlled processing. This raises the question whether a short SOA, which mainly allows for automatic processing, would lead to similar results in a visual-to-auditory semantic priming paradigm with naturalistic objects.

Source estimations of evoked activity

Source estimates of the evoked 30-40 Hz activity were calculated on PCA components which were selected in order to capture the auditory response most accurately and at the same time to minimize the influence of artifacts as well as activity other than the auditory evoked activity. This was done with pooled trials of the congruent as well as incongruent condition to enlarge the total trial number of the data for the PCA. Therefore, this procedure does not allow for an analysis of a possible condition difference, since the components reflect the pooled data of both experimental conditions. Since the source estimates were determined based on visual inspection of the maxima of the localized activity and afterwards labeled according to the Automated Anatomical Labeling software such that no statistic comparison was done for the two groups, the difference between the patients and the non-clinical control participants (see Figure 5.4-15 and 5.4-16) can hardly be interpreted in this case. The results for the source estimation of the present MEG data indicate an involvement of right inferior frontal as well as right temporal areas can be interpreted as being generally in line with earlier MEG findings on auditory responses (Luo & Poeppel, 2012; Pulvermüller et al., 1996).

Taken together, the present behavioral findings reveal facilitated auditory object recognition in patients with SZ as well as healthy control participants in a crossmodal visual-to-auditory semantic priming task. The MEG findings are in line with previous reports of a reduction of evoked gamma power in response to auditory stimuli in SZ (Leicht et al., 2010). The current findings add to the existing literature in that a crossmodal priming effect was found in patients with SZ similar to findings in healthy participants (Schneider et al., 2008). On the neural level, the results indicate an impairment in early sensory processing as indicated by reduced gamma-band power in SZ in response to auditory inputs. An interaction between the effects of group and condition suggests that the modulation of neuronal activity in the crossmodal priming task is sensitive for SZ. This assumption is supported by positive correlations between the severity of specific positive, negative and general symptoms of the disease and neuronal activity in the gamma range. The direction of the correlations, however, raises further questions about the functional significance of this neuronal marker. Future research has to disentangle the differential effects of power regulation in healthy participants and patients with psychosis.

6. General Discussion

The studies of this thesis complement recent work on unisensory processing in schizophrenia (Brenner et al., 2009; Butler et al., 2005; Gruetzner et al., 2013; S. Hirano et al., 2008; Leicht et al., 2010) with investigations of multisensory processing in SZ in the EEG and MEG using paradigms with a high degree of ecological validity, i.e. with a speech detection task and a crossmodal semantic priming paradigm. The present experiments are thereby in line with the contemporary focus on sensory processing in SZ and the growing interest in detailed analyses of sensory processing in SZ and its neuronal processes, correlates and underlying mechanisms.

One of the advantages of this rather "sensory" perspective is that it does not exclude top-town influences, but still acknowledges sensory processing as a separate matter with relevant implications in its own right, which offers new perspectives and reinterpretations of existing findings in SZ research. One example is the group of cognitive biases in SZ. Specifically, the "bias against disconfirmatory evidence", which is defined as the tendency of patients to stick to initial beliefs in ambiguous situations although new information which could be used to adjust initial judgements is presented (Veckenstedt et al., 2011; Woodward, Moritz, Cuttler,

& Whitman, 2006). Another cognitive bias with a strong implication for the symptoms of SZ is the phenomenon of "jumping to conclusions" (Moritz & Woodward, 2005; Rubio et al., 2011), which refers to the tendency in patients with SZ to judge and draw conclusions rather quickly in contexts in which only little relevant information is available. Both cognitive biases are highly relevant in the context of the emergence and maintenance of false beliefs and delusions, and both are grounded on information that was at some early processing stage delivered via sensory channels. For these two domains at the intersection of perception and decision, findings on deficient sensory processing in schizophrenia can add relevant pieces to the puzzle. The finding that patients with psychosis show a strong tendency to judge quickly based on rather little basic information provides insights in mechanisms of paranoid thinking, which points to the mechanisms of development and maintenance of a very frequent and defacing symptom of schizophrenia. It can be assumed that the lack of sufficient basic information might "force" affected individuals to speculate rather than to conclude based on the available information, and it can be assumed that this tendency might even increase with decreasing quality of basic sensory processing.

Outlook

In general, EEG and MEG studies on SZ comprising larger samples of patients with SZ would be necessary to diminish heterogeneity of the patients with SZ within the samples and enhance the statistical robustness, and thereby broaden the scope of interpretation of the findings. Larger samples would furthermore provide the opportunity to investigate differences between diagnostic subtypes of SZ in relation to measures of neuronal activity as well as other relevant variables, for instance duration of illness, medication and age at onset, which would improve research progress in SZ substantially.

For the present work, one important factor that has likely influenced the results are the specific characteristics of the present patient samples. Age and education as well as other characteristics of all the participants might have driven the results and specifically, the nature of the patients with SZ are of particular relevance for the interpretation of both studies on SZ. The sample of the present MEG study consists of very few patients suffering from the first psychotic episode, but primarily of patients having a considerable duration of illness (on average 8.97 years, see table 8), which might have led to adaptive changes in neuronal functioning during the course of the disorder. This may account for some of the differences of

the present findings as compared to other studies, for instance regarding the lack of differences in total/induced power: Recently, in medication-naïve first-episode SZ patients, a reduction of induced power in the high-gamma range (60-120 Hz) was found in an MEG study using Mooney faces (Sun et al., 2013). Interestingly, gamma power in lower frequency ranges did not differ significantly between healthy controls and patients with SZ in that study. So far, it is speculative how the observed sensory impairments in SZ develop over time, i.e., during later stages of the disorder. The above-mentioned proposed compensatory up-regulation of GBA (chapter 5.5) might develop during the course of the disorder in response to a progressive decline of sensory and neurophysiologic functions, and might not present during the very early stages of the first psychotic episode. Therefore, it might be possible that the results of the present study reflect primarily neuronal functioning at later stages of SZ, whereas other findings (e.g. Grützner et al., 2013b), specifically Sun and colleagues (2013) might feature early alterations of neuronal functioning in SZ. If this was the case, it could be argued that corresponding to the development of the compensatory up-regulation of early evoked GBA, other effects in total/induced power vanish as compared to the –possibly stronger- effect in evoked power, i.e., possible deviations in total/induced power might not be visible relative to the larger changes in evoked power. Findings such as these raise questions about the role of total/induced vs. evoked GBA as well as the functional relevance of different frequency ranges of the gamma band in different stages of SZ.

Investigating patients with specific psychotic symptoms of different diagnostic categories including disorders other than SZ can be beneficial for future studies on neuronal functioning in SZ and in psychoses in general, rather than sticking to SZ as one diagnostic category: experiments including participants with psychotic disorders such as delusional disorder, brief psychotic disorder or psychosis induced by medication could provide insights into mechanisms leading to specific symptoms, which could consecutively lead to a better understanding of the differences and similarities between diagnostic subtypes. This approach would require to focus on and evaluate single symptoms in detail and to investigate neurophysiological processes accompanying task performance as well as resting states and acute episodes with specific predominant symptoms. Thereby, neurophysiologic investigations on broader samples with psychotic symptoms could add to psychiatric and psychological diagnostics by providing evidence for neurophysiological differences as well as similarities between current diagnostic categories.

Finally, the present analyses of the EEG as well as MEG study focused on local power changes, which excludes coordinated brain activity. To detect changes in long-range communication between brain areas and to identify deficits in the functioning on the level of neuronal networks in SZ, investigations of coupling and connectivity would be necessary. The investigation of coordinated activity of distant brain regions involving networks rather than single cortical sites would yield valuable insights into deficits on the neuronal level in SZ. While a hyperactivity and hyperconnectivity of the default mode network has been shown in SZ using fMRI (Lavigne et al., 2014; Ma, Calhoun, Phlypo, & Adalı, 2014; Pomarol-Clotet, Salvador, et al., 2008; Whitfield-Gabrieli et al., 2009), analyses on the level of neuronal networks using methods with a high temporal resolution such as EEG and MEG are sparse (Andreou et al., 2014; Angelopoulos, Koutsoukos, Maillis, Papadimitriou, & Stefanis, 2014; Roiser et al., 2013).

7. Bibliography

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Erklärung nach § 9 Abs. 1, Nr. c der Promotionsordnung zur Doktorin/zum Doktor der Philosophie oder der Naturwissenschaften des Fachbereichs Psychologie der Universität Hamburg vom 03. Februar 2004

Hiermit erkläre ich, dass die von mir vorgelegte Dissertation nicht Gegenstand eines anderen Prüfungsverfahrens gewesen ist.

Hamburg, den 08. Mai 2014

Eidesstattliche Erklärung nach § 9 Abs. 1, Nr. d der Promotionsordnung zur Doktorin/zum Doktor der Philosophie oder der Naturwissenschaften des Fachbereichs Psychologie der Universität Hamburg vom 03. Februar 2004.

Hiermit erkläre ich an Eides statt, dass ich die vorliegende Arbeit selbständig und ohne fremde Hilfe verfasst habe. Andere als die angegebenen Quellen und Hilfsmittel habe ich nicht benutzt und die wörtlich oder inhaltlich übernommenen Stellen als solche kenntlich gemacht.

Hamburg, den 08. Mai 2014 _____