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Electrophysiological correlates of fearful face recognition in schizophrenia

PhD Thesis

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LIST OF ABBREVIATIONS

ACC	Anterior cingulate cortex
APA	American Psychiatric Association
CNTRICS	Cognitive Neuroscience for Treatment Research to Improve Cognition in Schizophrenia
CPZ	Chlorpromazine
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DLPFC	Dorsolateral prefrontal cortex
EEG	Electroencephalogram
EOG	Electrooculogram
ERD	Event-related desynchronization
ERS	Event-related synchronization
ERO	Event-related oscillation
ERSP	Event-related spectral perturbation
ERP	Event-related potential
FEEST	Facial Expressions of Emotion Stimuli and Tests
GFP	Global field power
GLM	General linear model
HLM	Hierarchical linear model
ISI	Inter-stimulus interval
ITC	Inter-trial coherence
MATRICS	NIMH-Measurement and Treatment Research to Improve Cognition in Schizophrenia
PANSS	Positive and Negative Symptom Scale
ROI	Region of interest
SD	Standard deviation
SCL-90	Symptom Checklist – 90
ToM	Theory of mind
VPP	Vertex positive potential
vMMN	Visual mismatch negativity

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1. INTRODUCTION

The focus of this dissertation, the investigation of the electrophysiological correlates of fearful face recognition impairments in schizophrenia can be best interpreted in the context of social cognition in schizophrenia, an area of research that has come to the attention of cognitive neuroscience research in the past decades. With the shift from positive symptoms as treatment targets to the more devastating negative and cognitive symptoms of the disorder, neuroscience research has adopted the framework of investigating these variables in their association to each other and to functional outcome measures, delineating potential pathways of impairments leading from basic neurocognition, to social cognition and clinical symptoms, and to functional outcome. Facial emotion recognition, as a key component of social cognition, can be placed within this framework. Our aim was to investigate the nature of facial emotion recognition impairment in schizophrenia at a neurophysiological level that would possibly render implications for broader levels of information-processing impairments in schizophrenia.

1.1. Social cognition in schizophrenia

Humans are a highly social species, adapted and attuned to a complex social environment. From an evolutionary perspective, our survival has depended on the refined social skills we have acquired to navigate through an intricate social world. Individuals with schizophrenia find themselves seriously disadvantaged in their social environment, unable to correctly read and respond to social signals, becoming vulnerable to social stress derived from their complex, social environments (Brune, 2001).

Social cognition refers to the mental operations underlying social interactions, which include processes involved in perceiving, interpreting, and generating responses to the intentions, dispositions, and behaviors of others (Brothers, 1996; Penn et al., 2008). It further involves „the ability to construct representations of the relation between oneself and others and to use those representations flexibly to guide social behavior" (Adolphs, 2002). Four primary domains of social cogniton have emerged in schizophrenia research: (1) emotion processing, (2) social perception, (3) theory of mind (ToM), and (4) attributional style (Green and Leitman, 2008; Penn et al., 2008). Emotion processing refers to the ability of identifying or discriminating emotional expressions by perceiving or scanning social details and scenes.

Social perception refers to the ability of perceiving or scanning social cues and using the context for forming a behavioral response. Theory of mind refers to the ability to represent the mental states of others or to make inferences about others' intentions; this includes understanding hints, false beliefs, irony, and metaphor. Attributional style refers to assigning causality (internal, personal, or situational) to events.

There is now evidence that patients with schizophrenia are impaired in each of these social cognitive domains and that these impairments are a hallmark feature of the illness (Green et al., 2012). However, as social cognition is a broad, multifaceted construct, measures of social cognition are varying, lacking a consensus in their methodology. One main question concerns the underlying structure of social cognition in schizophrenia. It has been a question of debate to what extent social cognition is empirically and neurobiologically separable from, but related to non-social neurocognition (Fett et al., 2011; Green and Leitman, 2008). It is not known whether the social cognitive assessments used in schizophrenia reflect a single factor or a cluster of separable factors. A recent study aimed to reveal the underlying factor structure of social cognition in patients with schizophrenia (Mancuso et al., 2011) through an exploratory factor analysis used variabled from a wide range of social cognition tasks. It revealed three dimensions of social cognition to be characteristic of people with schizophrenia, which were the following: (1) hostile attributional style, (2) lower-level social cue detection, and (3) higher-level inferential and regulatory processes. These factors exhibited distinct patterns of correlation with clinical features and functional outcome.
It is still debated whether the aforementioned impairments should be conceptualized as „deficits", in a quantitative manner, or rather as „biases", in a qualitative manner. The heterogeneity existing across the schizophrenia spectrum suggests that both deficits and biases may exist, and contribute to maladaptive social functioning (Tas et al., 2013).

The research on social cognition in schizophrenia can be regarded as a relatively new field that has come into scientific focus with the rapid advent of neuroscience. The need for the explanation of the complex symptomatology seen in schizophrenia has shifted from a classical clinical framework to an integrated neuroscientific framework based on the investigation of information-processing mechanisms. The aim has become to understand the anatomical and physiological structure and function of neural networks which underlie complex social cognition and behavior within the broader perspective of individual cognitive, emotional, and social development. After returning to Bleuler's core concept of schizophrenia

(Bleuler, 1911), who believed that schizophrenia „is characterized by a specific kind of alteration of thinking and feeling, and of the relations with the outer world that occur nowhere else" (Burns, 2006), schizophrenia has become the „arch" representative of social brain disorder. According to Bleuler, underneath the often obvious and varied symptoms, such as hallucinations and delusions, there existed a less obvious inner unity, which can be characterized by the four „A"s: ambivalence, autism, disturbance of association and affect. Modern neuroscience aims to explain these symptoms in a neurobiological framework involving social, cognitive, and affective processes, the impairment of which result in disturbed basic everyday functioning.

In sum, social cognitive research in schizophrenia has had two distinct goals: to understand the nature of specific clinical symptoms (e.g., relations to paranoia or thought control) and to understand social cognition's role in functional outcome.

Impairment in everyday functioning is profound in schizophrenia, even after successful treatment of clinical symptoms, especially positive psychotic symptoms. A recent literature review (Harvey and Strassnig, 2012) summarized evidence on the empirical association between schizophrenia and vocational disability and has corroborated the fact that patients with schizophrenia have significant impairment across multiple dimensions of functioning, and will typically remain impaired for the duration of normal working ages. Thus, the focus of attention in schizophrenia research and treatment has turned from positive symptoms towards the perhaps most devastating symptoms of the disorder: negative symptoms, and the loss of cognitive and social cognitive skills which result in the alienation of the individual from the social world.

1.1.2. Neurocognition, social cognition and the MATRICS initiative

As a result of the realization of the importance of neurocognition and social cognition in their close relation to functional outcome, NIMH-Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) (Green and Nuechterlein, 2004) initiative was launched by leading experts in schizophrenia research from academia, the National Institute of Mental Health and the pharmaceutical industry. The rationale of the committee was to identify target domains of neurocognition that have a translational potential and to establish a standardized test battery of the selected domains for clinical trials. The committee identified seven domains of cognitive impairment as target domains in schizophrenia: (1)

reasoning and problem solving; (2) processing speed; (3) attention and vigilance; (4) working memory; (5) verbal learning and memory; (6) visual learning and memory. Social cognition was identified as an additional seventh domain (Green et al., 2005; Nuechterlein et al., 2008).

Although the MATRICS committee regarded social cognition as a high priority area, as can be seen in its proportions to neurocognitive domains, its representation in the consensus test battery remained limited because of its inconsistent terminology and differences in the measures of social cognition, making direct comparisons of findings in the field more difficult. Thus, the MATRICS committee delineated three major areas to promote research in social cognition in schizophrenia (Green and Leitman, 2008): first, the agreement on the definition, measures and factors of social cognition; second, improving the interface between social cognition and cognitive neuroscience to identify neural substrates of social cognition performance in schizophrenia; and third, to develop animal models for social cognition.

The MATRICS initiative called general attention to the importance of neurocognitive and social cognitive deficits in schizophrenia and has led to the development and refinement of numerous neurocognitive test batteries assessing cognitive deficits in schizophrenia. Consequently, the MATRICS initiative facilitated studies and literature reviews investigating the exact nature of the relationships between neurocognition, social cognition, clinical symptoms, and functional outcome. Perhaps most importantly, it has also boosted research in the field of social cognition to further clarify its nature and make it a more methodologically approachable construct for further translational research.

1.1.3. Neurocognition, social cognition, clinical symptoms and functional outcome

The association between social cognition and general cognition or basic neurocognition in schizophrenia has been a question of debate, especially within the context of their relationship to domains of functional outcome. One key question in schizophrenia is the degree of overlap between the circuits that underlie deficits in basic cognition versus those that underlie deficits in social cognition. The question is also raised whether specific types of social cognitive functions arise through computational processes that are similar to those in basic cognition, even though different brain regions may be involved (Green et al., 2005). As ‘cognition’ is contained in the term social cognition, it seems obvious that the processing of socially

relevant stimuli relies on basic neurocognitive functions, such as attention, memory, and various other cognitive processes, yet research has shown that social cognition and neurocognition are largely distinct domains (Allen et al., 2007; Pinkham et al., 2003; Sergi et al., 2007; van Hooren et al., 2008).

It has been suggested that social cognition functions as a mediator between neurocognition and functional outcome (Addington et al., 2006; Brekke et al., 2005; Meyer and Kurtz, 2009; Sergi et al., 2007). Still, as social cognition explains additional variance in outcome that cannot be accounted for by neurocognition, it seems to be an independent predictor of functional outcome in itself (Brekke et al., 2005; Pinkham and Penn, 2006). Furthermore, some studies showed that social cognition may even exceed the predictive power of neurocognition and other symptoms of schizophrenia in explaining variance in functional outcome (Fett et al., 2011; Pijnenborg et al., 2009).

With regard to the role of clinical symptoms in their association to social cognition and functional outcomes, the literature provides a generally mixed picture on this relationship. The relationship of social cognition with positive symptoms (e.g.delusions, thought disorder, hallucinations) and negative symptoms (e.g. avolition, anhedonia, alogia, emotional withdrawal) has been inconsistent across studies. Negative symptoms were found to have the strongest relationship with neuro- and social-cognition (Milev et al., 2005; Ventura et al., 2011), however, recent modeling studies suggest that social cognition is separable from negative symptoms (Rassovsky et al., 2011; Sergi et al., 2007). Though there has been somewhat greater consistency in the associations between attributional style and paranoid delusions or beliefs (Bentall et al., 2001; Combs et al., 2009; Fornells-Ambrojo and Garety, 2009), relations to positive symptoms are similarly inconsistent (Shamay-Tsoory et al., 2007; Woodward et al., 2009). In a recent structural equation modeling study using a mediation model, Lin and colleagues (Lin et al., 2013) found that mainly negative symptoms mediated the influence of neurocognition and social cognition on functional outcome in schizophrenia. The authors posited that negative symptoms impair neuro- and social-cognitions possibly through lowered motivation to attend the tasks and in turn make an impact on functioning, or also that negative symptoms decrease the motivation to participate in social activities, which directly influences functional outcome.

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1.1.4. Impaired emotion perception in schizophrenia

Of the social cognition domains, emotion perception has been identified and studied the most frequently in schizophrenia. Even though on a subjective level patients with schizophrenia report experiencing as much positive and negative emotions as healthy controls and do not seem to have diminished hedonic capacity when providing "online" (e.g. in the moment) self-report in response to stimuli (Kring and Neale, 1996), they do report experiencing greater negative affect than controls when exposed to unpleasant, neutral, and pleasant stimuli (Cohen and Minor, 2010). This chronic elavation in negative mood, anhedonia, is commonly included in the negative symtoms of schizophrenia (Earnst and Kring, 1999), and since Kraepelin (Kraepelin, 1917) and Bleuler (Bleuler, 1911), anhedonia has been regarded as one of the core deficits in schizophrenia.

Recent research has suggested that the reduced capacity to experience positive emotions in schizophrenia might be due to emotion dysregulation mechanisms (Cohen and Minor, 2010; Horan et al., 2006; Strauss and Herbener, 2011). In experimental settings schizophrenia patients showed difficulty disengaging attention once it had been engaged by a salient unpleasant stimulus in an emotional stroop task (Strauss et al., 2008), indicating a difficulty for them in attenuating negative emotional states, resulting in chronic depression in mood and anhedonia. This might be related to the well-known „negativity bias", whereby patients show a strong inclination to misidentify neutral stimuli as negatively valenced (Kohler et al., 2003; Premkumar et al., 2008). Such inabilities to accurately identify emotional valence might be the basis for a bias to interpret situations in a negative light, and thus result in schizophrenia patients experiencing relatively more negative emotions than healthy controls. In sum, research suggests that emotional abnormalities seen in schizophrenia may primarily relate to dysfunctions in negative emotion processing.

A number of studies have investigated the emotion perception deficit in schizophrenia using diverse methodological, clinical, and demographic variables. A meta-analysis (Kohler et al., 2010) of behavioral indices of emotion perception in schizophrenia has shown a large effect size (d=0.91) for emotion perception impairment in patients with schizophrenia as compared to healthy controls, despite heterogeneous moderating effects of illness-related and

demographic factors. They concluded that deficits in emotion perception in schizophrenia are an intrinsic and stable aspect of the illness.

A more recent meta-analysis (Irani et al., 2012) aimed to clarify the strength of the effect between emotion perception and functional outcomes. Their results corroborated a significant relationship between emotion perception and functional outcome in individuals with schizophrenia with effect sizes in the medium range. These results also support the notion that studying social cognitive processes such as emotion processing in schizophrenia is promising to provide: (1) a greater understanding of the key mechanisms that might influence the clinical presentation and functional outcome, (2) the identification of endophenotypic markers for genetic research in the vulnerability to schizophrenia, and (3) the delivery of remediating therapies.

1.1.5. Facial emotion recognition in schizophrenia

Within emotion perception, the domain of facial emotion recognition has gained considerable interest, although emotion recognition impairments in the auditory domain have also been extensively studied (Leitman et al., 2010).

Facial emotion recognition can be considered as a main building block of social cognitive abilities. Understanding and expressing facial emotions in nonverbal communication is a key component of interpersonal adaptation. According to Darwin: “The interpretation and expression of affect is fundamental to human experience” (Darwin, 1872). Faces constitute social signals that are granted attentional priority, and this preference is expressed early in life, with infants preferentially attending to face-like stimuli rather than to scrambled or inverted faces (Gliga and Csibra, 2009; Rosa et al., 2011). Through the scanning of other people’s faces, the social world summons our attention like no other domain: social signals are prioritized by attention, social interactions are intrinsically rewarding, and the maintaining of social relations permeates interpersonal behaviors, fosters collaboration. People are typically the most goal-relevant stimuli in our lives.

The robustness of the impairment of facial affect recognition in schizophrenia has been confirmed in studies which showed that the impairment is stable across the time course of the illness, independent of the clinically effective treatment (Addington and Addington, 1998; Wolwer et al., 1996a), and is observable in individuals at-risk for schizophrenia (Wolwer et al., 2011) as well as in unaffected biological relatives of patients (Bediou et al., 2007).

In order to interpret the neural underpinnings of facial emotion recognition deficit in schizophrenia, I will present a model by Ochsner (Ochsner, 2008) integrating social, cognitive and affective processes in which the ability of facial emotion recognition can be embedded. The model is regarded only as a broader theoretical framework for the clearer positioning of facial emotion recognition within the social-affective information processing stream, rather than as a specific model from which our electrophysiological hypotheses were derived from.

1.2. The social-emotional processing stream (Ochsner, 2008)

The neural circuitry underlying social cognition is a complex, interrelated neural network, including both cognitive and emotional processing systems. The diverse methods and approaches used in this new field make it difficult to put the disparate pieces of data together to fit into core neurofunctional constructs.

The theoretical framework by Ochsner identifies a set of psychological and neural processes that encode socially and emotionally relevant inputs and guide socially adequate responses. The model enumerates social cognitive and affective abilities grouped into five hierarchically distinct lower-level and higher-level core constructs that are valid and reliable entities in so far as they are suggested to have distinct but related neural correlates. As depicted in **Figure 1**, these lie along a hierarchy of information processing stages engaged when we initially learn the value of a stimulus (Construct 1), subsequently re-encounter it and recognize its value (Construct 2), understand the feelings and beliefs of a person by relating to his/her mental states in an experiential, bottom-up way (Construct 3), and also in a top-down manner attributing intentions and making inferences (Construct 4), and finally trying to regulate responses to a given stimulus appropriate within the context (Construct 5).

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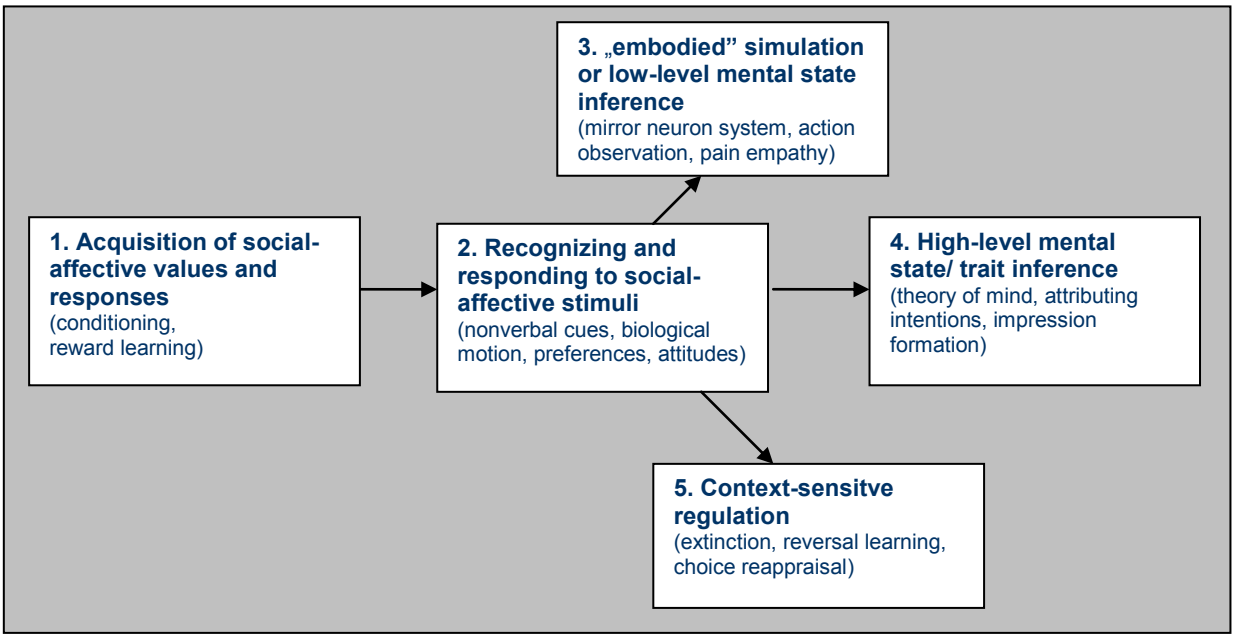

Figure 1: Diagrammatic illustration of the relationship between five proposed core constructs for social and emotional behavior. (From: Ochsner: The social-emotional processing stream: Five core constructs and their translational potential for schizophrenia and beyond. Biological Psychiatry, 2008; 64: 48-61.)

Regarding **Construct 1**, the basic need to learn which stimuli and actions lead to aversive as opposed to appetitive outcomes is mainly mediated through the amygdala. The neural constructs most strongly implicated in affective learning and conditioning are the amygdalae and the striatum, evolutionary old subcortical constructs that receive multi-modal perceptual inputs and also are highly connected to higher-level cortical regions (Holland and Gallagher, 1999). It has been well established that the amygdala is critical for acquiring conditioned fear responses to social stimuli, such as faces or facial expressions of fear and anger (Morris et al., 1998; Morris and Dolan, 2004). The ventral striatum has also been shown to play a crucial role for learning which stimuli or behavioral responses predict rewarding or reinforcing outcomes (Schultz, 2004). Representation of the affective valence of a stimulus is possible via projections from the amygdala and the striatum to the orbitofrontal and ventral medial prefrontal cortex-(Rolls, 2000).

In **Construct 2**, the amygdala not only plays a crucial role in learning the affective valence of stimuli, but also in the recognition of stimuli that directly or indirectly signal the presence of a potential threat, such as fearful facial expressions and the widened eyes that uniquely

characterize them (Adolphs et al., 2005). In a broader conceptualization the amygdala is regarded as a "surveillance" system that continuously monitors the environment for affectively salient stimuli and modulates activity in perceptual and memory systems to detect and encode them (Phelps, 2006; Whalen et al., 1998). Thus, facial emotion recognition would be part of Construct 2, faces being the most relevant social-affective stimuli. Another region shown to be important in negative affective experience is the insula, a cortical region connecting the temporal and frontal lobes (Craig, 2004; Critchley et al., 2005). The superior temporal sulcus has also been shown to play an important role in the recognition of social/affective values, especially in recognizing nonverbal social cues, such as faces and biological motion (Allison et al., 2000).

Within this socio-emotional processing stream framework, one step higher in the processing hierarchy, in **Construct 3**, are the lower-level mentalization processes. Based on these, **Construct 4** entails higher-level mentalization processes. Beyond simple recognition judgments of affective values of stimuli, the meanings of the value of the stimuli are embodied in our experience of it. In fact, all of our experiences are embodied in our physical reality, and not just our own first-person experiences, but these are used to help us vicariously understand the experience of others as well as abstract concepts (Barsalou et al., 2003; Gallese and Lakoff, 2005).

The stimulus-driven activation of shared representations establishes the direct experiential properties of a stimulus (such as perceptual, motor, visceral, or affective), but the activation of higher-level symbolic, abstract, semantic, or categorical representations are needed to be able to interpret the given experience in a given context. Social stimuli are often ambiguous and can be interpreted only if higher-level representations of mental states are activated that take into account the situational /contextual information of the stimulus. Perhaps the most studied faculty of higher-order representations has been the theory of mind. False belief tasks assess the human capacity to understand and explain other peoples' behaviour in terms of internal mental states, such as their beliefs, desires, feelings, and goals. Studies using this task have shown active regions in the brain such as dorsal and rostral medial prefrontal cortex, the posterior cingulate precuneus, temporal parietal junction, superior temporal sulcus, and the temporal pole, sometimes referred to as the "mentalizing network" (Gallagher and Frith, 2003). Furthermore, some of the regions of the medial prefrontal cortex that are implicated in

mental state inference of others have also been implicated in accessing and making judgments about one's own mental states (Ochsner et al., 2005).

The final stage in the social-emotional stream, as described by **Construct 5**, concerns the ability to regulate one's judgments and behavior toward others in a context-appropriate manner. These higher-level processes entail cognitive control: the use of language, memory, and selective attention, to reinterpret or reappraise the meaning of social-emotional stimuli (Ochsner and Gross, 2005). Brain areas involved in cognitive control are the dorsal and lateral prefrontal regions, as well as medial prefrontal regions. Activity in these control systems modulates activity in regions involved in emotion responding, such as the amygdalae or insula.

This above depicted model of the socio-emotional processing stream was proposed to serve as a simplified framework for organizing research on the neural bases of human social cognitive and emotional behaviour and to clarify constructs potentially underlying social cognition and emotion. It also provides a basic context for translational research, as it enables its application to clinical populations to help elucidate potential mechanisms of dysfunction. In the case of schizophrenia, substantial research aims to pin down the neural correlates of the various forms of emotional dysfunction, such as emotion recognition. In the following, a short overview on the impairments of the neural bases of emotion processing in schizophrenia will be given.

1.3. Structural and functional impairments related to facial emotion processing in schizophrenia

Literature on neurobiological impairments in emotion processing in schizophrenia has become abundant, but often inconsistent. Interpretation has been hampered by a range of dissimilar experimental designs and clinical patient samples recruited in the studies. In the following I will present some of the main findings in schizophrenia on the most important neural structures involved in emotion processing, with a main focus on facial emotion processing.

The amygdala, as mentioned earlier, has been shown to play a prominent role in emotion perception. According to a long-held view the vital role of the amygdala has been shown in

fear conditioning in rodents, primates and humans (Salzman and Fusi, 2010). However, a recent meta-analysis (Ball et al., 2009) and contemporary reviews hold that amygdala activation is related to both arousal and intensity, regardless of positive or negative emotional valence (Adolphs, 2010; Pessoa and Adolphs, 2010). Thus, a shift can be seen in conceptualizing the amygdala as simply a fear or threat 'processing' module toward the position that amygdala is also tracking stimulus intensity and deals with motivational salience (Adolphs, 2010). Because of its anatomical position and its strong interconnection with other crucial brain areas involved in emotion processing, the amygdala serves as an affective hub of information (Mende-Siedlecki et al., 2013).

Structural imaging suggests that patients with schizophrenia have smaller amygdala volumes than healthy controls (Namiki et al., 2007) and functional imaging data record abnormalities of amygdala activation during emotion processing in schizophrenia. Studies indicate that, compared with healthy controls, patients with schizophrenia and their nonpsychotic siblings fail to activate bilateral amygdala regions during induction of sad mood (Habel et al., 2004). Lower bilateral amygdala activation in patients relative to healthy controls has been reported during a facial identification task (Hempel et al., 2003) and in an emotional valence and facial discrimination task (Gur et al., 2002; Johnston et al., 2005). However, findings relating to amygdala activation in schizophrenia have not always been consistent. There seem to be conflicting results regarding reduced left (Gur et al., 2002) or right (Johnston et al., 2005) amygdala activation in emotion perception tasks. Moreover, several studies have reported enhanced activity in the amygdala in schizophrenia during the presentation of facial emotional expressions (Holt et al., 2006; Kosaka et al., 2002).

Amygdala dysfunction has been investigated as part of a distributed interactive system of the whole brain. Sepcifically, some studies investigated amygdala signals in their functional connectivity to other brain regions, such as the fronto-parietal network. Results with schizophrenia patients showed that patients display significantly weaker amygdala-prefrontal cortical coupling, specifically during negative emotional distraction (Anticevic et al., 2012). Furthermore, a functional connectivity study with healthy subjects has shown a decreased connectivity between the amygdala and the facial areas in those participants who were more vigilant for threatening facial features, interpreting weaker connectivity of the amygdala with facial areas as representing social withdrawal (Miyahara et al., 2013). Some authors interpret these findings as evidence for impaired emotional regulatory processes in schizophrenia,

which may reflect an impaired capacity to downregulate amygdala responses (Modinos et al., 2010).

In a recent meta-analysis on functional neuroimaging data Li and colleagues (Li et al., 2012) concluded that “a marked underrecruitment of the amygdala, accompanied by a substantial reduction in activation throughout a ventral temporal-basal ganglia-prefrontal cortex “social brain” system may be central to the difficulties patients experience when processing facial emotion”.

The hippocampus, as a "memory-storage" for the brain, could be involved in emotion processing in that it could provide a resource for referencing and placing emotions in the context of previous experiences. Most of the studies reported an underactivation of the hippocampus in schizophrenia patients in facial emotion perception tasks (Takahashi et al., 2004; Williams et al., 2004). However, some studies found increased hippocampus activation in non-paranoid patients (Russell et al., 2007).

The fusiform gyrus is considered to be one of the most specific areas of face recognition in the brain (McCarthy et al., 1997). However, findings show inconsistencies in the involvement of this area in face recognition in schizophrenia. When patients performed a facial emotion discrimination and identification task, their bilateral fusiform gyri were not activated, while the controls showed the expected activation in response to faces in right lateral fusiform gyrus (Quintana et al., 2003). Moreover, underactivation in the right fusiform region was found in patients during remission (Johnston et al., 2005). Greater activation in schizophrenia has been observed in bilateral fusiform gyri during the presentation of neutral faces (Surguladze et al., 2006).

Findings seem to be more consistent in the decreased involvement of the cortical areas in facial emotion perception in schizophrenia. The orbitofrontal cortex forms an interface between emotion and cognition (Rolls, 2000), and, together with the middle temporal lobe, precuneus, and posterior cingulate, is implicated in empathy and in making social judgments (Farrow et al., 2001). In addition, the medial prefrontal cortex facilitates the understanding of the mental state of others, or, as has been referred to earlier, serves as the center for theory of mind. Some researchers have reported hypoactivations in schizophrenia patients in the orbitofrontal cortex during facial emotion perception (Reske et al., 2007), while others

observed reduced activation in the medial prefrontal cortex when viewing negative emotional stimuli (Takahashi et al., 2004; Williams et al., 2007). These results are consitent with the general notion of a frontal hypoactivation in schizophrenia (Johnston et al., 2005).

Regarding structural and functional abnormalities in schizophrenia it is important to take into account the fact that schizophrenia is a neurodevelopmental disorder, and several impairments of the nervous system shown to be associated with emotion processing in schizophrenia are related to the maturation of the brain in late adolescence. The connections between the various subcortical regions and the prefrontal cortex and molecular changes within the prefrontal cortex itself also appear to undergo substantial change during adolescence (Weickert et al., 2007). It has been hypothesized that testosterone in adolescence may affect the ability to respond appropriately to emotional faces (Richards et al., unpublished data). If this is correct, then the deficit in emotional face recognition among patients with schizophrenia may emerge shortly after puberty, as the prefrontal cortex and its connections with the amygdala may fail to mature normally (Morris et al., 2009).

1.4. Impaired visual integration of faces in schizophrenia

After having reviewed some of the main impairments in brain structures and their connectivities in schizophrenia related to facial emotion processing, some behavioral evidence will be reviewed on the level of impairment of basic visual perception potentially leading to impaired facial emotion recognition in schizophrenia.

Several studies have explored facial scanning, scanpath patterns and gaze impairment in schizophrenia (Itier and Batty, 2009; Morris et al., 2009). Impairment in eye movements while viewing facial images has been long reported in schizophrenia (Manor et al., 1999). Examination of patterns of eye fixation to high resolution pictures of human faces versus nonbiological stimuli showed that subjects with schizophrenia exhibit reduced scanpath lengths, shorter saccades, more time spent ‘gazing’, and a tendency toward fewer fixations for the face stimulus (Kosmidis et al., 2007). Thus, disturbed spatial and temporal patterns of eye movement in some people with schizophrenia may reflect sub-optimal processing of face stimuli.

Other visual scanpath studies of face processing in schizophrenia showed that schizophrenic patients did not concentrate their fixations on salient features of faces, such as eyes (Williams et al., 1999). Evidence indicates that the eye region of faces is used to discriminate fear from other expressions (Adolphs, 2008). It has been shown that the eye region of fearful faces is processed faster and earlier in healthy adults than other regions, and is sufficient to explain the effect of fearful faces in a preconscious processing task (Yang et al., 2007). As patients with schizophrenia have a particular deficit in attending to the eyes, it would be expected that patients have a greater deficit in recognizing fear. Kohler and colleagues (Kohler et al., 2003) using low-and high-intensity images found that patients were more impaired than healthy controls in identifying easier high-intensity expressions, and this difference was most pronounced when recognizing fear. Thus, although patients with schizophrenia are impaired in overall emotion recognition, they appear particularly impaired in recognizing fear, regardless of task difficulty.

Studies investigating the direction of gaze as a referential point in schizophrenia (Hooker and Park, 2005) have shown that schizophrenia patients are as accurate as healthy control subjects at identifying direct gaze when it occurs, but they are more likely to misinterpret averted gaze as directed at them. Results suggested that this tendency to endorse direct gaze was not a consequence of a perceptual deficit in judging angular displacement. Schizophrenia patients seem to have a self-referential bias in judging the direction of gaze that could lead to the misinterpretation of another person's intentions during the course of social interactions.

Altogether, findings suggest that emotion perception deficits in schizophrenia patients may reflect a failure to integrate salient features of a face due to dysfunctions in local processing of detailed, relevant information, and in the networks that synchronize local and global processing of biologically relevant face stimuli. Furthermore, some researchers have suggested that abnormalities in visual scanpaths could be emerging as a novel candidate for a schizophrenia biomarker, as evidence has shown that viewing behaviors in schizophrenia remain atypical regardless of symptom remission and may be present in unaffected relatives of individuals with schizophrenia (Beedie et al., 2011).

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1.5. Emotion and cognition

The investigation of the neural underpinnings of facial emotion processing inevitably raises the classical neuropsychological question of the interaction between affective and cognitive processes, as this area of research lies at the interface of the two. Faces are not only a subcategory of objects, as they not only provide distinctive information about a person's identity, gender, or age, but also convey more subtle signals related to emotion, trustworthiness, attractiveness, or intention of other people. However, little is known about how these various dimensions are coded, through what processes, and how they are integrated into a single face percept reflecting an emotional state.

Traditionally, neuroscientists have described cognition and emotion as separable processes implemented by different regions of the brain, such as the amygdala for emotion and the prefrontal cortex for cognition. On the one hand, emotional processes can influence cognitive processes (in a bottom-up manner); on the other hand, cognitive processes can regulate or modify our emotions (in a top-down manner). However, neurons in these structures often have overalapping representations, whereby single neurons encode multiple cognitive and emotional variables. Current research suggests that these neural stuructures are inextricably linked and represented in dynamic neural networks composed of interconnected prefrontal and limbic brain structures. Recent studies suggest that both the functional and the electrophysiological characteristics of the amygdala and the prefrontal cortex overlap. They intimately depend on each other, mediating cognitive, emotional, physiological, and behavioral responses that are closely linked (Salzman and Fusi, 2010). However, the question remains what the role of these interacting pathways might be in the case of emotionally laden stimulus processing.

1.5.1. Emotional attention

Enhanced sensory processing of emotional stimuli, also termed "emotional attention" (Pourtois et al., 2005), has been consistently demonstrated in at least two functional properties of brain activity: (1) the amplitude of neural responses to emotional relative to neutral stimuli is consistently enhanced in several areas along sensory pathways, including both specific (e.g. category-specific) and non-specific (e.g. early sensory cortex) regions (Lindquist et al., 2012), and (2) the time-course of emotion effects suggests a distinctive spatio-temporal dynamic as

compared with other attentional modulations (e.g. in fronto-parietal areas), with relatively early responses observed in some limbic regions, such as the amygdala (Luo et al., 2010; Pourtois et al., 2010) or orbitofrontal cortex (Pourtois et al., 2013). These findings suggest that this boosting of sensory processing by emotion reflects increased processing efficiency for emotionally salient events (Vuilleumier et al., 2002; Vuilleumier, 2005), which may beneficially enhance attention towards them, and may also play a role in the more efficient encoding and subsequent consolidation in memory of emotional events (LaBar and Cabeza, 2006).

A central question about these bottom-up or top-down effects concerns which brain mechanisms are responsible for the preferential selection of emotionally salient stimuli in the environment. There is abundant evidence that visual inputs propagate rapidly throughout the brain and reach high-level cortical regions in the range of 120 ms post-stimulus onset (Bar et al., 2006; Kawasaki et al., 2001) allowing quick perceptual categorization and motor decision processes to be performed in less than 150 ms (Thorpe et al., 1996), that is, before the typical latency associated with voluntary attention control (Hillyard and Anllo-Vento, 1998). Thus, the question arises: Is the perception of emotion-laden stimuli "automatic"? This question has received considerable interest because specific answers ("yes" or "no") suggest potentially different relationships between emotion and cognition (less or more independence between the two, respectively). Evidence both for and against automaticity have been presented (Pessoa and Adolphs, 2010).

1.5.2. Emotional "automaticity"

One of the most influential theories of rapid emotion effects was based on animal work (LeDoux, 1996; Shi and Davis, 2001) and observations in human patients with blindsight after damage of the primary visual sensory area (Anders et al., 2004; Pegna et al., 2005) which showed that some emotional responses in amygdala and conditioning may still arise for visual stimuli despite damage to cortical relays. Thus, it has been hypothesized that sensory inputs might reach the amygdala through subcortical pathways that bypass cortical processing, through a subcortical "quick and dirty" route via the superior colliculus and pulvinar (Tamietto and de Gelder, 2010). Neuroimaging results also showed activation in these two regions during unconscious processing of emotional stimuli (Liddell et al., 2005;

Morris et al., 1998). Also, emotional faces evoke responses in the amygdala when attention is diverted to other stimuli (Anderson et al., 2003; Vuilleumier and Schwartz, 2001). These and many related findings suggest that at least some types of emotional perception occur outside of top-down directed attention.

Other findings have suggested, however, that the perception of emotion-laden items requires attention, as revealed by attentional manipulations that were designed to more strongly consume processing resources, leaving relatively few for the processing of unattended emotional items (Lim et al., 2008; Pessoa et al., 2002).

As an alternative explanation to the subcortical route, most recent intracranial and MEG results converge to suggest a two-stage model of emotional attention and interaction with task relevance (Pourtois et al., 2013). First, the amygdala appears to guide an early (120–140 ms) discrimination between emotional (threat-related) and neutral stimuli even when visual stimuli are weak because they are task-irrelevant (Luo et al., 2010) or outside the current focus of attention (Pourtois et al., 2010). This early effect may take place in parallel to simultenaously with stimulus categorization in the visual cortex, and rely on an initial feedforward sweep of inputs throughout the visual pathways. Second, this early emotion response in the amygdala can trigger an increase of the neural response in the visual cortex (Pourtois et al., 2010; Vuilleumier and Schwartz, 2001), via both direct and indirect pathways projecting back to the cortex (Amaral et al., 2003; Vuilleumier, 2005). This boosting may thus increase processing efficiency and competitive biases for emotional relative to neutral stimuli, resembling an attention gain control effect that may add or combine with other modulatory influences.

Referring to the „automaticity" of the processing of emotional stimuli, Pourtois and colleagues (Pourtois et al., 2013) have proposed that emotional stimuli are "special" only to the extent that they have the propensity to engage dedicated neuronal systems relative to neutral stimuli, which are in turn capable of rapidly influencing perceptual or attentional systems, or both, such that these stimuli may gain additional "weight" in the competition for awareness (Armony and Dolan, 2002; Pourtois et al., 2005). The authors argue that emotional stimuli do not necessarily undergo a privileged route that neutral stimuli would not recruit. Whereas some neural responses and their subsequent impact on sensory processing might be unique to emotionally significant stimuli, their perceptual analysis is likely to be similar to

emotionally neutral stimuli. In sum, a number of results from neuropsychological studies in brain-damaged patients (see Tamietto and de Gelder, 2010; Vuilleumier and Schwartz, 2001; Williams and Mattingley, 2004), as well as fMRI (Morris et al., 1998; Whalen et al., 1998), ERP (Liddell et al., 2005; Williams et al., 2004) and MEG studies (Bayle et al., 2009) in healthy participants indicate that emotional information is processed (at least to some extent and under certain circumstances) regardless of voluntary top–down attention and even without conscious awareness. Unconscious processing by itself is not necessarily specific to emotional stimuli, since substantial processing of complex, non-emotional information can also take place without conscious awareness and still recruit the corresponding specialized processing pathways (Kouider and Dehaene, 2007; Righart et al., 2011). What is particular to the case of emotion processing is that neural substrates engaged without awareness or attention may include additional structures, relative to neutral stimuli, including the amygdala, which have direct ouputs to influence sensory processing as well as many other brain systems controlling perception and behavior.

The question of emotional attention can be related to psychopathologies seen in mental illnesses through the effects of the disruption of the emotional attention system. This system might be either amplified or attenuated by top–down modulations from higher-order frontal regions involved in emotion regulation processes, such as functional alterations within prefrontal-amygdalar regulatory circuits. In schizophrenia, for example, impairment in these regulatory processes might be associated with different psychopathological conditions which might increase vulnerability to and maintenance of anxiety and negative affect (Bishop et al., 2004; Bishop et al., 2007; Bishop, 2007). Such disruptions might also manifest through changes in the “firing threshold” settings of the amygdala circuitry itself. This could account for attention selection biases towards negative stimuli typically observed in some psychopathological conditions, such as general anxiety or depression (Bar-Haim et al., 2007; Bishop et al., 2007; De Raedt and Koster, 2010). Alternatively, emotional attention could be exacerbated due to purely intrinsic changes in amygdala and hyper-reactivity of the sensory feedback loops (Pourtois et al., 2013).

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1.6. Electrophysiological correlates of facial emotion recognition

Electrophysiological measures allow us to gain insight into the neuronal-scale brain avtivity underpinning complex processes such as facial emotion recognition. Scalp EEG signals are produced by partial synchronization of neuronal-scale field potentials across areas of cortex of centimetre-squared scale. Although once viewed as a form of brain 'noise', it appears increasingly probable that this synchronization optimizes relations between spike-mediated 'top-down' and 'bottom-up' communication, both within and between brain areas. This optimization might have particular importance during motivated anticipation of, and attention to, meaningful events and associations and in the response to their anticipated consequences (Fries et al., 2001; von Stein and Sarnthein, 2000). Analysis of event-related EEG data has traditionally been proceeded in one of two directions. In the time-domain approach, a set of single trials or epochs time-locked to a certain class of events/stimuli are averaged, yielding an event-related potential (ERP) waveform at each recording site. The frequency-domain approach averages changes in the frequency power spectrum of the EEG epoch that are time-locked to (i.e., following) the same events, producing a two-dimensional representation (i.e., time and frequency) that is called the event-related spectral perturbation (ERSP). Both analysis approaches of electrophysiological data can be used to disentangle neuronal processes during facial emotion recognition tasks. In the following we present a theoretical background of both approaches, as both were used in our two studies.

1.6.1. ERP correlates of facial emotion recognition

Use of ERP paradigms to investigate neural activity during emotion processing has become a major approach in cognitive-affective neuroscience, since this method captures the exact time course of the emotional information-processing cascade from early to later processing stages with a millisecond-resolution (Luck et al., 2011). In their seminal work on ERP correlates of emotional face processing Eimer and Holmes (Eimer and Holmes, 2002) reported an earlier component about 120ms post stimulus that can distinguish fearful from neutral faces suggesting that processing of facial emotions begins before face identification. Thus, they

identified two distinct stages of facial emotion processing. These include an early initial stage represented by a frontocentrally distributed positivity indexing an initial rapid detection of emotionally significant stimuli; and a later, sustained, and more broadly distributed positivity for fearful faces beyond 250ms post-stimulus reflecting subsequent higher-level, attentional processes, such as the conscious evaluation of emotional content. The authors claim that although selective brain responses to emotional faces are triggered at very short latencies, they are strongly dependent on attention.

The majority of ERP studies on facial affect recognition in schizophrenia have been based on investigating the temporal cascade of information processing, pinpointing salient components of ERPs thought to be related to distinct stages of facial emotion recognition and comparing their amplitude to those produced by healthy controls. These stages of facial emotion recognition are indexed by the following ERP components:

A positive potential about 100 ms post-stimulus, the P100, is recorded at occipital electrodes and is believed to reflect early sensory processing of visual stimuli. As this is considered the earliest component in the information processing stream of faces, it is viewed as a mere sensory component reflecting early visual object recognition that is non-face-specific (Yeap et al., 2006).

The simple perception of a face elicits a negative waveform that peaks approximately around 150-180ms post-stimulus, the N170, and is observed at occipitotemporal sites, reflecting early perceptual processes of structural encoding of the face (Eimer, 2000a; Eimer, 2000b). This is thought to be the first face-secific component and is thought to arise primarily from the fusiform gyrus and can be readily distinguished from the perceptual ERP response to other classes of stimuli (Herrmann et al., 2004b). Thus, it is regarded as the ERP component of "faceness", independent of emotion or identity. In addition, the N170 component has been reported to be lateralized, suggesting a right-lateralized topography for face stimuli (Herrmann et al., 2004b).

Emotion effects at early phases of emotion processing, especially those of negative stimuli, have been reported at around 120ms post-stimulus, possibly reflecting rapid emotion processing based on crude visual cues in faces (Horan et al., 2010a; Luo et al., 2010; Stefanics et al., 2012; Vuilleumier and Pourtois, 2007).

The role of emotional valence in later, "middle-range" components such as the face-specific N170 or the vertex positive potential (VPP) component – occurring within a time range between 150-200ms post-stimulus - is not sufficiently clear. While some studies support the notion that the N170 is not modulated by emotional content (Eimer et al., 2003), or that it is sensitive only to fearful expressions (Blau et al., 2007; Pourtois et al., 2005), other studies found that the N170 and VPP are affected by both pleasant and unpleasant emotional expressions, as compared to neutral ones (Luo et al., 2010; Stefanics et al., 2012; Williams et al., 2006).

Later components -including the N300, P300, and a sustained P300-like component, the late positive potential (LPP) - have been regarded as classical indices of attention-dependent processing, reflecting a later evaluation of information (Polich, 2007). P300 potentials are conceptualized to represent a neurophysiological correlate of voluntary resource allocation during updating of working memory in an environmental context (e.g. (Donchin and Coles, 1988). They have also been shown to be related to the affective valence of stimuli, and as such can be regarded as indices of emotional attention. Studies have shown that emotional stimuli elicit larger P300 amplitudes compared to neutral ones (Campanella et al., 2002; Miltner et al., 2005; Schutter et al., 2004) with some studies specifying this effect only to fearful stimuli (Williams et al., 2006), suggesting that signals of danger enhance ongoing stimulus evaluation. As apparent from Hajcak and Olvet's study (Hajcak and Olvet, 2008), even later processing stages are significantly affected by emotional valence: neural activity indexing increased attention, such as the LPP, might persist 800-1000ms after stimulus presentation.

1.6.1.2. ERP deviations of facial emotion recognition in schizophrenia

ERP studies of emotion recognition paradigms with schizophrenia patients yielded controversial results as to where and when abnormal activation patterns occur in the course of emotion processing as compared to healthy controls. Deficits in both early and late ERP components of facial emotion processing have been found.

Deficits in the earliest components, such as the P100 (Wolwer et al., 2012) suggest a deficit in early sensory and perceptual processing.

The face-specific N170 has been one of the most researched ERPs in face processing paradigms in schizophrenia. N170 deficits have been found more pronounced over the right scalp (Herrmann et al., 2004b). Deficit in the N170 (Turetsky et al., 2007; Wynn et al., 2008) in face vs. non-face discrimination tasks suggests a dysfunction in face-selective visual processing capacities. Johnston and colleagues (Johnston et al., 2005) reported that schizophrenia patients manifested lower VPP, that represents an anterior counterpart of the N170 early encoding stage of facial processing, and that it was correlated to subsequent P3 amplitude reduction.

Regarding later components, deficits in the N250 (Wynn et al., 2008) suggest a disturbance in later evaluative affect-recognition processes; and in the P300 (Turetsky et al., 2007), they indicate disturbed higher-order cognitive processes associating the structural representation of a face with its affective and contextual information.

Alterations in activation patterns at different processing stages have led to the question where in the time course of emotional information processing the effect of emotions enters and modifies the information processing cascade. The variability of findings has given room for interpreting results as supporting both a bottom-up, initial sensory-encoding-deficit-view (Turetsky et al., 2007), and also a later, top-down contextual-attention deficit view (Horan et al., 2010a). Accordingly, these diverse results among patients with schizophrenia and their interpretations necessitate further research into the neurobiological basis of emotion processing.

1.6.1.3. Topographical distribution: Hypofrontality in schizophrenia

The notion of hypofrontality in schizophrenia has been supported by numerous reports of prefrontal dysfunction in schizophrenia, beginning with the pioneering regional cerebral blood flow study of Ingvar and Franzén (Ingvar and Franzen, 1974) in chronic schizophrenic patients and confirmed with PET by Buchsbaum and colleagues (Buchsbaum et al., 1984). Based on PET and fMRI studies with sensory and cognitive processing paradigms, a pattern of hypofrontality in schizophrenia has consistently been shown (Buchsbaum, 1995; Buchsbaum and Hazlett, 1998), according to which patients with schizophrenia show a lower

frontal-occipital activation ratio than healthy controls. This may be a powerful explanation for characterizing a pattern of brain organization involving a relationship between the executive functions in the frontal lobes and sensory processing in the occipital lobes. In an oversimplified model, the pattern of hypofrontal and hyperoccipital function matches the deficits in planning and organization and the excessive sensory elaboration seen in schizophrenia (Buchsbaum, 1990). However, despite the many reports of a diminished frontal lobe function in schizophrenia, the concept of hypofrontality has been questioned, for example by Gur et al. (Gur and Gur, 1995), who found no resting state metabolic abnormalities in schizophrenia patients as compared to matched healthy controls. Lower activation of frontal regions has been shown mainly in cognitive paradigms tapping on executive tasks including memory and attention functions. However, the underrecruitment of frontal functions in emotion processing paradigms has been less obvious. Lower frontal activation in networks important for the appraisal and identification of positive and negative emotional stimuli and production of affective states may result in a restriction of the range of positive and negative emotions identifiable. Hypoactivation of frontal circuits may also be associated with a misinterpretation of nonthreatening and ambiguous stimuli as threatening and also resulting in impairments in reasoning, contextual processing, and effortful regulation of affective states (Phillips, 2003).

1.6.1.4. Emotion-related visual mismatch responses in schizophrenia

Most of the studies investigating facial emotion perception impairment in schizophrenia used paradigms where facial emotions were in the focus of visual attention. Although in real-life situations our attention is mostly engaged by events appearing in the center of the visual field, important events, such as emotionally relevant stimuli, may emerge at the periphery. Behavioral priming studies also confirmed that affective processing may occur outside of the focus of visual attention (Calvo and Avero, 2008; Calvo and Nummenmaa, 2007; Calvo et al., 2006). Thus, besides research on conscious emotion processing mechanisms, the processing of unattended emotional stimuli also constitutes a significant part of social cognitive abilities in schizophrenia.

The visual mismatch negativity (vMMN) component of the event-related potentials is the visual counterpart of the auditory mismatch negativity (MMN: for review see (Naatanen et al., 2007)). The auditory MMN has been widely studied in schizophrenia, and reports usually

indicate impaired automatic auditory processing (Umbricht and Krljes, 2005). Both the auditory MMN and vMMN signals are typically elicited by stimuli with an infrequent (deviant) stimulus feature embedded in a stream of frequent (standard) stimuli. A vMMN response is elicited by deviant color (Czigler et al., 2002), orientation (Astikainen et al., 2004), movement (Pazo-Alvarez et al., 2004), spatial frequency (Sulykos and Czigler, 2011), contrast (Stagg et al., 2004), and even abstract sequential regularities of visual stimulation (Stefanics and Czigler, 2012), see (Czigler et al., 2007; Czigler and Sulykos, 2010; Kimura, 2011) for reviews). Mismatch responses are considered as automatic prediction error signals (Friston, 2010) representing the updating of generative models of environmental regularities after the violation of the model's prediction by a deviant stimulus (Stephan et al., 2006). Urban and colleagues found that deviant stimulus features (motion direction) elicited reduced vMM signal in schizophrenic patients (Urban et al., 2008).

Several studies demonstrated that vMMN is elicited by simple deviant features (see Kimura et al. (Kimura et al., 2011) for a review, and Maekawa et al. (Maekawa et al., 2012) for a clinically-focused review). To date only a few studies investigated visual mismatch negativity in healthy subjects using abstract regularities (Stefanics et al., 2011) or complex natural visual stimuli such as emotional facial expressions (Kimura et al., 2011; Stefanics et al., 2012b), or body parts (Stefanics and Czigler, 2012). A recent study by Kimura and colleagues (Kimura et al., 2011) reported that occipital, temporal and frontal regions play a major role in the generation of the facial expression-related mismatch response. As Stefanics and colleagues (Stefanics et al., 2012b) summarized, occipital and temporal visual areas together with frontal generators automatically represent regularities in the emotional content of unattended faces appearing outside of the focus of attention and store them as predictive memory representations. The biological significance of such representation might be orienting our attention to sudden changes in emotional expression of conspecifics in our environment, analogously to auditory MMN (Naatanen et al., 2011), and also maintaining a predictive model of the environment. Although the processing of unattended facial emotions is likely to play an important role in social interactions, to our knowledge no study so far investigated the neural correlates of these processes in patients with schizophrenia.

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1.6.2. Time-frequency domain correlates of facial emotion recognition

EEG emerges from the activity of an ensemble of generators producing rhythmic activities in several frequency ranges (Basar-Eroglu et al., 1992). Usually, the activity of these generators is random, induced, but when sensory stimulation occurs, the generators become coupled and act together in a coherent way. Superimposition of this coherent activity in particular frequency ranges could, at least partially, determine ERP components. The transition from a disordered, spontaneous EEG to an ordered state triggered by specific stimulation results in a synchronization and enhancement of EEG activity, and gives rise to event-related oscillations (ERO) in several frequency ranges (Ramos-Loyo et al., 2009).

While EEG is one of the oldest tools for identifying and characterizing certain neurological and psychiatric diseases, recent progress in understanding the origin and physiological significance of brain rhythms has gained renewed interest in this area of clinical research (Basar and Guntekin, 2008). Recent efforts in clinical neuroscience have been made towards understanding how psychiatric diseases rest upon the fundamental scaffolding of brain function, especially fast time-scale oscillatory- and assembly-based action (Buzsaki and Watson, 2012).

Conventional time-domain ERP analysis yields only a partial insight into the electrophysiological processes triggered by facial expressions since it captures only event-locked, but not induced activity (which is non-event-locked, i.e., not phase-locked (Makeig, 1993). In particular, if a brain response to an event is not phase-locked across trials precisely enough, the potentially important induced activity will be averaged out. Accordingly, oscillatory changes ‘induced’ by experimental events can be poorly represented in, or completely absent from the time-domain features of the ERP ‘evoked’ by the same events. In order to gain a full insight into the electrophysiological activity linked to facial expression recognition, both evoked and induced activity together can be analyzed by calculating the Event Related Spectral Perturbation (ERSP) during stimulus processing (Makeig, 1993). ERSP measures relative changes from the spectral power baseline, allowing the study of the time course of the EEG signal energy in specific frequency bands. The strength of phase-locking can be assessed by calculating the phase-locking factor, the Inter Trial Coherence (ITC) (Makeig et al., 2004). ITC is a measure of consistency of relative phase at a given latency in response to environmental events and was reported to vary with task conditions in

visual experiments (Delorme and Makeig, 2004; Freunberger et al., 2007; Mishra et al., 2012).

1.6.2.1. Theta-band oscillatory activity involved in emotion recognition

Oscillatory brain activity in relation to facial emotion processing has been less extensively researched than event-related brain activity (Guntekin and Basar, 2007). Previous findings with healthy controls showed that facial feature decoding (Sakihara et al., 2012) and emotion recognition (Balconi and Lucchiari, 2006) were associated with oscillatory activity in the theta band (4-7 Hz) 150-200ms after stimulus presentation. In addition, based on a study of facial expression processing using MEG, Maratos and colleagues (Maratos et al., 2009) found that theta oscillations play an important role in integrating activity within emotion-processing networks. Furthermore, both animal (Buzsaki, 2002) and human studies (Jacobs et al., 2007) suggest that low frequency oscillations may coordinate the spiking of neurons, and thus contribute to higher functions, like attention and memory. Previous investigations have shown decreased temporal coding and neural activity in the low frequency band in patients with schizophrenia (Doege et al., 2009; Shin et al., 2010; Uhlhaas et al., 2008).

Only a few studies examined oscillatory brain activity linked to emotion recognition in psychiatric conditions. Aftanas and colleagues (Aftanas et al., 2003) found disrupted event-related synchronization over the left hemisphere in patients with alexithymia compared to healthy controls when viewing affective pictures. Furthermore, a recent hypothesis put forward by Ulhaas and colleagues (Uhlhaas and Singer, 2010; Uhlhaas and Singer, 2011) suggests that aberrant development of neural oscillations during adolescence in schizophrenia may lead to impaired neural activation and temporal coding and thus lead to neurocognitive dysfunctions, such as deficits in facial emotion recognition. A study by Ramos-Loyo and colleagues (Ramos-Loyo et al., 2009) found decreased theta activity over central and frontal regions in patients with schizophrenia in a facial emotion recognition task. However, in this study neither the changes from baseline in oscillatory activity (synchronization), nor ITC were measured. In sum, time-frequency domain studies of facial affect recognition are far less available than time-domain analyses. To our knowledge, our studies are the first to combine both time-domain and time-frequency domain analyses in studies of fearful face recognition in schizophrenia patients.

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2. OBJECTIVES AND COLLABORATIONS

2.1. General objectives and collaborations

Our research on fearful facial emotion recognition in schizophrenia was embedded in a broader psychophysiological research context with the purpose to gain insight, at the electrophysiological level, into the neural processing of fearful face recognition in schizophrenia and to examine the extent to which this neural processing is disrupted in schizophrenia as compared to healthy controls. To this end our electrophysiology lab team, in collaboration with colleagues from the Psychology Institute at the Hungarian Academy of Sciences, together designed two electrophysiological paradigms to be conducted at the electrophysiology lab at the Clinic for Psychiatry and Psychotherapy at the Semmelweis University, Budapest, Hungary. My colleagues were Gábor Csukly (Semmelweis University) and Gábor Stefanics (Hungarian Academy of Sciences). Our advisor was Pál Czobor (Semmelweis University). Professors István Bitter (Semmelweis University) and István Czigler (Hungarian Academy of Sciences) supervised our work. The subsequent section will describe briefly the two experimental paradigms that we used in our studies of fearful facial emotion recognition studies.

2.2 Experimental paradigms

The first paradigm was based on a serial visual presentation design, where emotional faces were presented in the focus of visual attention. This paradigm which probes the processing of attended facial emotional stimuli constitutes the principal focus of the present dissertation. ERP data acquired using this paradigm were subjected to analyses, in two separate investigations: one in the time-domain (Study 1) and the other one in the time-frequency domain (Study 2).

The second paradigm was used in Study 3 to investigate the neural processing of unattended emotional facial stimuli in the two groups. To this end, the ERP paradigm applied in this study did not require overt responses to the face stimuli, as facial emotional expressions were presented outside of the attentional focus. This paradigm was based on the extraction of the visual Mismatch Negativity (vMMN) event-related potential.

While the processing of the attended faces (i.e., 1st paradigm with Studies 1 and 2) constitutes the primary focus of this dissertation, the second paradigm will be presented briefly here, since it provides subsidiary information in the context of our broader emotion recognition investigation in schizophrenia.

2.3. Specific objectives

STUDY 1: Time domain characterization of event-related potentials (ERPs) during fearful face recognition in patients with schizophrenia as compared to matched healthy controls

In our first investigation we aimed to evaluate the time sequence and topography in the brain electrical activity through event-related potentials (ERPs) during fearful face recognition in patients with schizophrenia as compared to matched healthy controls. Of particular interest was the temporal and topographical distribution of these electrocortical responses to fearful facial expressions. We also investigated the correlation between electrophysiological measures of fearful facial emotion recognition and emotion recognition performance as measured through the on-line emotion recognition task performed during the EEG recordings. We also aimed to investigate the correlation between bioelectrical changes and symptom dimensions of psychopathology.

STUDY 2: Time-frequency domain characterization of ERPs during fearful face recognition in patients with schizophrenia as compared to matched healthy controls

In our second investigation, using the same data as in our first study, we conducted a time-frequency analysis for both evoked and induced neural activity as captured by the Event Related Spectral Perturbation (ERSP), which can be indexed as Event Related Synchronization (ERS) or Desynchronization (ERD). Event-locked activity was measured by the phase locking factor, the Inter Trial Coherence (ITC). Furthermore, we aimed to investigate the associations between electrophysiological measures of fearful facial emotion

recognition and emotion recognition performance as measured through a more detailed off-line emotion recognition task performed after the EEG recordings.

STUDY 3: Visual Mismatch Negativity (vMMN) study of fearful face recognition in schizophrenia

The ERP paradigm applied in this study did not require overt responses to the face stimuli, as facial emotional expressions were presented outside of the attentional focus. This paradigm was based on the extraction of the visual Mismatch Negativity (vMMN) event-related potential. We studied the differences between patients and control subjects by comparing their vMMN responses to unattended rare (deviant) facial emotions embedded in a stream of faces expressing frequent (standard) emotions.

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3. METHODS

3.1. Methods Study 1 and Study 2

Subjects, Stimuli and Procedures and Recordings were identical in the two studies, as Study 2 is a second investigation of the same data as in Study 1. The Methods of the two studies differ starting with the Data analysis. While in Study 1 we used a time domain approach, in Study 2 a diffent signal processing approach was used and a different objective was set using time-frequency analysis techniques.

3.1.1. Subjects

Twenty-four patients meeting the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, (2000) criteria for schizophrenia (13 men and 11 women, mean age: 34 yr, SD = 10.2) and twenty-four healthy controls (13 men and 11 women, mean age: 33.1 yr, SD = 9.9) were enrolled in the study. Healthy controls were individually matched to the patients by gender, age (+/- 5 years), and years of education (+/- 3 years), thus resulting in 24 matched pairs. With the exception of three left-handed patients and two left-handed healthy controls all participants were right-handed and had normal or corrected-to-normal vision. Participants did not receive payment for their participation, and provided written informed consent after all procedures were fully explained according to procedures approved by the Institutional Review Board of the Semmelweis University, Budapest, Hungary.

Patients were recruited from both the inpatient and outpatient units of the Department of Psychiatry and Psychotherapy of the Semmelweis University, Budapest (inpatient: outpatient ratio = 9:15). All patients were assessed on the Positive and Negative Syndrome Scale (PANSS; (Kay et al., 1987) by a trained psychiatrist or psychologist. All patients were taking antipsychotic medication at the time of testing (mean CPZ equivalent dose of 601 mg/day, SD=445.5). Chlorpromazine-equivalent doses for antipsychotics were computed according to Woods (2003) and Janssen, Weinmann, Berger, and Gaebel (2004) (Janssen et al., 2004; Woods, 2003). Twenty three patients were taking second generation antipsychotics, and one patient was taking first generation antipsychotic medication. The ratio of schizophrenia subtypes among patients was as follows: 13 paranoid, 2 catatonic, 6 disorganized, and 3 undifferentiated. The exclusion criteria for patients with schizophrenia were any other DSM-

IV Axis I disorder, any other central nervous system disease, mental retardation, history of head injury with loss of consciousness for more than 1 hour, and alcohol or drug abuse.

Exclusion criteria for healthy controls included history of any psychiatric or neurological disease, mental retardation, history of head injury with loss of consciousness for more than one hour, and alcohol or drug abuse. Demographic information for both groups and clinical characteristics of the schizophrenia group are presented in **Table1.**

Table 1. Basic demographic and descriptive characteristics of the two study groups*****

	Patients (n= 24)	**Controls (n= 24)**
Gender (Male/Female)	13/11	13/11
Age (years)	34.2 (10.3)	33.2 (9.8)
Education (years)	13.9 (10.1)	15.0 (2.6)
Symptom Checklist 90 (Global Severity Index)	98.6 (66.6)	22.9 (23.5)
Handedness (right/left)	21/3	22/2
Duration of illness (years)	9.7 (7)	N/A
CPZ equivalent (mg)	601.9 (445.5)	N/A
Antipsychotic medication (Atypical/Typical)	23/1	N/A
PANSS total	59.4 (21.6)	N/A
PANSS positive	14.5 (6.0)	N/A
PANSS negative	15.1 (7.5)	N/A
Schizophrenia Subtypes: Paranoid/Catatonic/Disorganized/Undifferentiated	13/2/6/3	N/A
Inpatients/Outpatients	9/15	N/A

***:** continuous variables are characterized by mean (SD); categorical variables are represented by frequencies (n).

3.1.2. Stimuli

The facial stimuli used in the experiment were chosen from Ekman and Friesen's Face stimuli (Ekman and Friesen WV, 1976) with hair removed from the stimuli to avoid gender cues other than facial structure and features. After standardizing the size, resolution and luminance, the photographs were cropped to produce an ellipse-shaped image that contained only the face with the eyebrows, eyes, nose, and mouth of the individual on a dark grey background. Five female and five male faces were used, each displaying a neutral and a fearful expression, yielding altogether 20 stimuli.

3.1.3. Procedures

After the recruitment of the participants, in the case of patients with schizophrenia, an initial appointment was made for a clinical interview to assess PANSS scores. This semi-structured PANSS clinical interview lasted about 40- 60 minutes lead by a trained clinical psychologist or psychiatrist. After participants' agreement to take part in the study an appointment was made with each participant in the EEG lab of the clinic for the experiment. The experiment lasted approximately 2.5-3 hours, including initial screening, EEG recordings and tests. Participants were first informed about the study, procedures, and a written informed consent was obtained by them. Then a general screening test, the SCL-90 was administered for each participant, which took about 5 minutes to complete. Then subjects were seated in a dimly lit, sound-attenuated room. A computer screen was placed at a viewing distance of approximately 50cm. The EEG was set up, participants were applied a 128-channel electrode cap and electrodes were then plugged in. After the EEG equipment was set up and a clear, acceptable signal was obtained on all 128 electrodes plus the 2 EOG channels using real-time online monitoring of the electrode array participants were again explained the paradigm and given a trial run to get accustomed to the task, the stimuli and the use of the response buttons. The design of the experiment was constructed such that each block lasted for about 6-9 minutes, depending on the participants's response times, and participants were encouraged to take a short break between blocks while staying seated. They were also offered a refreshment (a drink or glucose) if needed. Altogether, the EEG paradigm took approximately 1.5 hours to complete.

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The experiment was programmed and presented with the Presentation 13.0 software (Neurobehavioral Systems, Inc.). Stimuli were presented for 200ms, followed by a blank screen with a fixation cross until the participant's behavioural response. The interval between the response and presentation of subsequent stimulus varied between 600ms and 700ms. As non-face control stimuli, phase-randomized patches were generated from the Ekman-faces that contained all of the same visual information as the face stimuli used, just "scrambled" up. Stimuli (faces) were phase-randomized using the 'Weighted mean phase (WMP) type phase scrambling' (Dakin et al., 2002). These patches were presented with a 1:4 ratio to facial stimuli, also for 200ms. Occasionally (with a 1:10 ratio to stimuli) a schematic picture of an eye was presented to the participants for 1000ms followed by a 1000ms interval of a blank screen, giving them the chance to blink and thus to achieve reduction in blink-related artefacts during facial stimulus presentation.

Participants were instructed to respond as quickly and accurately as possible by pressing one of two buttons whenever they perceived the facial expression displayed as neutral, and the other button whenever they perceived the facial expression displayed as fearful. No response was asked to be given to the non-face patches and to the schematic eye. **Figure 2** gives an overview of representative experimental trials.

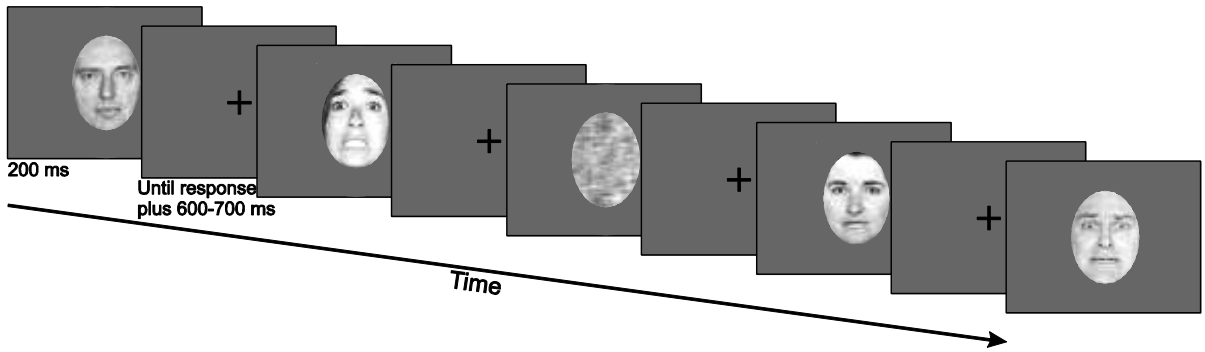

Figure 2. Overview of representative experimental trials

After the EEG recordings, the electrodes and the electrode cap were unmounted from the participants' head and they were asked to stay seated in front of the computer and to complete a computerized emotion-recognition task, the Ekman-60 faces test (FEEST). This off-line task lasted about 15 minutes for each participant. Finally, after a short debriefing, participants were thanked and were asked for their contact information.

3.1.4. Instruments and measures

PANSS – Positive and Negative Symptom Scale (Kay et al., 1987)

The scale has seven positive-symptom items, seven negative-symptom items and 16 general psychopathology symptom items. Each item is scored on a seven-point severity scale. The 30-item PANSS was conceived as an operationalized instrument that provides balanced representation of positive and negative symptoms and gauges their relationship to one another and to global psychopathology.

SCL-90 – Symptom Checklist – 90 (Derogatis LR, 1977)

The Symptom Checklist-90 (SCL-90) is a general screening measure used as a method for screening and detecting clinical symptoms or indicators of psychological distress. It is one of the most widely used measures of multiple aspects of psychological distress in clinical practice and research. SCL-90 includes 90 item rated on 5-point scale, ranging from 0= not at all, to 4= extremely. SCL-90 measures nine primary distress dimensions: somatization; obsessive compulsive; interpersonal sensitivity; depression; anxiety; hostility; phobic anxiety; paranoid ideation; and psychoticism. According to the Derogatis criteria for ‘caseness' (i.e.: high risk for a psychiatric disorder), a global severity index of >114 on the SCL-90 was an additional exclusion criteria for healthy controls (DeRogatis and Melisaratos, 1983; Unoka, 2004). The Hungarian version of the SCL-90 was validated by Unoka et al (2004). No subjects were excluded from the control group based on these criteria.

Ekman-60 faces test

This computer-based test is one of the components of the Facial Expressions of Emotion—Stimuli and Tests (FEEST; (Young, 2002). Sixty facial expressions were presented in a random order on a computer screen and participants indicated, using the mouse to click on the appropriate button at the bottom of the screen whether the emotion expressed was happiness, sadness, anger, fear, disgust or surprise. Each image remained on the screen for a maximum of five seconds; presentation of the next image was triggered by the participant responding to the previous one, so there was no time pressure.

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3.1.5. Recordings

EEG was recorded from DC with a low-pass filter at 100 Hz using a high-density 128-channel BioSemi ActiveTwo amplifier (Metting van Rijn et al., 1990). The electrode cap covered the whole head with an equidistant-layout. Eye movements were monitored by two electrooculogram (EOG) electrodes placed below the left and above the right external canthi. Data were digitized at 24 bit resolution and a sampling rate of 512 Hz. Subsequent data analyses were carried out off-line using built-in and self-developed functions as well as the EEGLAB toolbox (Delorme and Makeig, 2004) in Matlab (MathWorks, Natick, MA). Further statistical analyses were carried out using the SAS ® 9.2 software (SAS Institute Inc., Cary, NC). EEG was re-referenced to the common average potential and filtered off-line between 0.1 and 30 Hz using zero-phase shift Butterworth filter. Epochs of 100ms prestimulus to 600ms poststimulus were extracted from the continuous EEG for further analysis and corrected for prestimulus baseline. To avoid potential artifacts, epochs with a voltage exceeding ±120 μV on any EEG or EOG channel were rejected from the analysis. Total trial number per each picture type (fearful and neutral) was 192. After artefact rejection, for the controls an average of 167 trials (SD=20.6) and 168 trials (SD=17.2) remained in the fearful and neutral conditions, respectively. For patients with schizophrenia the analogous numbers were the following: 155 trials (SD=26.7) for the fearful condition and 156 trials (SD=26.3) for the neutral condition.

3.1.6. Data Analysis Study 1

As a preliminary analysis and "quality check", we investigated whether a face-specific response (N170 component) was detectable in our neutral facial stimuli as compared to the non-face patches. To this end, we used the General Linear Model (GLM) analysis.

In our principal analyses, first we aimed to identify the time periods during which any of the two groups showed a statistically significant discrimination in the ERPs for the fearful vs. neutral stimuli. Second, we aimed to test whether in the identified time periods there was a significant difference between the ERP waveforms between the two groups. Finally, we aimed to delineate the group differences in the scalp topography of ERPs that are associated with facial emotion processing.

In particular, affect-related modulations for each of the ERP time intervals were tested by computing the difference wave for the fear vs. the neutral stimuli using the Global Field Power (GFP). Specifically, the principal statistical analysis investigated the effect of valence in each group and compared the valence effects between the two groups in time windows with >10 consecutive time points significantly differing from zero in any of the two study groups.
Random regression hierarchical linear modeling (HLM) (Bryk AS, 1992; Gibbons et al., 1988) was the primary statistical approach; this method (in contrast to the traditional ANCOVA analysis) makes allowance for heterogeneity among treatment groups and takes into account the time-dependent correlation structure of the sampling points. In the HLM model, repeated assessments of the difference wave within each specified time window served as the dependent variable. The two independent variables were "study group" and "time" (sampling point relative to stimulus onset). Study group served as the between-subject factor, and Time (ms) as the within-subject, random effect factor. Interaction between study group and time was included in the model and was tested by F-statistics. Significance of the Least Squares Mean (LSM) effects was tested by the t-statistics and indicated whether there was a statistically significant valence effect in a given group. In order to compare the valence effect between groups, we formulated a pairwise group contrast for the two groups. Analogous HLM analyses were conducted for the reaction time and error data, as well as for the ERP amplitudes in exploratory analyses in each of 5 brain regions of interest: frontal, central, parietal, temporal, and occipital areas (see Figure 6. top left map for channel layout and regions of interest). ERP amplitudes are expressed in microvolts throughout the text.

3.1.7. Data analysis Study 2

Study 2 is a second investigation of the same data as in Study 1. Therefore, Subjects, Stimuli and Procedures and Recordings were identical to Study 1. In the second investigation a diffent signal processing approach was used and a different objective was set, namely to explore theta oscillatory activity during fearful face recognition using time-frequency analysis techniques.
Stimulus-related theta activity changes were measured by calculating the event-related spectral perturbation (ERSP), which is a 2-D image of mean change in spectral power (in dB) from baseline. The ERSP measures average dynamic changes in amplitude of the broad band EEG frequency spectrum as a function of time relative to an experimental event. Stimulus-

locked evoked activity was measured by inter-trial coherence (ITC), which is the 2-D image of strength (0 to 1) of the phase-locking of the EEG signals to the time-locking events (Makeig et al., 2004).

To compute the ERSP, baseline spectra are calculated from the EEG immediately preceding each event. The epoch is divided into brief, overlapping data windows, and a moving average of the amplitude spectra of these is created. Each of these spectral transforms of individual response epochs are then normalized by dividing by their respective mean baseline spectra. Normalized response transforms for many trials are then averaged to produce an average ERSP, plotted as relative spectral log amplitude on a time-by-frequency plane (Delorme and Makeig, 2004).

Details of time-frequency analysis

The method described here generalizes the narrow-band measures of event-related synchronization and desynchronization introduced by Pfurtscheller and Aranibar (Pfurtscheller and Aranibar, 1977) and includes both phase-locked and non-phase-locked contributions.

The principle of calculating the ERSP is to compute the power spectrum of the EEG signal from a sliding time window. For n trials, if Fk(f,t) is the power of trial k at frequency f and time t, the ERSP value is calculated as

$$ERSP(f,t) = \frac{1}{n}\sum_{k=1}^{n} | F_k(f,t) |^2$$

In order to obtain the Fk(f,t) function (the signal power at a given frequency and time point), the EEG signal was convolved with Hanning-windowed sinusoidal wavelets. The number of wavelet cycles increased evenly with frequency (starting at three cycles at 6 Hz) for optimal time-frequency resolution.

The formula to calculate the inter-trail (phase) coherence (ITC) differs from that used to compute the ERPS in an important aspect. To compute ITC, the length of each trial activity vector is normalized to 1, before their complex average is calculated. This results in that the only information about the phase of each trial's spectral estimates is retained, and the amplitude of the signals is not taken into account (Delorme and Makeig, 2004)

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$$ITC(f,t) = \frac{1}{n}\sum_{k=1}^{n}\frac{F_k(f,t)}{|F_k(f,t)|}$$

We analyzed epochs extending from 350ms before to 850ms after stimulus onset in the 1–50 Hz frequency range. The sliding window was 150ms wide, and it was applied 200 times with an average step size of 6ms. Since no zero padding was applied the analyzed time interval extended from 200ms before to 650ms after stimulus onset. The ERSP time-frequency matrices were baseline corrected by the average power calculated from the -350ms to 0ms pre-stimulus period. Dynamical changes in oscillatory activity were studied by computing ERSPs for each individual trial, then averaging them separately for the fearful, neutral and patch stimuli (Herrmann et al., 2004a; Tallon-Baudry and Bertrand, 1999). Mean ERSP and ITC values were calculated by averaging across electrodes within Regions of Interest (ROIs). **Figures 3** and **4** show ERPS and ITC from 1Hz through 50Hz in the different ROIs.

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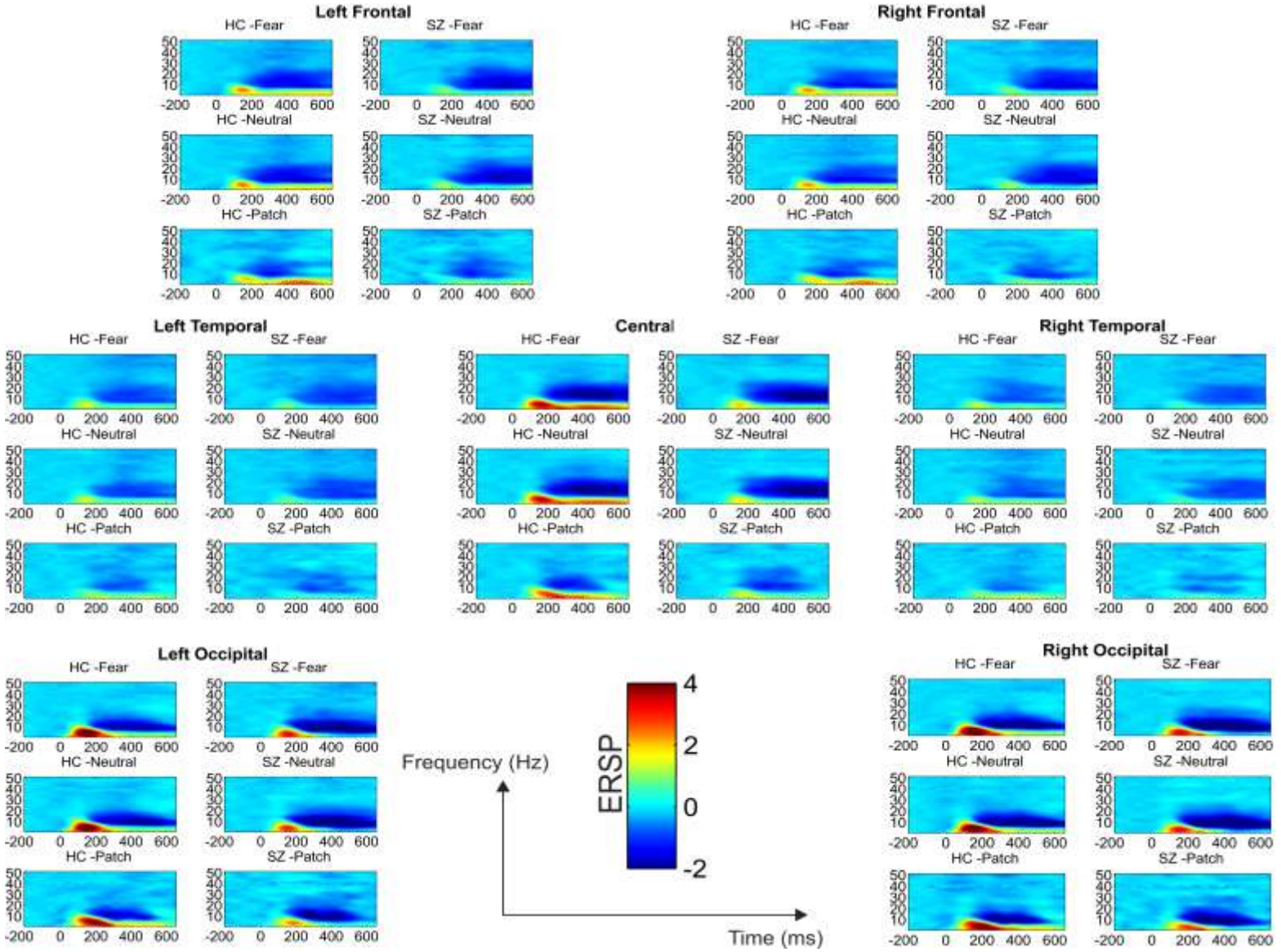

Figure 3. Event-Related Spectral Perturbation (ERSP) by regions of interest (ROI), study group (HC = Healthy Control Group; SZ = Schizophrenia Group) and stimulus condition (Neutral Face; Fearful Face, Non-face Patch).

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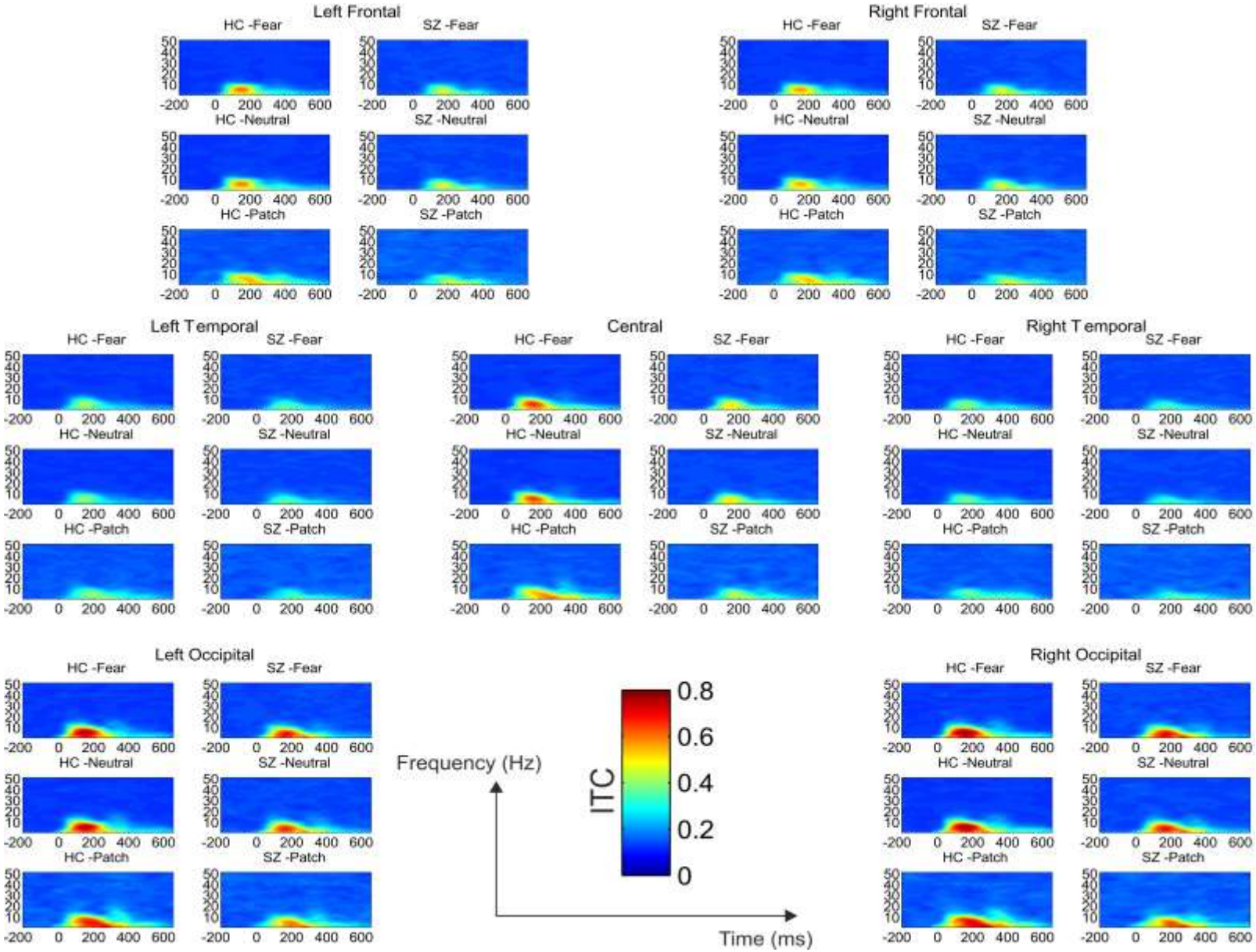

Figure 4. Inter-Trial Coherence (ITC) by regions of interest (ROI), study group (HC = Healthy Control Group; SZ = Schizophrenia Group) and stimulus condition (Neutral Face; Fearful Face, Non-face Patch)

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3.2. Methods Study 3

As mentioned before, the second, vMMN paradigm will be presented briefly, as the unattended processing of facial emotional expressions was not the focus of this dissertation but still constitutes part of our broader research context. The broader research project on facial emotion recognition in schizophrenia in our lab encompassed two paradigms, the attended and the unattended facial emotion recognition paradigms. The ERP paradigm applied in this study did not require overt responses to the face stimuli, as facial emotional expressions were presented outside of the attentional focus. This paradigm was based on the extraction of the visual Mismatch Negativity (vMMN) event-related potential. We studied the differences between patients and control subjects by comparing their vMMN responses to unattended rare (deviant) facial emotions embedded in a stream of faces expressing frequent (standard) emotions.

As the two paradigms were run in one and the same session (on the same subjects and in the same experimental setting) subjects were identical to those in Studies 1 and 2.

3.2.1. Stimuli and procedure

Visual stimuli were presented on a computer monitor. Stimulus presentation was designed in a manner to facilitate the forming of memory traces to emotions rather than to individual faces. To this end, black and white photographs of 5 female and 5 male faces were used as stimuli, taken from the Pictures of Facial Affect set (Ekman P and Friesen WV, 1976), as in Studies 1 and 2. On each screen, 4 images of faces expressing the same emotion, specifically, images of 2 males and 2 females expressing the same facial emotion (happy or fearful) were presented in the upper-left, upper-right, lower-left and lower-right quadrants of the monitor. Faces presented outside the center of the visual field enable studying mismatch responses to deviants without attentional confounds. Also, using four different faces on each stimulus panel likely prevents local adaptation effects to contribute to possible deviance effects. In the center of the monitor a black fixation cross was presented. Pictures appeared on a dark-grey background at a viewing distance of 0.5 m. **Figure 5** illustrates the stimuli used in the experiment. The presentation order of the individual pictures was randomized with the restriction that a picture of the same person was not presented on subsequent stimulus displays. Stimulus duration was 200ms. In two experimental blocks fearful facial emotions

were presented as frequent standards and happy facial emotions were presented as rare deviants (standard P=0.9, deviant P=0.1). In the remaining two blocks the standard and deviant emotions were swapped. The order of the four blocks was randomized across participants. A total of 100 deviant and 900 standard stimuli were presented for each emotion. The task of the subjects was a feature detection task entirely unrelated to the change in the facial expressions, with the purpose to "distract" their attention from the faces: they had to respond with a speeded button-press to the unpredictable changes in the length of either the horizontal or vertical lines of a black fixation cross presented in the center of the visual field. From time to time, the cross became either wider or longer, with a mean frequency of 11 changes per minute (SD=3).

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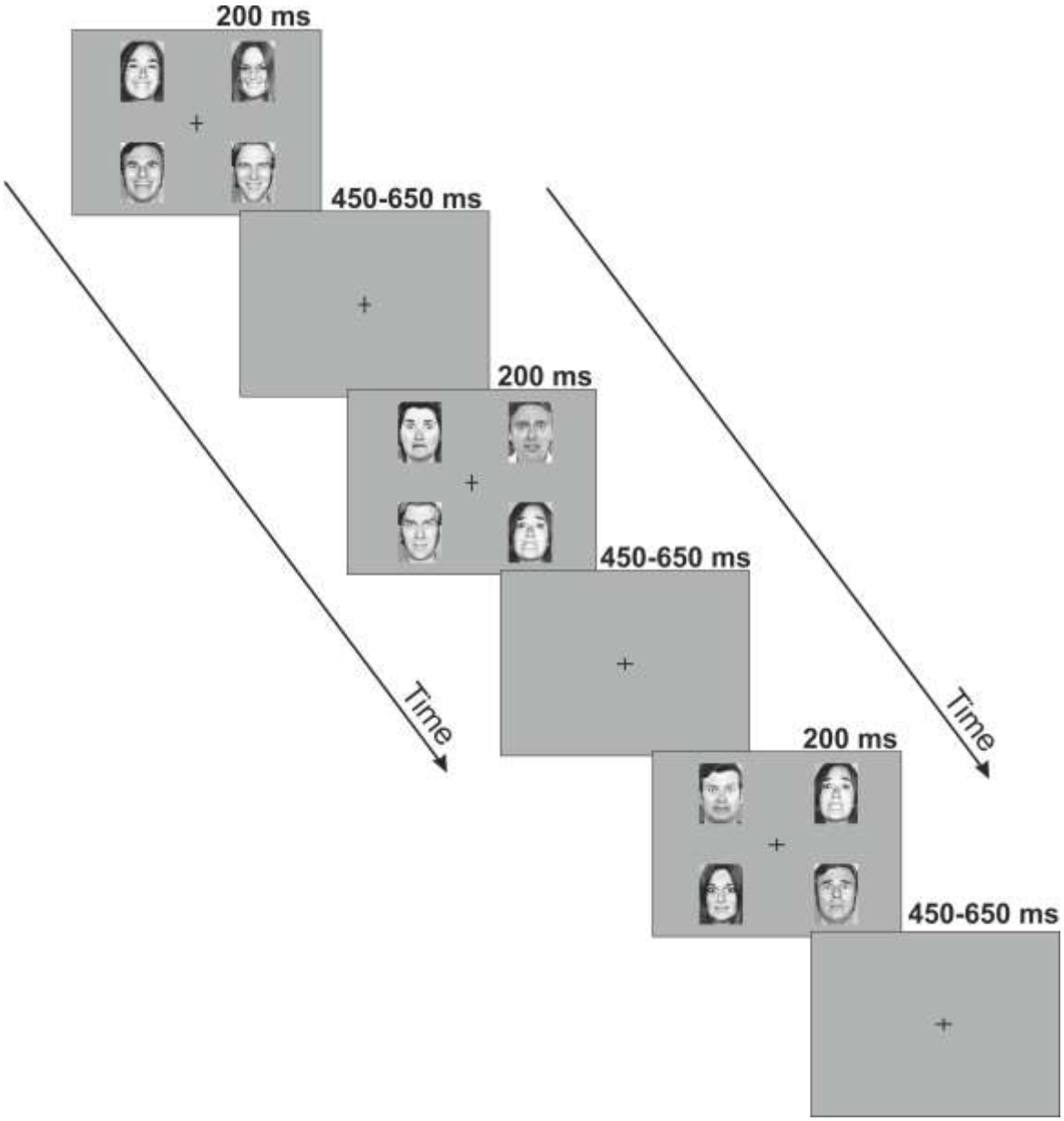

Figure 5. Schematic illustration of the pattern of emotional stimuli used in the experiment.

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3.2.2. Data Analysis

3.2.2.1. Generation of difference waveforms

Difference waveforms (mismatch responses) were created by subtracting ERPs to standards from the ERPs to deviants, separately for the two emotions (**Figure 6**). In half of the blocks the roles of deviants and standards were reversed, responses to standard fearful faces were subtracted from responses to deviant fearful faces, and responses to standard happy faces were subtracted from responses to deviant happy faces. The only difference between standard and deviant emotions was the frequency of presentation in the given block. Since exactly the same pictures were used as deviants and standards, responses to physically identical stimuli were subtracted to calculate mismatch responses. Six Regions of Interest (ROIs) were formed (pre-frontal, central, temporal left, temporal right, occipital left and occipital right) according to previous visual mismatch studies (Stefanics et al., 2012b; Yao and Dewald, 2005) **(Figure 7).** Mean ERP responses were calculated by averaging across electrodes within ROIs. (Electrode clusters selected for analyses are marked with black dots in black frames in **Figure 7**).

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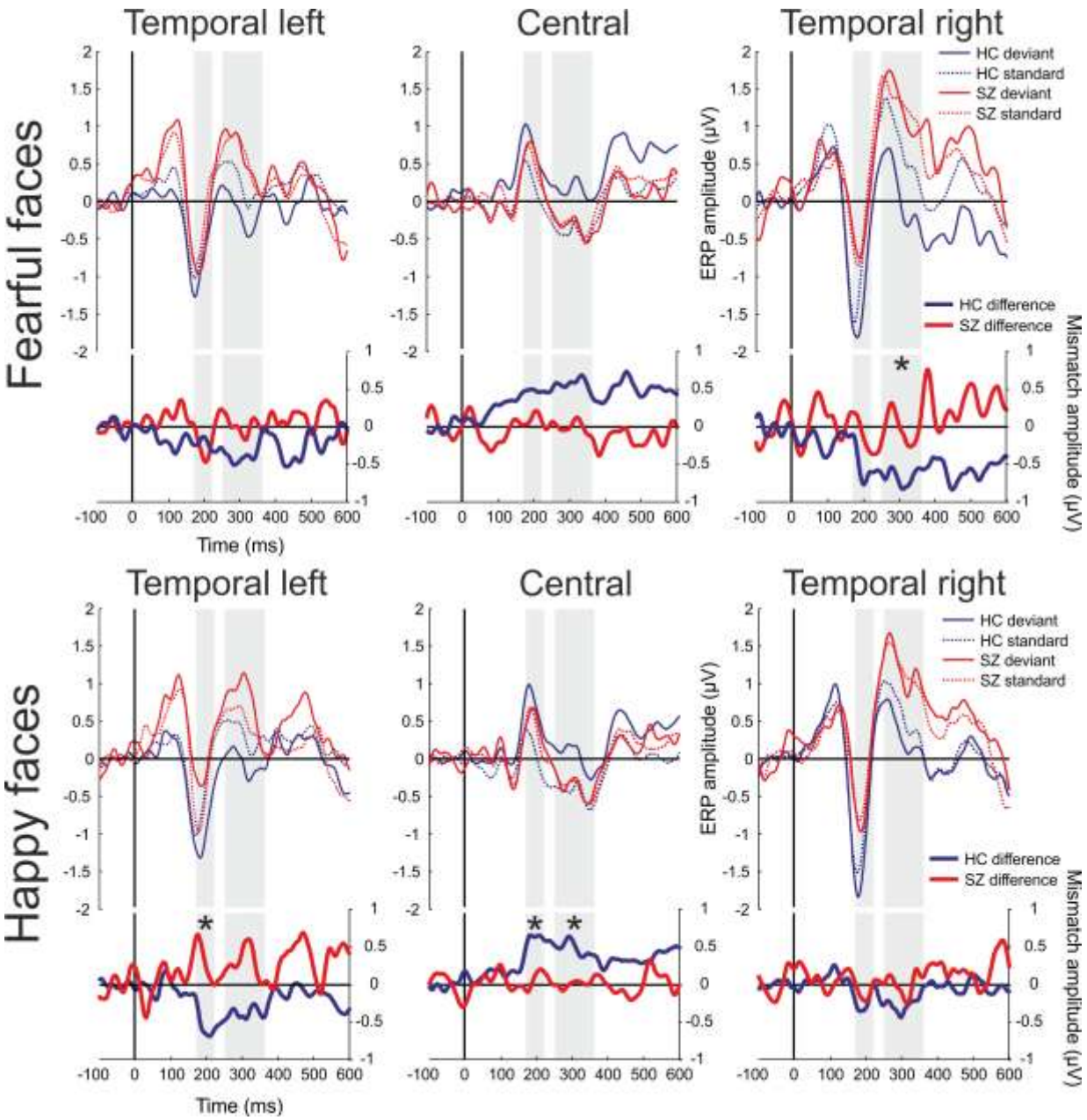

Figure 6. Event-related potentials and mismatch waveforms by region.
HC = Healthy Controls, SZ = Patients with Schizophrenia. Upper panel: ERPs for fearful faces; lower panel: ERPs for happy faces. Shaded intervals indicate time windows of amplitude measurements. Only those ROIs were used for between-group comparison where the mismatch waveform in at least one of the study groups differed significantly from zero after correction for multiple testing. Asterisks mark time windows where significantly larger mismatch responses were found in the healthy control group compared to the patients.

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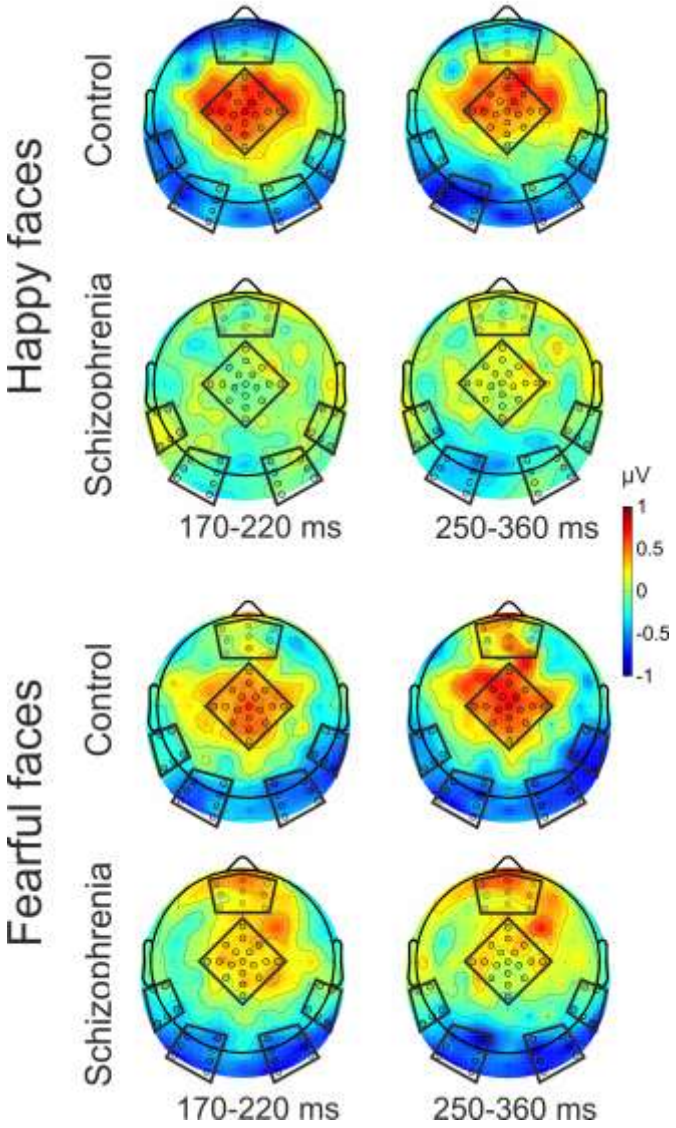

Figure 7. Scalp topography of the mismatch responses.
Electrode clusters selected for analyses are marked with black dots in black frames (ROIs).

3.2.2.2. Study Group Comparison

Time windows of 170-220ms and 250-360ms were selected for analyses based on results from the same control population (Stefanics et al., 2012b). These time windows correspond well to those used in our first paradigm and other similar paradigms (Astikainen and Hietanen, 2009; Kimura et al., 2011; Zhao and Li, 2006). The means of the difference waveforms were calculated within these intervals and served as dependent variables in the main analysis. Group differences were characterized by Cohen's d. Difference between study groups was investigated by ANOVA with mismatch response amplitude as dependent and study group as independent variable. Only those ROIs were used for comparison where the mismatch waveform in at least one of the study groups differed significantly (t-test, $P<0.05$) from zero after Hochberg correction for multiple testing across all ROIs. In other words, those ROIs were selected for study group comparison where the deviant and the standard waveforms differed significantly (i.e: the difference waveform represents a statistically validated mismatch signal). The ANOVA was done separately for the two emotions and the two time windows. The p-values for the between-group comparison were also corrected for multiple comparisons (Hochberg correction) in each time window separately.

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4. RESULTS

4.1. Results Study 1

4.1.1. Behavioral results of the 'online' emotion recognition task

4.1.1.1. Hit rates in the two study groups

In the emotion recognition task during the EEG experiment, the difference between the hit rates of controls and schizophrenia patients was significant ($F(1,46)=9.4$, $p=0.004$), with controls showing a slightly higher hit rate than patients. In particular, both groups showed a relatively high recognition rate of emotions: controls correctly recognized emotions with a median value of 95%, schizophrenia patients with a median value of 91%. The effect of emotion on hit rates ($p=0.4$) and the interaction between study group and emotion were not significant ($p=0.7$).

4.1.1.2. Reaction times in the two study groups

Controls had a significantly ($F(1,48)=33.2$, $p<0.0001$) shorter reaction time (Mean=639ms, SD=196ms) during the emotion recognition task than patients with schizophrenia (Mean=747ms, SD=270ms). The main effect of emotion and the emotion by study group interaction were not significant ($p>0.5$).

4.1.2. Electrophysiological results

4.1.2.1. Preliminary analysis of the N170 for face vs. non-face stimuli

To test whether a face-specific N170 response was detectable in our neutral facial stimuli as compared to the non-face patches, the effects of stimulus condition (face vs. non-face), study group (control vs. schizophrenia) and the interaction of these effects on the N170 component were analyzed by GLM analysis. According to our expectations, we found a significantly larger N170 component in both groups to neutral faces as compared to non-face patches in the occipital region, where the N170 component reached its maximum ($F = 31.1$, $p < 0.0001$, non-face: -1.6 (SD=4.6) and face: -6.5 (SD=5.0) for the control group; non-face: -1.1 (SD=3.9)

and face: -6.1 (SD=3.6) for the schizophrenia group). There was no significant group difference regarding the N170 component (effect of study group: F=0.2, p=0.66), nor was there a significant interaction effect (F=0, p=0.98).

4.1.2.2. Analysis of the difference GFP waveforms

GFP is a robust measure of the spatiotemporal characteristics of brain activity, corresponding to the spatial standard deviation of the electrical potentials recorded at each time point across all electrodes (Lehmann and Skrandies, 1980). GFP difference waveforms were determined separately in the two study groups by subtracting the GFP to fearful stimuli from the GFP to neutral stimuli. Then we analyzed the GFP difference waveforms in order to identify emotion effects, i.e., to identify the time intervals where they significantly differed from zero (i.e., an effect of emotion on the ERPs was detectable). Based on this approach the time windows in the mid-latency (150-170ms) and late latency (330-450ms) range were selected for further analysis (**Figure 8**).

Figure 9 provides topographical maps of ERP amplitudes for Neutral and Fearful faces, and Neutral minus Fearful difference waves for both time intervals for both groups. Regions of Interest (ROIs) are also depicted in Figure 4. ROIs were defined based on previous studies using similar paradigms and analysis methods (Aftanas et al., 2001; Knyazev et al., 2009).

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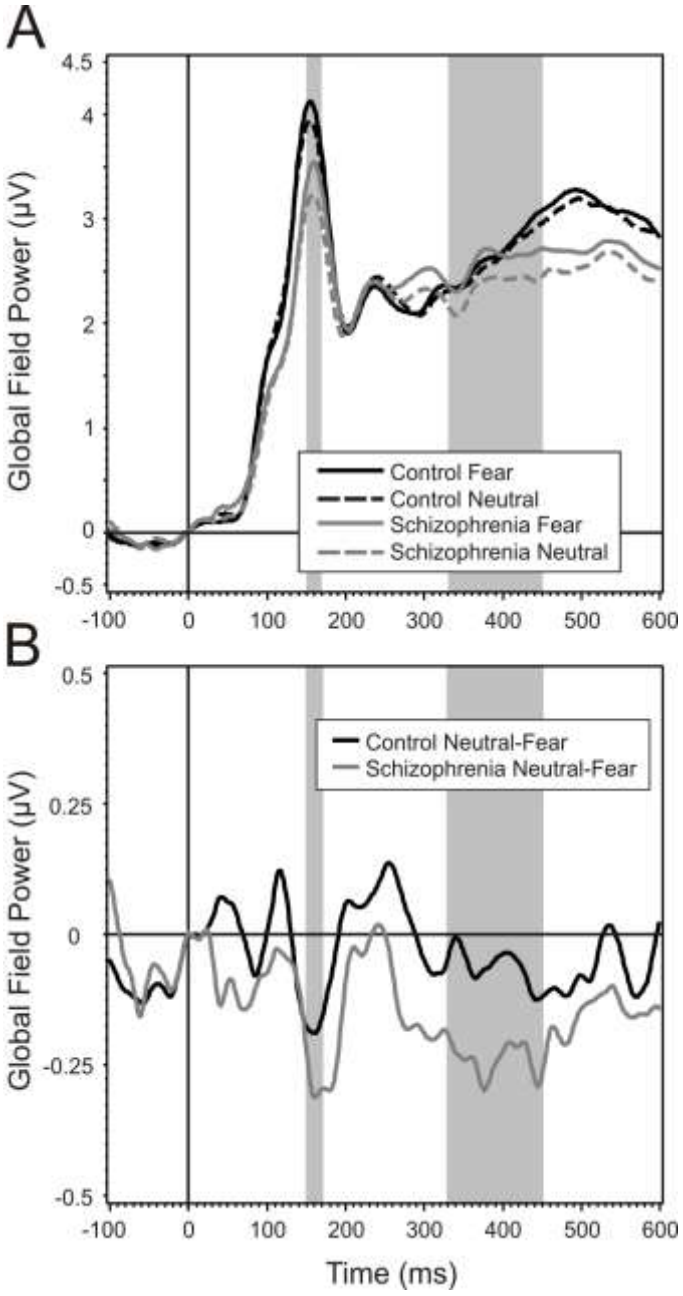

Figure 8. Grand Average GFP (Global Field Power) and GFP difference waves in the two groups

Part A. Grand Average GFP (Global Field Power) of the control and schizophrenia groups in the two conditions, fear and neutral.

Part B. GFP difference waves in the two groups, derived by subtracting the GFP to fearful stimuli from the GFP to neutral stimuli in each group. Grey-colored time intervals refer to the two intervals (150-170ms and 330-450ms) in which any of the two groups' GFP difference waves significantly differed from zero, showing an emotion effect, i.e. discrimination in the processing of fearful vs. neutral faces. Only in the earlier time window (150-170ms) did both groups' GFP difference waves show a significant difference from zero. In the later time window (330-450ms) only the schizophrenia group's GFP difference wave significantly differed from zero.

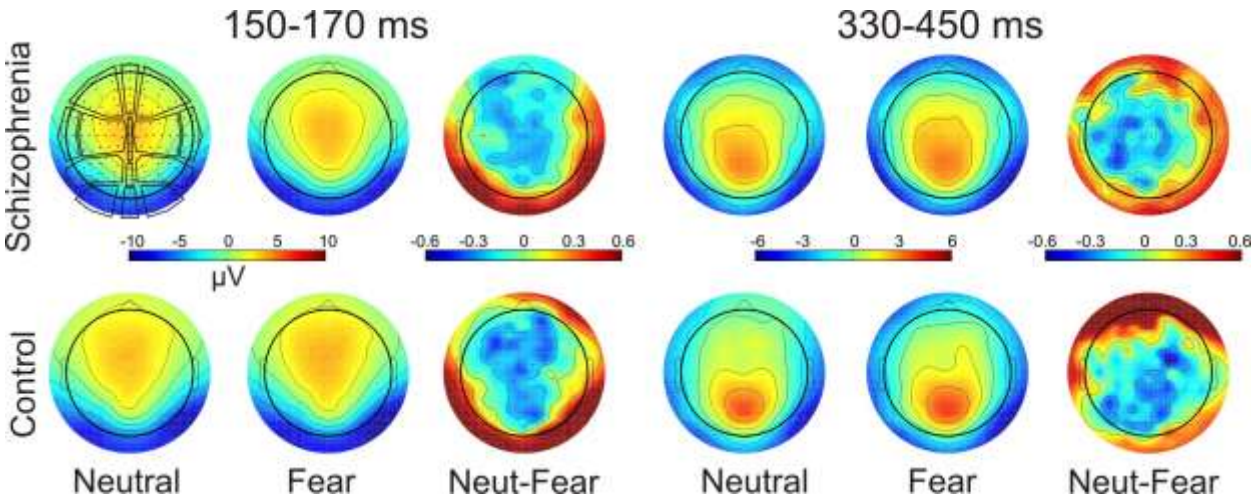

Figure 9. Topographical maps of ERP amplitudes for Neutral and Fearful faces, and Neutral minus Fearful difference waves. The left panel shows data from the 150-170ms, the right panel from the 330-450ms interval. Upper row: schizophrenia group, lower row: control group. Plots show mean amplitude within the selected intervals. Top left map shows channel layout, and Regions of Interests used for statistical analysis.

4.1.2.3. Comparison of the GFP difference waveforms in the two study groups in the mid-latency range

GFP difference waveforms in the 150-170ms time window for both groups showed a significant difference from zero, i.e. $p<0.05$ for all time points in this time window, indicating that in this time period both groups exhibited a differential processing of fearful vs. neutral faces.

4.1.2.4. Comparison of GFP difference in the two study groups in the late latency range

In the 330-450ms time window GFP difference waveforms showed a significant difference from zero in the schizophrenia group ($p<0.05$ for all time points in this time window), but not in the healthy control group ($p>0.24$ for all time points in this time window). To test whether the emotion effect in the difference GFP waveform between the study groups in this time range was significant, the GFP difference waveform was analyzed with a repeated measures HLM analysis, using study group, time, and the interaction of these two factors as independent variables. The analysis yielded a significant main effect of study group

(F(1;46)=77.2, p<0.0001), while the main effect of time (F(50;2300)=0.04, p=0.999) and the interaction of time and group (F(50;2300)=0.03, p=0.999) were non-significant.

4.1.2.5. Comparison of the event related potentials by regions in the two study groups in the late latency range

In order to gain further insight into the significant group difference in GFP that we identified in the late latency range, in further exploratory analyses we investigated the topographical specificity of the group differences in this latency range. In order to reduce the spatial dimensions of the data set, we conducted analyses for 5 clusters of electrodes corresponding to conventional topographical regions (frontal, central, parietal, temporal, and occipital areas). The clusters had three levels, right, left, and sagittal, except for the temporal region, which had only two levels (right and left, see Figure 9 top left map for regions of interest). Separate analyses were conducted for each of the brain regions.

The mean differences between emotions in terms of least square means in the two study groups are presented in **Table 2** and **Figure 10**. HLM analyses revealed significant differences between study groups in all regions except the right-frontal, central sagittal, parietal sagittal and the right-occipital areas. For controls, a significant left frontal activation during the processing of fearful vs. neutral faces was apparent, however, this frontal activation was absent in the schizophrenia group. The differential topographical response to fearful vs. neutral faces among patients was the most pronounced in the occipital regions, thus suggesting a hypofrontality in the patient group.

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Table 2. Estimated mean differences in ERP amplitudes between emotions (neutral minus fear) in the 330-450ms time interval by brain regions in the control and schizophrenia group. [a]

	Control Group		**Schizophrenia Group**			
Region	**Lsmean Difference (μv)**	**Standard Error**	**Lsmean Difference (μv)**	**Standard Error**	**t Value**	**p value**
Frontal Left	0.34	0.023	-0.06	0.02	12.32	**<.0001***
Frontal Sagittal	0.46	0.024	0.06	0.02	11.91	**<.0001***
Frontal Right	0.10	0.021	0.12	0.02	-0.65	0.52
Central Left	-0.13	0.016	-0.25	0.02	4.99	**<.0001***
Central Sagittal	-0.26	0.020	-0.19	0.02	-2.41	0.02
Central Right	-0.24	0.014	-0.11	0.01	-6.69	**<.0001***
Parietal Left	-0.22	0.018	-0.12	0.02	-3.56	**<0.001***
Parietal Sagittal	-0.21	0.023	-0.16	0.02	-1.51	0.14
Parietal Right	-0.12	0.021	0.07	0.02	-6.26	**<.0001***
Temporal Left	0.08	0.025	-0.05	0.02	3.72	**<0.001***
Temporal Right	-0.02	0.023	0.26	0.02	-8.43	**<.0001***
Occipital Left	0.04	0.027	0.26	0.03	-5.91	**<.0001***
Occipital Sagittal	0.08	0.025	0.28	0.02	-5.85	**<.0001***
Occipital Right	0.28	0.029	0.37	0.03	-2.14	0.04

Differences between study groups in all regions are significant, except in the right-frontal, central sagittal, parietal sagittal and the right-occipital areas.

a: Difference between the two study groups was investigated by random regression hierarchical linear modeling (HLM) analysis of variance using GFP difference as dependent variable and group membership as independent variable.

* Significant value after Hochberg correction for multiple comparison

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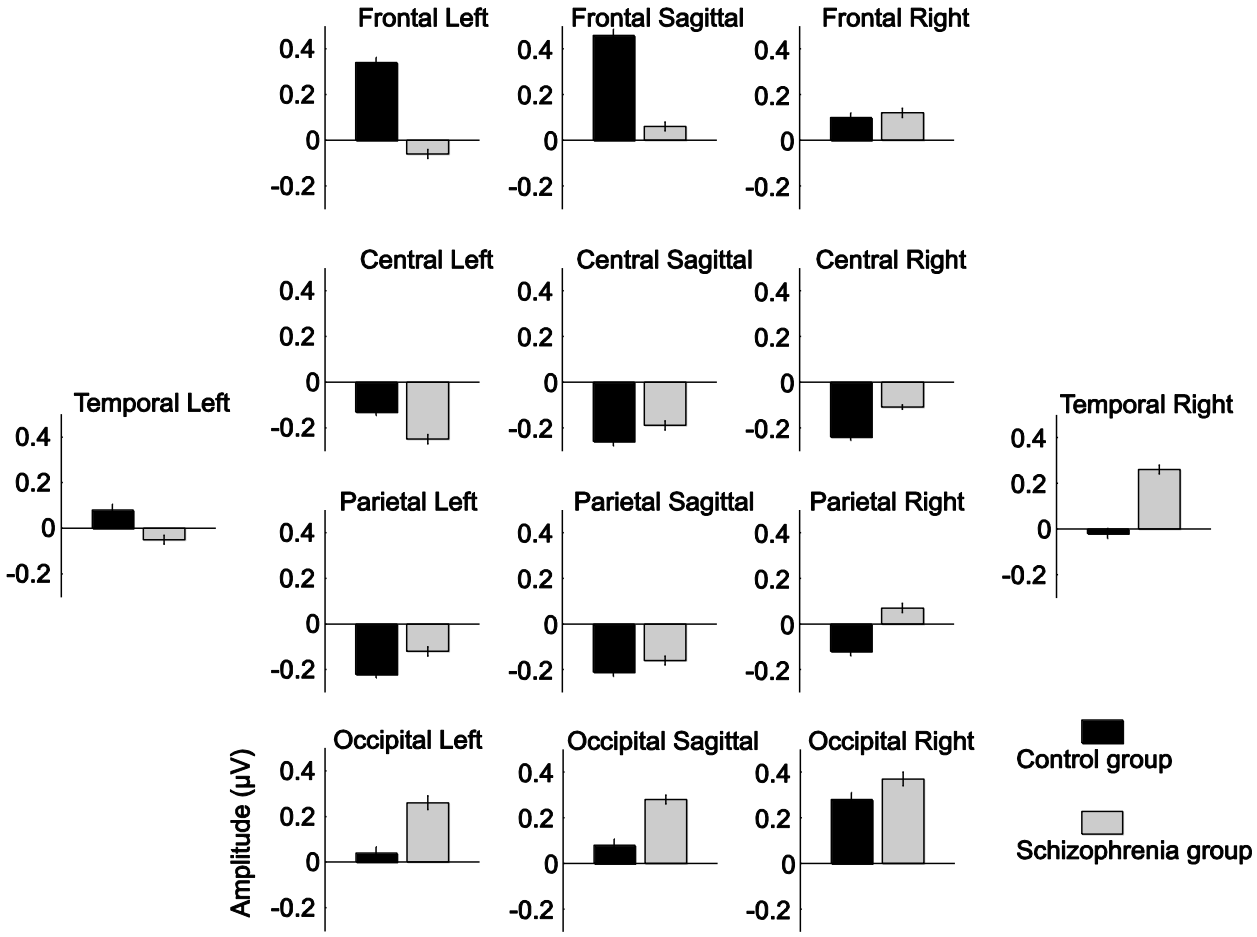

Figure 10. Estimated mean differences in ERP amplitudes between emotions (neutral minus fear) in the 330-450ms time interval by brain regions in the control (black) and schizophrenia (grey) group.

4.1.2.6. Correlation between psychopathological, behavioral, and electrophysiological results in the schizophrenia group

Association between potentially important covariates, such as behavioral indices, clinical symptoms of schizophrenia, and medication as a confounder with the GFP difference values were investigated by HLM analyses. In these analyses the response variable was the GFP difference and the explanatory variables included the covariate of interest, time, and the interaction. A separate analysis was performed for each covariate. In the earlier, 150-170ms time window, after Hochberg correction for multiple comparisons, there were no significant correlations between psychopathology, behavioral results, medication, and EEG data (for all values $p>0.05$). For the later, 330-450ms time window, however, with regard to ratings of psychopathology, the main effect of symptom severity was highly statistically significant for

both positive and negative symptoms. The effect of time and the interaction did not reach significance in any of the analyses ($p>0.1$). The results are summarized in **Table 3,** where the estimated changes are shown for one standard deviation (SD) unit increase in the independent variables (PANSS scores and the behavioral results including emotion recognition and reaction time, respectively, and CPZ-equivalent). As shown in the table, increase in the PANSS positive scale was associated with a significant increase in the GFP difference values (resulting in more negativity for the GFP difference, as shown by the negative sign of the regression estimate), while one SD unit increase in the PANSS negative scale was associated with a decrease in the GFP difference (yielding a more positive value for the GFP difference). Thus, more positive symptoms were associated with a larger difference between emotion-related GFP (with a greater emotional response to fearful faces, deviating from the response to neutral faces), while negative symptoms were associated with a smaller difference between emotion-related GFP (with a smaller emotional response to fearful faces, becoming more similar to the response to neutral faces).

The correlation of GFP difference values with hit rates or reaction times did not obtain significance.

With regard to medication as a potential confounder, the correlation of GFP difference values with the CPZ-equivalent showed significance, with a direction similar to that of the PANSS positive subscales: larger doses of antipsychotic medication were associated with a larger difference between emotion-related GFP (with a greater emotional response to fearful faces, deviating from the response to neutral faces).

Table 3. Relationship between GFP difference (neutral minus fear) and psychopathological and behavioral indices and medication in the schizophrenia group[a]. (N=24)

Relationship of GFP difference with	Regression Slope Estimate[b]	StdErr	tValue	p
PANSS total score	-0.021	0.012	-1.800	0.087
Positive symptoms subscale	-0.088	0.011	-7.660	**0.00001**
Negative symptoms subscale	0.044	0.012	3.744	**0.001**
General psychopathology subscale	-0.024	0.012	-2.007	0.058
CPZ-equivalent	-0.046	0.012	-3.93	**0.00009**
Hit rate	0.016	0.010	1.538	0.138
Reaction time	0.001	0.009	0.061	0.952

a: Relationship was investigated by random regression hierarchical linear modeling (HLM) analysis of variance using GFP difference as dependent variable and psychopathological and behavioral indices and CPZ-equivalent as explanatory variables (in separate analyses).

b: Regression Slope Estimates represent regression coefficients from the HLM analysis, and indicate GFP difference in microvolts between neutral and fear stimuli associated with a unit increase in the independent variable.

4.2. Results Study 2

4.2.1. Preliminary analysis: Scalp topography of ERSP

Based on prior studies applying similar paradigms to study facial emotion processing (Balconi and Lucchiari, 2006; Zhang et al., 2012) and also based on our own results from the first investigation, the 140-200ms time window (+/- 30ms around 170ms) was selected for analysis. **Figure 11** shows the topographical distribution of the ERSP in the selected 140-200ms time window.

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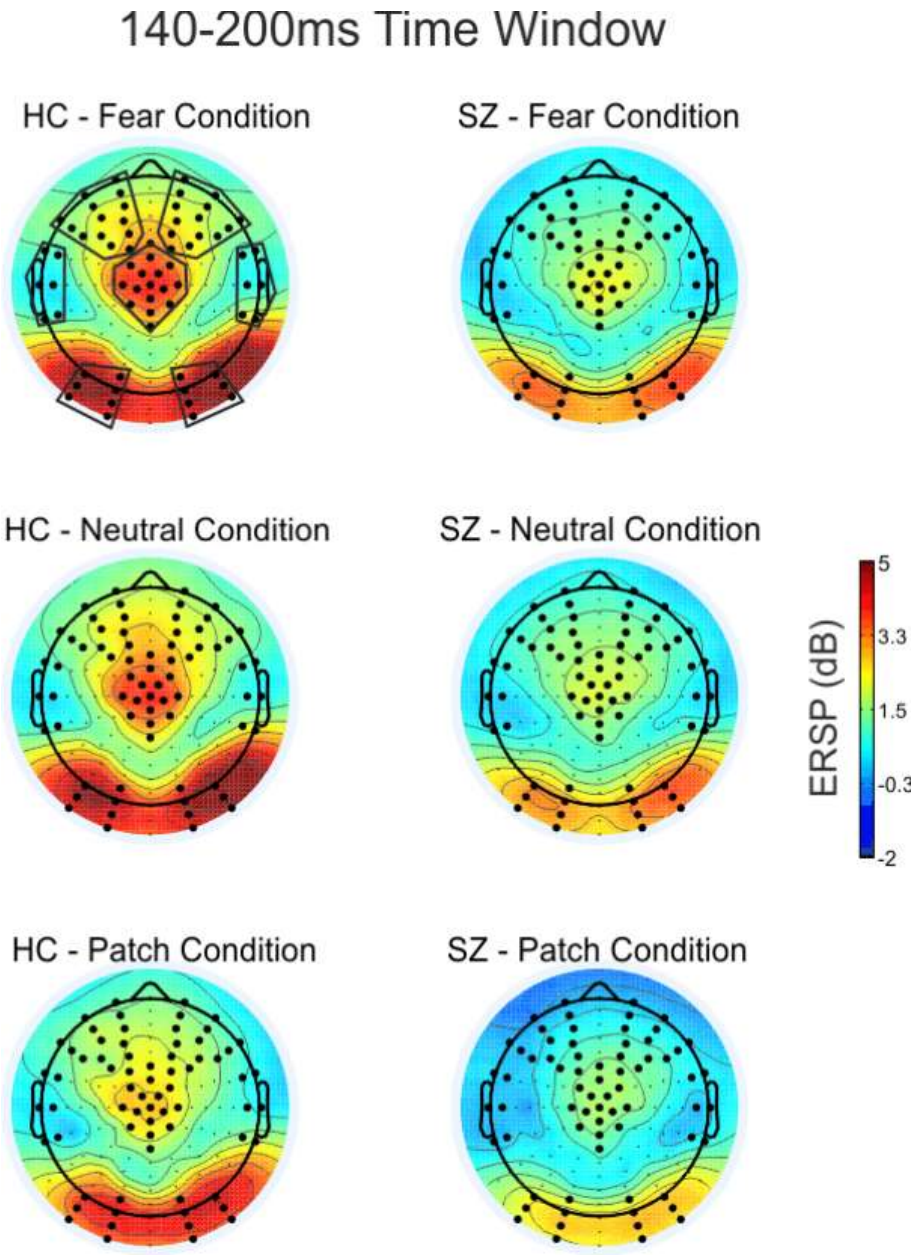

Figure 11. Scalp topography of the event related spectral perturbation (ERSP) in the two study groups in the three experimental conditions in the 140-200ms time window. Electrode clusters selected for analyses (Regions of Interests) are marked with black dots in black frames in the upper-left scalp map.HC = Healthy Control Group; SZ = Schizophrenia Group.

The different effects on ERSP and ITC were tested by three-way analyses of covariance (ANCOVA) of study group (healthy control (HC) vs. schizophrenia (SZ)) × ROI (left and right frontal, central, left and right temporal, left and right occipital) × stimulus type (fear vs. neutral vs. non-face patches). In order to investigate the interactions, post-hoc t-tests were conducted. Since between-group comparisons were evaluated over seven regions, Bonferroni correction for multiple comparisons was applied to the post hoc tests, and the alpha value was set to 0.05/7=0.007. The alpha value for a marginally significant difference was set to 0.014.
The associations of emotion recognition performance (as indexed by the FEEST) with ERSP and ITC were investigated by Pearson correlation. Relationship between ERSP, ITC and emotion recognition performance during EEG was examined by Spearman correlation in both study groups separately. In the latter case the Spearman correlation was used, since the results of this recognition task was strongly left-skewed. All correlations were controlled for age, gender and education (partial correlations were calculated).

4.2.2. Behavioral results

Details of the behavioral tasks are summarized in **Table 4**. For this investigation we used data from the same subjects as in Study 1. However, we also used an additional emotion recognition task additionally to the one used during the EEG experiment. This was a more complex offline emotion recognition task (FEEST) where subjects not only had to decide between a neutral or a fearful face, but had to differentiate between faces depicting the six basic emotions. Control subjects significantly outperformed patients in both behavioral tests, namely on the emotion recognition task as indexed by the FEEST, and on the emotion recognition task during the EEG experiment. In the emotion task during EEG (as previously discussed in Study 1) both groups showed a relatively high recognition rate of emotions (>90%). Controls had a significantly shorter reaction time during the emotion recognition task than patients with schizophrenia. Due to technical difficulties three healthy control subjects' emotion recognition scores were not obtained thus only n=21 control participants' data were entered in the between-group comparison.

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Table 4. Demographic data, clinical characteristics, and behavioral results [a]

	Patients with Schizophrenia ***(n=24)***	**Healthy Controls** ***(n= 24)***	**Statistics**	**p value[b]**
Gender (Male/Female)	13/11	13/11		
Age (years)	34.2 (10.3)	33.2 (9.8)		
Education (years)	13.9 (10.1)	15.0 (2.6)		
Handedness (right/left)	21/3	22/2		
Symptom Checklist 90 (Global Severity Index)	98.6 (66.6)	22.9 (23.5)		
Duration of illness (years)	9.7 (7)	N/A		
Chlorpromazine equivalent (mg)	601.9 (445.5)	N/A		
Antipsychotic medication (Atypical/Typical)	23/1	N/A		
PANSS total	59.4 (21.6)	N/A		
PANSS positive	14.5 (6.0)	N/A		
PANSS negative	15.1 (7.5)	N/A		
Schizophrenia Subtypes: Paranoid/Catatonic/Disorganized/Undifferentiated	13/2/6/3	N/A		
Inpatients/Outpatients	9/15	N/A		
FEEST [c]	79% (9.3)	85.9% (7.5) [d]	t=2.7	**0.01**
Emotion recognition during EEG (overall)	91%	95%	Chi^2=9.8	**0.002**
Reaction time during EEG (overall)	747ms (270)	639ms (196)	Chi^2=11.2	**0.001**

[a]: continuous variables are characterized by mean (SD); categorical variables are represented by frequencies (n).

[b]: level of significance: In case of FEEST, the difference between study groups was tested by unpaired t test, in case of emotion recognition, and reaction time during EEG differences were tested by Kruskal Wallis Chi^2

[c]: FEEST = Facial Expressions of Emotion – Stimuli and Tests

[d]: Due to technical difficulties three healthy control subjects' emotion recognition scores were not obtained; thus, only n=21 control participants' data were entered in the between-group comparison

4.2.3. Electrophysiological results: Stimulus-related changes in theta response

4.2.3.1. Between-group differences in ERSP

A significant main effect of study group ($F(1,46)=10.9$, $p=0.002$) was observed, which was caused by decreased theta power in patients with schizophrenia compared to healthy controls. A significant main effect of region ($F(6,46)=26.4$, $p<0.0001$) was caused by the activity gradient Occipital > Central > Frontal > Temporal Right > Temporal Left pattern. A main effect of stimulus type ($F(2,46)=7.4$, $p=0.002$) was caused by increased theta activity to faces relative to non-face patches (Fear vs. Non-Face: $t=3.8$, $p=0.0004$; Neutral vs. Non-Face: $t=3.7$, $p=0.0006$), while no significant difference was found between fear and neutral faces ($t=1.02$, $p=0.31$).

There was a significant 3-way interaction between study group, ROI, and condition ($F(12,46)=3$, $p=0.004$). Post-hoc tests revealed that theta activity was decreased in the patient group relative to the controls in the left frontal ($t=3$, $p=0.005$), central ($t=3.5$, $p=0.001$), right temporal ($t=3.2$, $p=0.002$), and both occipital regions (Left: $t=2.8$, $p=0.007$; Right: $t=2.9$, $p=0.005$) for the fear condition; in the central ($t=4$, $p=0.0002$), both occipital (Left: $t=2.9$, $p=0.006$; Right: $t=2.8$, $p=0.007$) and right temporal regions ($t=3$, $p=0.004$) for the neutral face condition; and in the left frontal ($t=3.6$, $p=0.0009$) and right temporal regions ($t=2.9$, $p=0.007$) for the non-face condition The largest between-group difference (1.2 in terms of Cohen's d) was detected over the central region for the fear condition. Time course of the theta activity in the ROIs are shown in **Figure 12**.

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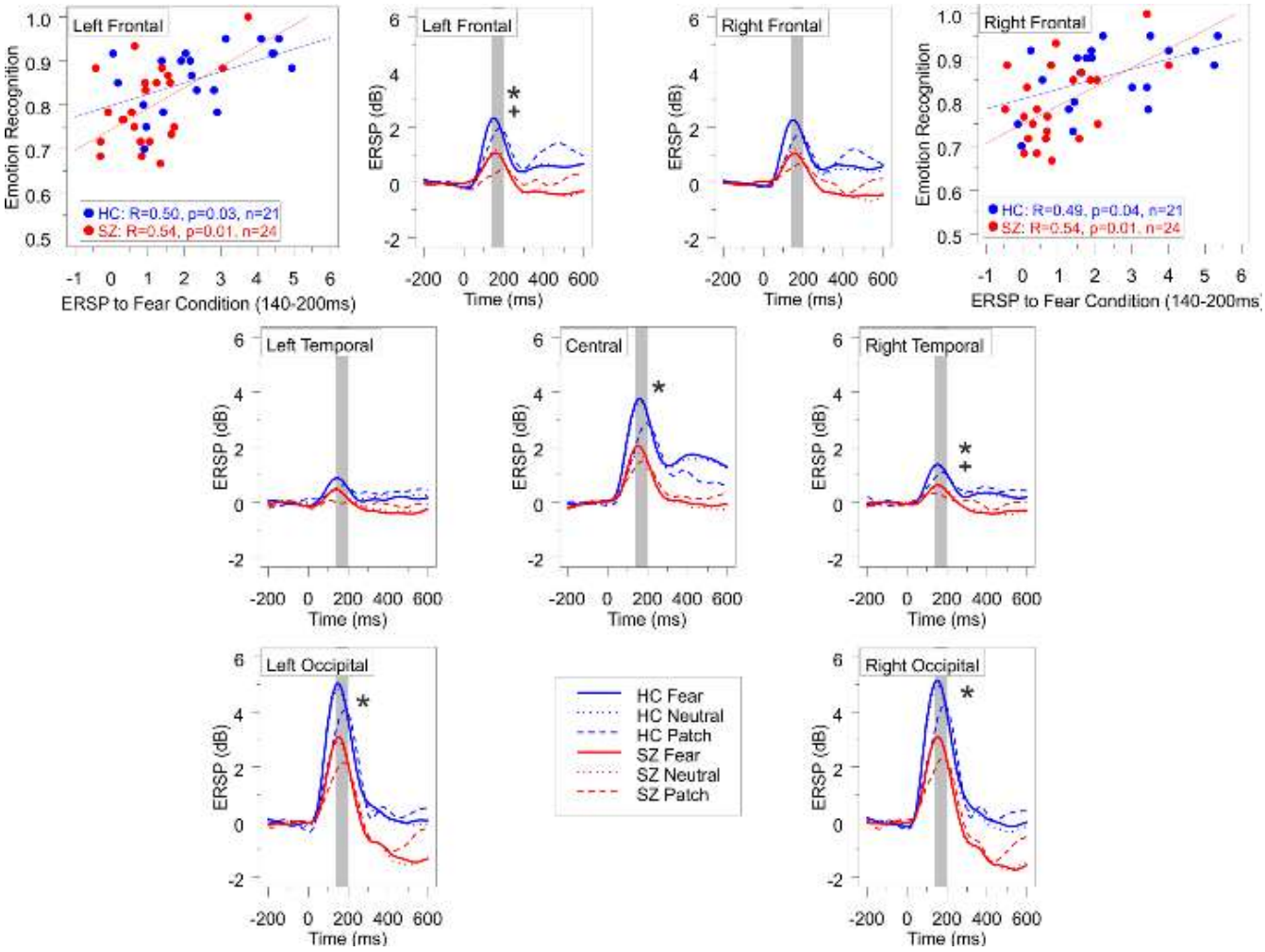

Figure 12. Between-group differences in event-related theta spectral perturbation (ERSP) in the three conditions, and correlations between ERSP values at frontal regions and emotion recognition as indexed by the FEEST scores. Asterisks mark time windows where significantly larger ERSP to face stimuli were found in the healthy control group compared to patients with schizophrenia. Crosses mark time windows where significantly larger ERSP to non-face stimuli were found in the healthy control group compared to the patients. HC = Healthy Control Group; SZ = Schizophrenia Group

4.2.3.2. Association between theta ERSP and behavioral results

Correlations between theta activity to fearful faces and emotion recognition performance as indexed by the FEEST were significant in both study groups in the left frontal (Controls: r=0.5, n=21, p=0.03; Patients: r=0.54, n=24, p=0.01), and right frontal ROIs (Controls: r=0.49, n=21, p=0.04; Patients: r=0.54, n=24, p=0.01). Correlations are shown in the top left and right panels in **Figure 12**. Emotion recognition correlated significantly with theta activity to neutral faces in the left (Controls: r=0.34, n=21, p=0.17; Patients: r=0.62, n=24, p=0.003) and right (Controls: r=0.41, n=21, p=0.09; Patients: r=0.56, n=24, p=0.008) frontal ROIs only in the patient group. All correlations were controlled for age, gender and education.

Stronger increases in theta activity were associated with higher emotion recognition rates in all cases. No significant association between ERSP to the non-face patch and emotion recognition was found in any of the ROIs ($p>0.05$).

Correlations between emotion recognition performance during EEG recording and theta activity did not reach significance in any of the study groups ($p>0.05$).

4.2.4. Electrophysiological results: Phase-locking in the theta band

4.2.4.1. Between-group differences in theta phase-locking (ITC)

As can be seen in **Figure 13**, where group differences in inter-trial theta coherence are shown in the three conditions, a significant main effect of study group ($F(1,46)=5.1$, $p=0.03$), region ($F(6,46)=209$, $p<0.0001$; Occipital > Central > Frontal > Temporal Right > Temporal Left), and stimulus type ($F(2,46)=5.7$, $p=0.006$) was found. Patients with schizophrenia showed a decreased phase-locking relative to control subjects. ITC to faces was increased relative to non-face patches (Fear vs. Non-Face: $t=3$, $p=0.005$; Neutral vs. Non-Face: $t=2.6$, $p=0.01$), furthermore, ITC to fearful faces was significantly increased relative to neutral faces ($t=2.7$, $p=0.01$).

There was a significant 3-way interaction between study group, ROI, and condition ($F(12,46)=2.4$, $p=0.02$). After performing post hoc tests and correction for multiple comparisons ITC decrease was marginally significant in the patient group over the central region for both face conditions (n=45, Fearful: t=2.7, p=0.009; Neutral: t=2.6, p=0.01). Between-group differences were 0.79 and 0.77 in terms of Cohen's d to fearful and neutral

stimuli, respectively. In the other ROIs between-group differences were not significant (uncorrected p values>0.014).

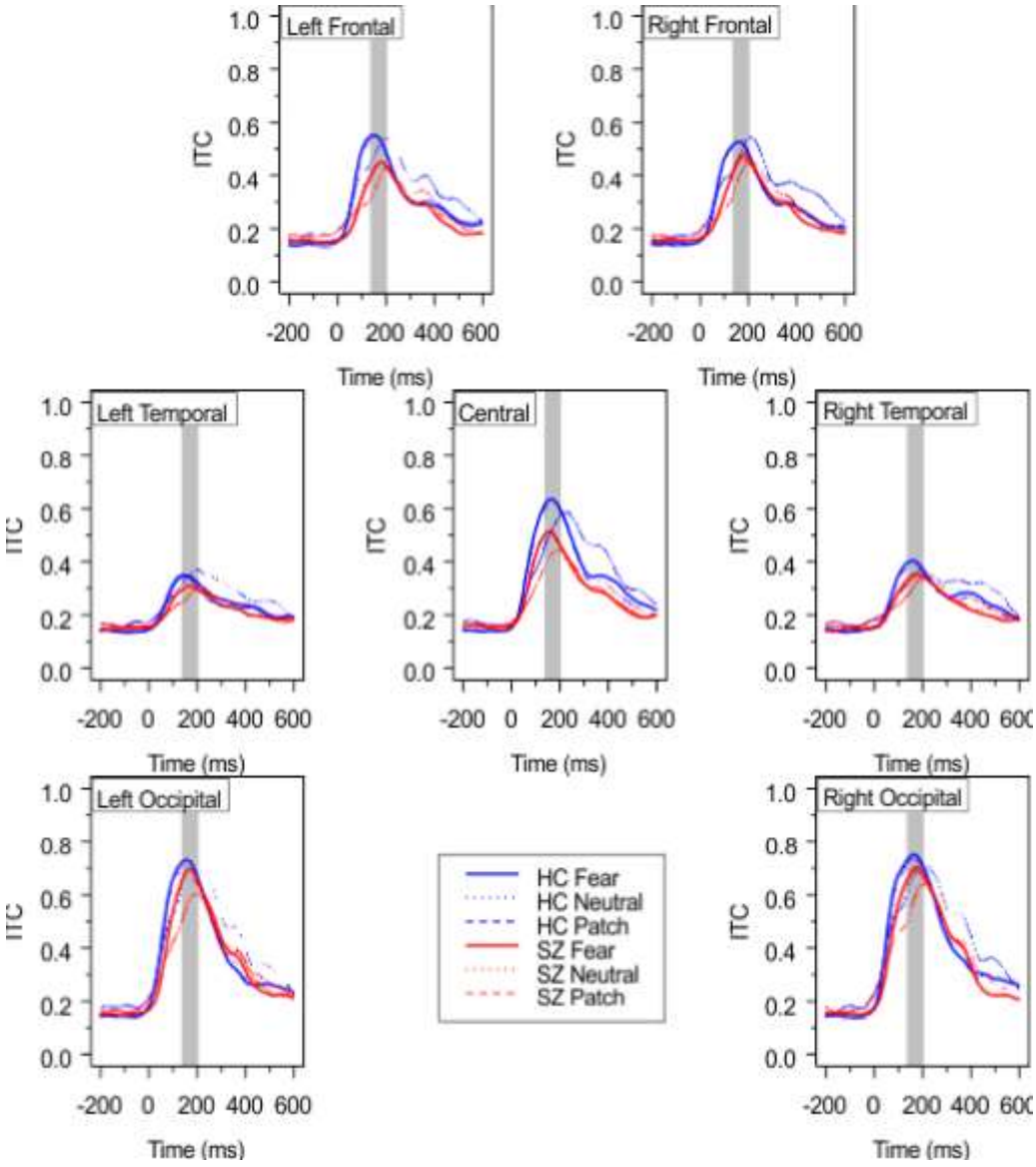

Figure 13. Between-group differences in inter-trial theta coherence (ITC) in the three conditions. HC = Healthy Control Group; SZ = Schizophrenia Group.

4.2.4.2. Association between ITC and behavioral results

Emotion recognition performance as indexed by the FEEST correlated significantly with ITC to both face conditions over the left frontal ROI in the patient group (Fearful: r=0.54, n=24, p=0.01; Neutral: r=0.49, n=24, p=0.02), and over the right frontal ROI in the control group (Fearful: r=0.55, n=21, p=0.02; Neutral: r=0.53, n=21, p=0.02). In the control group emotion recognition performance correlated significantly with ITC to the neutral face condition over the left temporal region, and reached only a tendency level with ITC to fear face condition in the same region (Fearful: r=0.44, n=21, p=0.07; Neutral: r=0.51, n=21, p=0.03). All correlations were controlled for age, gender and education.

In the control group emotion recognition performance during the EEG recording and ITC to both face conditions correlated significantly over the right frontal region (Fearful: r=0.47, n=21, p=0.05; Neutral: r=0.5, n=21, p=0.04). In the patient group emotion recognition performance during EEG recording correlated significantly with ITC to fearful face condition, and reached only a tendency level with ITC to neutral face condition over the right temporal region (Fearful: r=0.49, n=24, p=0.02; Neutral: r=0.41, n=24, p=0.06).

Stronger inter trial coherence (ITC) values were associated with higher recognition rates in all cases. No significant association between ITC to the non-face patch and emotion recognition was found in any of the ROIs ($p>0.05$).

4.3. Results Study 3

4.3.1. Behavioral Results

Regarding behavioral results, high hit rates and low false alarm rates in both groups, even in the patient group made it likely that subjects' attention was sufficiently engaged by the task and not diverted away from the task to the faces shown in the periphery.

4.3.2. Electrophysiological results

4.3.2.1. Mismatch responses for fearful faces

In the control group a significant mismatch response was detected in the 250-360ms time window over the left and right occipital and right temporal regions. No significant mismatch response was detected in the schizophrenia group in any of the ROIs for the fear condition. Significant group difference ($F(1,46)=6.6$, n=48, P=0.01) was found in the 250-360ms time

window over the right temporal region. This difference was 0.75 in terms of the effect size measure Cohen's d (SD). The difference between study groups did not reach significance over the occipital regions (P>0.1).

4.3.2.2. Mismatch responses for happy faces

In the control group a significant mismatch signal was detected over the central and the left temporal region in the 170-220ms time window, while no mismatch was detected in any of the ROIs in the schizophrenia group. A significantly larger mismatch response was observed in the control group compared to the patient group over the central ($F(1;46)=7.9$, $n=48$, $P=0.007$) and the temporal left ($F(1;46)=9.1$, $n=48$, $P=0.003$) regions. These differences were 0.81 and 0.89 SD, respectively.

In the control group in the 250-360 ms time window a significant mismatch signal was detected over the central and occipital ROIs, and again, no significant mismatch was detected in the schizophrenia group in any of the ROIs. The difference between the groups was significant over the central region ($F(1;46)=5.5$, $n=48$, $P=0.02$, Cohen's $d=0.68$).

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5. DISCUSSION

5.1. Discussion of Study 1

We investigated the electrophysiological response to fearful faces in schizophrenia, as of all other basic emotions fear seems to have the most prominent role in attention allocation and emotional processing. To our knowledge, this is among the first electrophysiological studies with dense-array 128-channel electrode placement to investigate the time course and topography of fearful facial emotion processing in patients with schizophrenia as compared to individually matched healthy controls.

Regarding behavioral data of the 'online' emotion recognition task during EEG, reaction times in schizophrenia patients were significantly longer, and emotion recognition performance was significantly worse than in healthy controls, a consistent finding in schizophrenia research. Nonetheless, both groups showed a relatively high hit rate (>90%) in correctly identifying fearful and neutral faces. Emotion showed no effect on hit rates or reaction times, suggesting there was no overt behavioral differentiation between fearful vs. neutral faces in either of the study groups. This absence of difference could be partly explained by taking into account the clinical characteristics of the patients. The patients' average PANSS scores were low and their average dose of antipsychotic medication was also in the lower to middle range, indicating a chronic-stable mental state of the participating patients.

Another explanation could be that the recognition task applied during the EEG recordings was too simple, as participants only had to decide between fearful faces, neutral faces, and non-face patches, and this resulted in little variation in performance and caused a statistical ceiling effect. This online task of a low cognitive demand perhaps should not be considered as an indication of performance accuracy, but rather as an indicator that participants were performing the correct task and their attention was fully captured by the task. Nevertheless, this lack of significant differences in emotion recognition performance between schizophrenic and control subjects has also been reported in several previous studies (Herrmann et al., 2004b; Turetsky et al., 2007). Johnston and colleagues (Johnston et al., 2005) pointed out that difficulties in emotion recognition in schizophrenia might correspond more to a generalized

performance deficit related to task complexity than to a specific recognition deficit for negative emotions. The longer reaction times observed in the schizophrenia group could support this assumption of a generalized processing slowness. Reports of ERP changes without overt behavioral differences are frequently observed in ERP literature (Ibanez et al., 2012; Johnston et al., 2005; Kotchoubey, 2006). This finding reveals that physiological responses may evidence subclinical aspects of early facial discrimination that may not necessarily reach consciousness or manifest explicitly through behavior.

Although fear-provoking faces seemed to elicit no differential response on a behavioral level in either study group, differentiation between fearful and neutral faces on an electrophysiological level was detectable in the time interval of 150-170ms in both groups, confirming previous results (Blau et al., 2007; Pourtois et al., 2005) and suggesting an early, consistently reported bioelectrical response to emotional faces. Patients also displayed an additional electrophysiological differentiation of fearful compared to neutral faces at a later, 330-450ms time interval, showing a deviation from zero in their emotion-related GFP, indexing greater processing effort for fearful face stimuli. Consequently, our results call attention to a later stage of facial emotion processing, which proved to be distinguishing between the patient and control groups. The finding of additional activity in schizophrenia patients to fearful stimuli in the later processing stage might reflect a hyperresponsivity to fearful stimuli, i.e. an additional cognitive-contextual processing component that was absent in healthy controls. Furthermore, earlier evidence has shown that schizophrenia patients might be oversensitive to emotional facial expressions in general, as they might find the emotions evoked by faces anxiogenic and thus avoid making eye contact or paying attention to these stimuli (Mandal et al., 1998).

The fact that more attention is allocated to the processing of fearful as compared to neutral faces at a later emotion processing stage might be further elucidated if we interpret the electrophysiological findings in the context of clinical symptomatology. Correlation analyses in this later time interval in the schizophrenia group revealed that more severe positive symptoms were associated with a greater difference in the GFP between the two conditions, suggesting a more accentuated, perhaps "hypernormal" processing difference of fearful vs. neutral faces in the schizophrenia group with more pronounced positive symptoms. By contrast, more severe negative symptoms correlated with a diminishing difference in the GFP, which suggests that schizophrenia patients with more negative symptoms show a smaller, closer-to-normal distinction at the electrophysiological level between fearful vs. neutral faces.

This reciprocal relationship suggests that the above finding is modulated by an underlying clinical symptomatology of fear processing in schizophrenia. Positive symptoms, such as paranoid delusions, seem to enhance neural hyperresponsivity to fear, while negative symptoms, such as blunted affect, seem to attenuate the neural response to fear.

Another potentially distinguishing factor between the neural activation pattern of fearful vs. neutral faces in the two study groups is the different topographical distribution of ERP signals associated with emotion processing. We investigated this possibility in our exploratory analysis. Previous studies presented results showing a pattern of hypofrontality in the schizophrenia group (Buchsbaum, 1995; Johnston et al., 2005), according to which patients with schizophrenia would show a lower frontal-occipital activation ratio than healthy controls in PET and fMRI paradigms. Regarding neural activation in the time interval where the two groups showed differential processing of fearful vs. neutral faces as measured by the GFP (i.e., the late latency range in the 330-450ms time window), detailed topographical analysis revealed a difference in topographical distribution of brain electric activity between the two groups. While controls showed no overall differentiation between fearful and neutral stimuli on the GFP level, a significant left frontal activation for the differential processing of fearful vs. neutral faces was still apparent, and this frontal activation was absent in the schizophrenia group. Instead, the differential topographical response to fearful vs. neutral faces among patients was the most pronounced in the occipital regions.

The posteriorization effect in the patient group raises the possibility that while normal controls recruit frontal areas for higher-order emotional contextual processing, patients with schizophrenia show an alternative, compensatory emotion processing pattern with an activation shift from frontal to more posterior regions. In a complex emotion recognition ERP-fMRI study Johnston and colleagues (Johnston et al., 2005) reported a posteriorization effect in schizophrenia patients as compared to healthy controls in the processing of emotional vs. neutral faces in the later emotion processing stage (P3a), which is similar to our aforementioned time window. The lateralization effects in our study are also consistent with Johnston et al.'s and with previous findings of lateralization differences between schizophrenia patients and healthy controls in emotion recognition tasks (Strik et al., 1994). Specifically, we found a bilateral response pattern in the 330-450ms time interval for schizophrenia patients when compared with a left-lateralized response in healthy controls. In sum, our topographical results also underline a distinct processing mechanism for fearful faces as compared to neutral ones in the schizophrenia group as compared to controls.

Taken together, our results indicate that while there is no overt behavioral differentiation between fearful vs. neutral faces in either of the study groups, there is evidence for differential processing of fearful vs. neutral faces between schizophrenia patients and matched healthy controls in terms of evoked brain responses which was manifested in the later stages of emotion processing. These results, together with the observed posteriorization effect might reflect a compensatory strategy of the schizophrenia patients for achieving similarly good results on a behavioral level through a greater processing effort of fearful faces as indexed by a greater difference in the GFP difference wave in the later time range on an electrophysiological level.

5.2. Discussion of Study 2

Our main findings are twofold: first, event-related theta activity and phase-locking predicted emotion recognition performance in both controls and patients with schizophrenia; second, event-related changes in theta activity and phase-locking were found to be significantly weaker in patients compared to healthy controls in the 140-200ms post-stimulus time window.

Measures of event-related changes in induced and evoked theta oscillatory activity (ERSP) and phase-locking across trials (ITC) to fearful and neutral faces relative to non-face stimuli in the 140-200ms time window were significantly larger in both study groups over all ROIs. This result corroborates previous results showing that activity in the theta frequency range plays a prominent role in face-specific information processing in this time window. Furthermore, it is known from previous studies applying simultaneous ERP and fMRI measures that electrophysiological activities in this time window are mainly localized to the fusiform face area and the superior temporal sulcus (Horovitz et al., 2004; Iidaka et al., 2006; Sadeh et al., 2010), regions specialized for face and facial feature processing.

In both study groups we found a strong positive relationship between event-related theta activity changes and emotion recognition performance as indexed by the FEEST over the frontal regions (**Figure 9**). As expected, such a relationship was observed only in response to facial stimuli; event-related theta activity to non-face patch stimuli was not associated with emotion recognition performance. A further positive correlation was found between emotion

recognition performance and theta phase-locking (ITC) to facial stimuli over frontal and temporal regions; again, ITC to non-face patch stimuli was not associated with emotion recognition performance. These findings support the notion that effective facial emotion recognition requires both stronger neural activation and temporal coding.

Overall, healthy controls showed significantly stronger event-related theta activity (ERSP) and phase-locking (ITC) in the theta band than schizophrenia patients. These findings are in line with previous investigations showing decreased temporal coding and neural activity in the low frequency band in patients with schizophrenia (Doege et al., 2009; Shin et al., 2010; Uhlhaas et al., 2008).

When theta activity (ERSP) was analyzed by region, differences between study groups were significant over central and both occipital regions only for face stimuli. In the right temporal and left frontal regions the differences between study groups were significant for both face and non-face stimuli (**Figure 9**). ERSP reached its maximum over the former (central and occipital) regions in both groups, which is in line with previous findings by Guntekin and Basar (Guntekin and Basar, 2009). In these regions between-group differences were present only for the face-stimuli. The largest between-group difference (1.2 in Cohen's d) in theta response (ERSP) was detected to fearful faces over the central region. When theta phase-locking (ITC) was analyzed by region, the between-group difference reached only marginal significance in the central region (0.8 in Cohen's d) (**Figure 10**).

A decreased event-related theta response was observed in the schizophrenia group compared to healthy controls also for non-face patch stimuli in the right temporal and left frontal regions. This finding supports the notion that there is a general visual decoding deficit in schizophrenia (Dias et al., 2011; Javitt, 2009; Martinez et al., 2012), which may contribute to the specific impairment seen in facial expression and emotion recognition.

Generally, no difference in ERSP was found between fearful and neutral facial stimuli. However, contrary to ERSP, phase-locking in the theta band was sensitive to the emotional valence of face stimuli. Overall phase-locking was significantly higher to fearful faces than to neutral faces. This finding is in line with previous studies showing larger ERP amplitudes for emotional compared to neutral faces in the 140-200ms time window (Blau et al., 2007; Eimer and Holmes, 2007), which corresponds well to that of the N170 ERP component. However, other studies reported no relationship between emotional content of the face and the N170 component (Ashley et al., 2004; Eimer and Holmes, 2002).

Neither ERSP nor ITC measures correlated significantly with scores on the Positive and Negative Symptom Scale or medication dose in chlorpromazine equivalents, which is in line found no correlations of response amplitude with symptom severity or medication dose (Herrmann et al., 2004a). However, another study reported a limited correlation between the N170 amplitude and positive psychotic symptom severity (Campanella et al., 2006). The only study that analyzed brain oscillations in relation to facial emotion recognition in schizophrenia did not report any correlations with symptom severity or dose of medication (Ramos-Loyo et al., 2009). It is worth to note, however, that in our cross-sectional study the average PANSS scores were relatively low, indicating a chronic-stable mental state of the participating patients, which might have limited our ability to find a correlation between symptom severity and theta oscillations. Further longitudinal studies, or the inclusion of patients with severe psychotic symptoms are needed to clarify the association.

A link between event-related theta activity during face decoding and emotion recognition ability was found. Subjects who showed stronger event-related theta response and phase-locking performed better at recognizing basic emotional expressions, which finding confirms that facial emotion recognition requires greater neural activation and temporal coding. Patients with schizophrenia showed weaker event-related theta activity and phase-locking, which led to less effective facial emotion recognition performance. Thus, our results support the notion that impairments in theta synchronization may contribute to social cognitive deficits and quality of life impairments in schizophrenia.

5.3. Discussion of Study 3

To our knowledge the current study is the first to compare visual mismatch responses, an index of automatic predictive mechanisms, to unattended facial expressions between patients with schizophrenia and controls. Non-conscious expectations were induced by frequent repetitions of unattended faces (standard) expressing a particular emotion and this expectation was violated by faces expressing a different emotion (deviant). ERPs to physically identical deviant and standard stimuli were compared to control for possible effects for differences in low-level physical features. We interpret the observed mismatch activity as prediction error responses to ‘unexpected’ emotions, since in the current study pictures of several male and female models were used to avoid the possibility of low-level adaptation to features of a

particular face. Thus, predictive memory representations were formed for emotions rather than to individual faces.

In the schizophrenia group, a tendency for mismatch responses was detected over the occipital regions for the fear condition in the 170-220ms and 250-360ms time windows. However, after correction for multiple testing mismatch responses in the patient group did not reach significance for any of the emotional conditions. These findings are in line with the results of Urban and colleagues, who also reported decreased visual mismatch responses in a schizophrenic group in a motion-direction oddball paradigm (Urban et al., 2008).

Our results showed that the magnitude of the deficit in mismatch generation in the visual modality is comparable to that detected in the auditory modality. Our results also indicate that the visual (emotion processing) system was capable of detecting the difference between frequent (standard) and rare (deviant) stimuli in healthy participants, while the same detection process was impaired in patients with schizophrenia. Alternatively, it is conceivable that the build-up of the expectation for a reappearing (repeating) emotion might have failed in schizophrenia patients, thereby preventing the elicitation of a mismatch response. In either case, our results demonstrate that impairment of emotion processing in schizophrenia is present already at the automatic, unconscious level. Our findings support the notion that impaired generation of mismatch signals may indicate impairment in automatic processing of emotions in patients with schizophrenia, which may lead to decreased emotion recognition and subsequently to a disability in social functioning.

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6. GENERAL DISCUSSION

6.1. Summary of main findings

In our investigations, we aimed to achieve a closer insight into the electrophysiological underpinnings of a fearful face recognition deficit in schizophrenia using quantitative EEG analyses. With correlating electrophysiological indices such as the ERP-derived GFP, ERSP and ITC with behavioral data on emotion recognition tasks and with ratings of psychopathology, our aim was to delineate associations between the electrophysiological data and emotion recognition ability that would differ in patients with schizophrenia as compared to healthy controls.

To our knowledge, our studies are among the first to examine both time-domain and time-frequency decomposition of EEG in response to fearful facial stimuli using a high density EEG electrode array, with findings showing not only deficits in schizophrenia but correlations in both groups between the EEG measures in response to faces and performance on a facial affect recognition task.

We have shown that patients significantly differ from healthy controls in several aspects of electrophysiological and behavioral measures, and that differential responses are obtained via these indices as a function of face vs. non-face stimuli and as a function of fearful vs. neutral face stimuli. In the following our main findings are summarized and later intrepreted in more detail:

1) We found evidence for differential processing of fearful vs. neutral faces between schizophrenia patients and healthy controls in terms of evoked brain responses, as indexed by the GFP. This was manifested in the later stages (330-450ms) of emotion processing.
2) In schizophrenia subjects, differentiation between fearful vs. neutral faces was modulated by clinical symptomatology of fear: positive symptoms seemed to enhance neural hyperresponsivity to fear, while negative symptoms seemed to attenuate the neural response to fear.

3) A posteriorization and hypofrontality effect in the patient group was shown by differential ERP response topography to fearful vs. neutral faces among patients compared to healthy controls, which was reflected in a pronounced activation mostly in the occipital regions and absence of activation in the frontal regions.
4) Event-related changes in theta oscillatory activity as indexed by the ERSP and ITC were significantly weaker in patients with schizophrenia as compared to healthy controls in the time interval of 140-200ms post-stimulus.
5) Event-related changes in theta oscillatory activity as indexed by the ERSP and ITC to facial expressions and not to non-face stimuli predicted emotion recognition performance in both groups in the time interval of 140-200ms post-stimulus.
6) While there was no overt behavioral differentiation in an online emotion recognition task between fearful vs. neutral faces in either of the study groups, control subjects significantly outperformed patients on the offline emotion recognition task as indexed by the FEEST.
7) Decreased visual mismatch responses in the schizophrenia group as compared to healthy controls in both the 170-220ms and 250-360ms time windows suggest impairment in the processing of emotions already at the automatic, unconscious level in patients with schizophrenia.

6.1.1. Face-specific processing

Regarding face-specific information processing, all three of our investigations indicated a face-specific processing stage in the 140-200ms time interval post-stimulus that was present in patients with schizophrenia as well as in healthy controls. Using event-related brain responses as indexed by the GFP, we found a significantly larger N170 component in both groups to neutral faces as compared to non-face patches in the occipital region. Measures of event-related changes in induced and evoked theta oscillatory activity (ERSP) and phase-locking across trials (ITC) to fearful and neutral faces relative to non-face stimuli in the 140-200ms time interval were also significantly larger in both study groups over all ROIs. These results corroborate the established finding that the 140-200ms time window reflects a face-specific processing stage, and that theta activity in this window plays a prominent role in face-specific information processing (Rousselet et al., 2007). Our results are consistent with previous findings from concurrent ERP and fMRI measures; they show that

electrophysiological activities in this time interval are mainly localized to the fusiform face area and the superior temporal sulcus (Horovitz et al., 2004; Iidaka et al., 2006; Sadeh et al., 2010), regions engaged in facial feature processing. These regions may serve as the generators of the synchronized electrophysiological activity as captured by several measures in the face-specific processing window. According to our findings, faces seem to be stimuli that successfully synchronize cortical theta activity in both groups in order to decode the structural properties of faces and to recognize facial stimuli as faces. This result is consistent with the finding that both study groups showed a strong positive relationship between event-related theta activity changes (ERSP) and emotion recognition performance over the frontal regions in this time window, and such a relationship was observed only in response to facial stimuli, but not to non-face patch stimuli. Similarly, a further positive relationship was found between emotion recognition performance and theta phase-locking (ITC) to facial stimuli over frontal and temporal regions, but again, not to non-face patch stimuli. These findings confirm previous findings that neural activity in the 140-200ms time window post stimulus plays a prominent role in face recognition.

6.1.2. Indices of impaired processing of fearful faces in schizophrenia

In our first investigation, regarding emotion effects in event-related brain responses as indexed by the GFP, schizophrenia patients showed a differentiation between fearful vs. neutral faces in the expected 150-170ms time window, just as healthy controls did. However, they also showed an additional electrophysiological differentiation of fearful compared to neutral faces at a later, 330-450ms time interval. Such a differentiation was absent for controls. Consequently, it was a later stage of facial emotion processing that proved to be distinguishing between the patient and control groups. Fearful face processing not being limited to the face-processing stage, as in controls, additional electrophysiological activity in a later processing stage might possibly reflect a greater processing effort for fearful face stimuli in the patient group. A speculative explanation for this additional electrophysiological activity in schizophrenia patients to fearful stimuli that was absent for healthy controls might be that patients show a hyperresponsivity to fearful stimuli on an electrophysiological level.

In our first investigation, based on event-related measures of fearful face processing, in the face-specific processing stage (150-170ms) schizophrenia patients' responses to fearful faces

were not significantly smaller than those of healthy controls. However, our results of the second investigation did delineate an impairment in this processing phase through a time-frequency analysis. Specifically, relative to controls, theta response showed a marked reduction in patients for fearful faces, with less reduction to neutral and no reduction to non-face stimuli. In additon, correlation results indicate that alterations of neural synchrony as reflected by theta reductions in facial emotion processing networks in schizophrenia are associated with impairments in facial affect recognition performance in schizophrenia. Together, these results highlight the involvement of theta-band oscillations in the processing of fearful faces. Furthermore, they suggest that neural synchrony in the theta band might be necessary for efficient fearful face processing, the impairment of which is detectable in schizophrenia.

There were no overt behavioral impairments in schizophrenia patients compared to healthy controls in the online emotion recognition task, while we found differences between the two groups in a more difficult, offline emotion recognition task. These differences may be underlied by the ERP components and event-related oscillations that differed between the two groups, suggesting that fearful emotion recognition is related to dysfunctional neural circuits in schizophrenia. Furthermore, differences observed in temporal and spatial distribution in the oscillatory activity and ERP components suggest that patients with schizophrenia might use alternative, compensatory emotion processing pathways. Patterns of hypofrontality suggest that this might occur via an activation shift from frontal to more posterior regions, together with a synchronization deficit in the areas involved in fearful face recognition.

6.1.3. Hyperreactivity to fearful faces in schizophrenia

One of our main findings from the first investigation is a hyperresponsivity of schizophrenia patients to fearful faces on an electrophysiological level as seen in the later processing stages of fearful face recognition. Our finding could be explained by previous studies which reported a difficulty in schizophrenia patients in disengaging attention from negatively valenced stimuli (Strauss et al., 2011), thereby leading to a negativity bias. During the investigation, many patients also explicitly reported of having found the fearful faces presented to them in the experiment very intense and unpleasant to look at for a long time. The fact that patients find faces more aversive than healthy controls might suggests an amygdala hyperactivity,

which may be associated with increased anxiety or fear of faces (Anticevic et al., 2012). The extent to which amygdala activity in patients reflects an increased emotional response, e.g. anxiety or fear, to face stimuli remains an unresolved issue; nonetheless, some evidence suggests that there are multiple processing stages or routes for fearful faces which vary in their dependence on amygdala function (Pourtois et al., 2013). It has been shown that highly anxious individuals may have a lower threshold for threat processing, they might be more readily triggered to attentional orienting to threatful stimuli, thus resulting in greater cueing effects for them to fearful faces (Mathews et al., 2003).

The experienced level of anxiety possibly induced by the experimental stimuli might also have a modulatory effect on electrophysiological responses in an experimental setting where dominantly fearful faces are shown to the participants. It might be of interest in future research to further delineate the relationship between experienced levels of anxiety, clinical symptomatology, and electrophysiological indices in schizophrenia to fearful faces. Our correlational results showed a relationship between electrophysiological findings and symptom severity, which calls attention to the modulatory effects of positive and negative symptoms on electrophysiological responses in schizophrenia. Schizophrenia patients with positive symptoms show a hyperresponsivity to fear, whereas negative symptoms, in turn, seem to reduce electrophysiological sensitivity to fearful faces and heighten the threshold for threat processing. These findings accentuate the heterogeneity in symptom presentation within the schizophrenia population and its importance in interpreting findings. Future research should consider including measures of anxiety, as electrophysiological correlates of fear processing might gain more meaning if also levels of anxiety are taken into consideration in correlational analyses.

6.1.4. Decrease in theta oscillatory activity in fearful face recognition in schizophrenia

One of the main results from our second investigation is that healthy controls showed significantly stronger event-related spectral changes (ERSP) and phase-locking (ITC) in the theta band than schizophrenia patients during processing of fearful facial expressions. These findings are in line with previous investigations showing decreased temporal coding and neural activity in the low frequency band in patients with schizophrenia (Doege et al., 2009;

Shin et al., 2010; Uhlhaas et al., 2008). In schizophrenia research gamma-band oscillations have recently come into the spotlight as an index of impaired cognitive functioning, and impaired gamma-band oscillations are on their way of becoming a traceable endophenotype in schizophrenia (Buzsaki and Watson, 2012). Nonetheless, dysfunctions in theta-band activity related to impaired facial emotion recognition are also beginning to gain more and more focus. The significant role of theta in facial emotion recognition was corroborated by our correlational results, which indicated a strong positive relationship between event-related theta activity changes and emotion recognition performance as indexed by the FEEST.

The fact that theta-band oscillatory activity as indexed by both ERSP and ITC was decreased in the 140-200ms time range is consistent with the notion that there is a general visual decoding deficit in schizophrenia (Dias et al., 2011; Javitt, 2009; Martinez et al., 2012) as this time window has been shown to be specific for the processing of facial features (Eimer and Holmes, 2002). Even though in our first investigation we did not find a significant group difference as indexed by the GFP in this time range, which would reflect a general face processing deficit in schizophrenia, our time-frequency analysis does indicate an impairment in this time range in schizophrenia at the oscillatory level. Our correlational results also corroborate a deficit in emotion recognition performance in this time range in schizophrenia. Thus, our results suggest that different analytical approaches of the EEG can give a somewhat different, but complementary picture of processing mechanisms.

6.1.5. Combining time-domain and time-frequency analyses

In the two investigations we took two different approaches to examine the neurophysiological underpinnings of fearful face recognition in schizophrenia in relation to emotion recognition performance and psychopathological symptoms. Both approaches have certain limitations and advantages. The two approaches complemented each other in both statistical and methodological aspects.

The time-domain approach captures the time-and phase-locked evoked activity in the brain, but not phase-incoherent brain dynamics. These, however, are captured by the time-frequency domain approaches, the ERSP and ITC, which yield additional information of the ongoing brain dynamincs than time-domain indices.

Our time-domain analyses shed light on event-related aspects of fearful face processing and our GFP difference index revealed that both groups showed a differentiation between fearful and neutral faces at a face-specific processing stage (170-200ms), but also at a later processing stage, around 330-450ms post-stimulus. Only this later time window proved to be distinguishing in terms of emotional valence processing between the two groups.
Regarding our second analytical approach (time-frequency) to fearful face processing, our findings pinpointed the face-specific processing range (140-200ms post-stimulus) to be distinguishing in terms of spectral power change between the two groups, espacially in the theta range. Therefore, we focused our further analyses to this time range.

Overall, we gained insight into two different processing stages in the information-processing cascade of fearful faces. In particular, we found processing deficits in patients with schizophrenia both in face-specific and in later, higher-level processing stages of fearful face processing. Our results are consistent with other findings in the literature, which indicate the heterogeneity in face processing deficits in schizophrenia (Turetsky et al., 2007; Wolwer et al., 1996b; Wynn et al., 2008). Combined time-domain and time-frequency domain analyses yield a more complex way to understand the neural underpinnings of fearful face processing in schizophrenia.
As new trends in cognitive neuroscience are emerging, time-frequency analyses are gaining more and more focus in schizophrenia research as well. A new approach would be to view psychiatric diseases from the perspective of oscillations and assembly- related fast timescale neural activity, that could lead to new understanding of the underpinnings of psychiatric symptoms in the form of “rhythmopathies,” “oscillopathies” or “dysrhythmias” , which may reflect malfunctioning networks (Schulman et al., 2011). This new research approach would possibly also open new avenues to novel and useful therapies (Buzsáki and Watson, 2012).

6.1.6. Processing of unattended facial emotions in schizophrenia

Results of our second paradigm, discussed briefly as a complementary paradigm to the attended facial emotion recognition paradigm in this dissertation, corroborate our results gained through the two investigations using the first paradigm. Specifically, the fact that schizophrenia patients showed significantly reduced visual mismatch responses to unattended facial emotional expressions may indicate impairment in automatic, preattentive processing of

emotions in patients with schizophrenia. In fact, our results from both paradigms seem to be complementary and underline emotion processing deficits in schizophrenia to be present at both conscious and non-conscous levels of information processing. The fact that this impairment was apparent in the face-specific processing stage, which was also the case in our first two investigations calls attention to a general structural encoding deficit in schizophrenia. Failure in building up a predictive model based on the regularities of facial expressions around us, and the comparison of any upcoming facial cue to this model indicates an impairment present already in the pre-attentive phases of facial emotion recognition. Regarding the fact that a great part of visual information in our everyday life lies beyond our attentional focus, impairment at this level can have considerable consequences that could affect social cognitive abilities, and thus the everyday functioning of schizophrenia pateints.

6.2. Fearful face processing deficit in the context of cognitive and emotional interference

The investigation on fearful face recognition can be embedded in a broader context of the interplay between cognitive and emotional processes. The question conceived within the context of emotional and cognitive processes hierachically competing for resources might have less relevance, as it seems to be not purely bottom-up or top-down processes regulating neural processing mechanisms, but both seem to work in a more parallel way. Our findings of both an earlier and a later deficit in the processing of fearful faces might be more easily interpreted in a framework that does not entail exclusivity. Relating back to Ochsner's model (2008), where processing of social-emotional stimuli is partly serial and hierarchical in nature, cognitive and emotional processes could also be conceived as more parallel in nature, allowing also for compensatory and alternative processing routes in the case of deficiencies, as suggested in latest findings (Pourtois et al., 2013).

Findings in affective-cognitive pathways in schizophrenia have shown deficient affect regulation strategies: activities in the affective division of the anterior cingulate cortex (ACC) as well as the dorsolateral prefrontal cortex (DLPFC), prefrontal systems that implement cognitive control processes and systems that appraise the affective properties of stimuli, were unsuppressed to explicit emotional interference despite cognitive effort reflected in the

DLPFC activity in the patients with schizophrenia. This finding suggests that regulation in monitoring of emotional salience by the affective division of the ACC may be dysfunctional in schizophrenia (Park et al., 2008). In a broader context, the underinvolvement of inhibitory cortical mechanisms to emotionally salient stimuli, and the use of alternative processing mechanisms, as also corroborated by a hypofrontal – hyperposterior activation to fearful faces as seen in our results might be an approach to further pursue and explain affective and cognitive deficits in schizophrenia.

6.3. Limitations

Certain limitations regarding methodological issues and medication should be considered. In our study stimuli were presented for 200ms and intertrial interval randomly varied between 600-700ms after button press. Thus, a carry-over effect, i.e. effects that might persist from one stimulus presentation to the next between individual trials, as in most ERP studies, is conceivable; however, due to the random sequences that we used these effects were likely to be cancelled out and were therefore unlikely to confound the findings. Nonetheless, future research should consider to use longer intertrial intervals in order to further minimize the possibility of carry-over effects. In addition, focusing on longer time windows after 500ms post-stimulus needs to be considered in order to investigate even later phases of emotion processing.

With regard to medication, a common concern in imaging studies of clinical populations is the potential influence of medication on results. In the current studies, all patients were receiving stable antipsychotic medication. Although in our studies no correlation was found between antipsychotic dose and electrophysiological measures, nonetheless, it cannot be ruled out that medication levels may have played a role in differences seen in electrophysiological measures. However, to date, little is known about the exact effects of antipsychotic medication on emotion processing. As stated by Horan el al. (Horan et al., 2010b), our current knowledge about the effect of antipsychotic medication on emotional processing is by far not as comprehensive as to be able to determine its extent, but evidence suggests that such effects are minimal (Berenbaum and Oltmanns, 1992; Horan et al., 2010b). To fully rule out the

possible effects of medication, it will be important to show whether a similar pattern of results is present when examinig either unmedicated patients, at-risk populations, or subjects in the prodromal stages of psychosis who are not yet taking medication. Also, longitudincal study designs of emotion processing would give more opportunities to detect potential medication effects and also to draw closer conclusions about the trait versus state nature of emotion processing deficits in schizophrenia.

A further limitation of our experimental design might be the fact that in this study we only used fearful faces as emotionally valenced faces compared to neutral faces. There are several reasons for this. Evidence suggests that patients with schizophrenia might show an overall impairment in emotion recognition, however, fear perception seems to be specifically impaired in this patient population (Kohler et al., 2003). Fear perception might be related to the „negativity bias", whereby patients show a strong inclination to misidentify neutral stimuli as negatively valenced (Edwards et al., 2001; Kohler et al., 2003; Premkumar et al., 2008; Tsoi et al., 2008). Taken together, research suggests that emotional abnormalities seen in schizophrenia may primarily relate to dysfunctions in negative emotion processing, out of which fear is one of the most salient emotions.

From a methodological perspective, fear is one of the most well-researched emotions in schizophrenia in electrophysiological studies. Therefore, in a first study of a series of planned studies, we chose the emotion of fear to investigate via electrophysiological reserach methods, to be followed by other valenced emotions in later related studies. Related to methodological issues, our study paradigm for electrophysiological analysis is best suited for a small number of stimulus variants, as for statistical purposes a great number of trials of the same stimuli are needed for analysis. Thus, to keep the study within managable and reasonable time limits, especially taking into consideration the limited span of concentration ablities of psychiatric patients, we chose only fearful and neutral faces to be included in or study.

Consequently, further research needs to be done to ascertain whether these emotion effects are present also during other negatively valeced emotions, such as anger or disgust, and to test whether the observed deficit in schizophrenia is isolated to the processing of fearful facial expressions. Also, we used only neutral faces as control condition and no other valenced emotions, thus, the use of positively valenced facial stimuli, such as happy faces, could be informative to detect differences in the processing of negatively versus positively valenced

facial expression and to be able to draw more general conclusions about emotion effects in schizophrenia. The inclusion of more emotional expressions would be essential to increase the ecological validity and the translational implications of results.

6.4. Future directions

Our findings regarding the neurobiological underpinnings of fearful face recognition in schizophrenia can be put into a broader context regarding relationships between social cognitive processes, neurocognition, psychopathological symptoms and measures of functional outcome. Social cognition is increasingly viewed as a viable treatment target (Pinkham and Harvey, 2013). This is in large part due to a growing body of evidence demonstrating that social cognitive abilities contribute to real-world outcomes (Couture, Penn, and Roberts, 2006; Fett et al., 2011) and that remediation of social cognitive impairments leads to improvements in functional outcome (Eack et al., 2010; Combs et al., 2009). A boom in several non-pharmacological treatment methods can be seen in the recent past targeting cognitive and affective impairments in schizophrenia. Such interventions include cognitive remediation strategies (Frommann et al., 2003; Wölwer et al., 2005; Medalia and Choi, 2009; Wykes et al., 2011), social cognitive rehabilitation programs, attentional shaping training (Russell et al., 2008), and cognitive behavioural therapies targeting emotional dysregulation in schizophrenia (Khoury and Lecomte, 2012).

Within the broad construct of social cognition, efforts have been made to identify specific domains of social cognition as potential candidates for becoming biomarkers for future drug development aiming to target improvement in social cognition in schizophrenia. Reliable biomarkers would also be necessary in the non-pharmacological pathway of improving social cognition in schizophrenia, for example through cognitive remediation techniques. Our results demonstrate robust impairments at the electrophysiological level of fearful face processing in schizophrenia. For emotional face processing deficits to become reliable biomarkers in schizophrenia, further investigations would be needed that include a variety of emotions other than just fear to make this deficit generalizable to facial affect recognition abilities. Futhermore, it would be important to investigate to what extent this deficit is specific for schizophrenia as compared to other psychiatric disorders and to further disentangle medication effects and the time-course of this deficit throughout the disorder.

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The longer-term goal of research into the treatment of brain disorders would be to move away from symptomatic treatments towards therapies that target the underlying aetiology. For example, as seen in our studies, deficits in fear processing in schizophrenia manisfest already at an electrophysiological level of information processing, but this phenomenon is most likely a symptomatic aspect of a more inherent brain dysfunction seen in schizophrenia. Findings from various fields might eventually be integrated to show that dysfunctions on various levels, ranging from molecular to behavioral levels, might have a final common pathway that leads to divergent symptoms in schizophrenia.

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7. SUMMARY

Objectives: To investigate the electrophysiological underpinnings of fearful face recognition in schizophrenia and to explore at what levels of facial information processing impairment occurs in schizophrenia patients as compared to healthy controls. We applied both time-domain and time-frequency domain analytical methods on our EEG data to extract indices as a function of facial emotion recognition to compare in the two study groups and to correlate these with indices of behavioral aspects of emotion recognition and dimensions of psychopathology. Two emotion recognition paradigms were designed to assess attended and unattended processing of fearful face recognition, respectively. **Methods**: 24 patients with schizophrenia and 24 individually matched healthy controls performed two forced-choice block-designed facial emotion recognition tasks while their EEG was recorded from 128 electrodes. Fearful, neutral, and happy faces were used from the standard Ekman facial stimuli. **Paradigm 1, Study 1**: Faces were presented in the focus of visual attention. We investigated the temporal and topographical distribution of the electrocortical responses to fearful facial expressions using event-related potentials as indexed by the Global Field Power (GFP). **Paradigm 1, Study 2**: Faces were presented in the focus of visual attention. We conducted a time-frequency analysis for both evoked and induced neural activity as captured by the Event Related Spectral Perturbation (ERSP) and the event-locked activity, as measured by the phase locking factor, the Inter Trial Coherence (ITC) in the theta frequency band. **Paradigm 2**, **Study 3**: Faces were presented outside of the focus of visual attention. We investigated nonconscious processing of emotional faces using the visual Mismatch (vMMN) event-related component. **Behavioral Results:** Schizophrenia patients were significantly slower and showed less accurate emotion recognition performance on both online and offline emotion recognition tasks. **Electrophysiological results** for conscious processing of fearful faces: **1/** Differential processing of fearful vs. neutral faces in schizophrenia patients as indexed by the GFP was manifested both in the face-specific processing stages (150-170ms), similarly to controls, however, additional neural activity was apparent in the later stages (330-450ms) of emotion processing only in schizophrenia patients. **2/** In schizophrenia subjects, differentiation between fearful vs. neutral faces was modulated by the clinical symptomatology. **3/** A posteriorization and hypofrontality effect in the patient group was shown by differential ERP response topography to fearful vs. neutral faces compared to healthy controls. **4/** Event-related changes in theta oscillatory activity were significantly

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weaker in patients with schizophrenia as compared to healthy controls in the time interval of 140-200ms post-stimulus, and this change in the theta band to facial expressions but not to non-face stimuli predicted emotion recognition performance in both groups. **5/** For unconscious processing, Visual mismatch (vMMN) responses were reduced in schizophrenia patients as compared to healthy controls in both the 170-220ms and 250-360ms time windows, and vMMN responses correlated with emotion recognition performance. **Conclusion:** Our results suggest a deficit affecting both the structural and emotional encoding of fearful faces in schizophrenia patients at both conscious and nonconscious stages of facial emotion processing. Our findings are interpreted in the context of emotional interference on cognitive processes and lend support to the notion that cortical markers of facial discrimination could be validly considered as vulnerability markers in schizophrenia.

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8. ÖSSZEFOGLALÁS

Célkitűzés: Kutatásunk célja annak vizsgálata volt, hogy a félelmet kifejező arcok neurális feldolgozásának mely szintjein és milyen mértékben mutatható ki eltérés szkizofrén betegeknél illesztett egészséges kontrollokhoz képest. Kutatásunkban mind kiváltott válasz alapú, mind idő-frekvencia alapú EEG elemzéseket végeztünk abból a célból, hogy a neurális feldolgozás ezen mutatói alapján összehasonlíthassuk a félelemkifejező érzelmi arcfelismerés feldolgozásának eltéréseit a két csoportban. További célunk volt, hogy az elektrofiziológiai mutatókat korreláltassuk az érzelemfelismerés viselkedéses mutatóival, illetve pszichopatológiai tünetdimenziókkal. Két érzelemfelismerési paradigmát alkalmaztunk az érzelmi arcfelismerés mind tudatos, mind nem tudatos szintű feldolgozásának vizsgálatára. **Módszerek**: 24 szkizofrén beteggel és 24 páronként illesztett egészséges kontrollal készült EEG-felvétel, mely során érzelmi arcfelismeréses feladatot végeztek a vizsgálati személyek a két paradigma alkalmazásával. Az EEG 128 csatornás BioSemi berendezéssel került regisztrálásra. A vizsgálat során bemutatott félelemkifejező, semleges, és boldog arcokat a standard Ekman arcinger készletből választottuk. **1. Paradigma, 1. Vizsgálat**: Az arcokat a vizuális figyelem fókuszában prezentáltuk, és a félelemkifejező arcok által kiváltott agyi kiváltott válaszok idői és téri mintázatát elemeztük a kiváltott válaszok alapján számított Global Field Power (GFP) mutató segítségével. **1. Paradigma, 2. Vizsgálat**: Az arcokat a vizuális figyelem fókuszában prezentáltuk. Idő-frekvencia alapú elemzést végeztünk mind az agyi kiváltott, mind az indukált idegi tevékenységet felölelő eseménykiváltott spektrális perturbáció (ERSP) és fázis koherencia (ITC) mutatókat használva a theta frekvenciatartományban. **2. Paradigma**, **3. Vizsgálat**: Az arcokat a vizuális figyelem fókuszán kívül, a periférián prezentáltuk. A nem tudatos érzelmi arcfeldolgozás különbségét a két csoportban a vizuális mismatch negativity (vMMN) kiváltott válasz mutató segítségével vizsgáltuk. **Viselkedéses eredmények:** Szkizofrén betegek szignifikánsabban lassabban és kevésbé pontosan ismerték fel az érzelmeket egészséges kontrollokhoz képest mind online, mind offline érzelemfelismeréses feladatban. **Elektrofiziológiai eredmények** a tudatos érzelemfelismerési paradigma alapján: **1/** A félelemkifejező versus semleges arcok feldolgozásában a szkizofrén betegek az egészséges kontrollokhoz hasonlóan eltérést mutattak kiváltott válaszok tekintetében az arcfeldolgozásra jellemző időintervallumban (150-170ms post-stimulus), azonban eltérően a kontrolloktól neurális aktivitást mutattak egy későbbi érzelemfeldolgozási szakaszban (330-450ms post-stimulus) is. **2/** Szkizofrén betegeknél a

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pszichopatológiai tünetek összefüggést mutattak a félelemkifejező versus semleges arcok közti különbséggörbével**. 3/** A félelemkifejező arcok által kiváltott agyi kiváltott válaszok topográfiai eloszlása alapján a szkizofrén betegek egyfajta hipofrontalitási választ mutattak egészséges kontrollokhoz viszonyítva **4/** A theta frekvenciában mutatott oszcillációs aktivitás szignifikánsan alacsonyabb volt szkizofrén betegeknél egészséges kontrollokhoz képest az arcfeldolgozásra jellemző 140-200ms-os időablakban. **5/** A nem-tudatos érzelemfelismerési paradigmában a vMMN kiváltott válaszok szkizofrén betegek esetében szignifikánsabban alacsonyabbak voltak, mint egészséges kontrolloknál mind a 170-220ms, mind a 250-360ms időtartományban, és ezek a válaszok korrelációt mutattak az érzelemfelismerési teljesítménnyel. **Konklúzió:** Eredményeink szkizofrén betegeknél a félelemkifejező érzelmi arcfeldolgozás mind strukturális, mind érzelmi vonatkozású dekódolási deficitjére utalnak mind tudatos, mind nem-tudatos információfeldolgozási szinteken. Eredményeinket tágabb kontextusba helyezve az érzelmek kognitív feldolgozásra kifejtett interferencia-hatásának keretében értelmezzük. Az érzelmi arcfelismerési deficit elektrofiziológiai mutatói a betegség potenciális biomarkerének tekinthetők.

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10. LIST OF PUBLICATIONS

10.1. Publications related to the dissertation

Komlósi S, Csukly G, Stefanics G, Czigler I, Bitter I, Czobor P. (2013) Fearful face recognition in schizophrenia: An electrophysiological study. Schizophr Res, 149 (1): 135-140.

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