

**Electrophysiological Investigation Of Facial Expression Processing In Patients With
Schizophrenia: Effects Of Cognitive Behavioural Therapy And Spatial Frequency
Filtering**

By

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ABSTRACT

Growing evidence supports the effectiveness of cognitive behavioural therapy (CBT) for psychosis, including CBT for voices (CBTv), which targets auditory verbal hallucinations (AVH). CBT may be a promising approach for improving information processing difficulties in schizophrenia, and by so doing, facilitating social cognition and daily functioning. While many studies have tested treatment effects in schizophrenia, none have specifically evaluated electrophysiological changes in brain activity following CBT in patients with schizophrenia.

Electrophysiological studies have revealed a number of event related potentials (ERPs) associated with impaired processing of emotional facial expressions in patients with schizophrenia. This well-documented difficulty with facial expression recognition has been associated with impaired low-level visual information processing. However, there is only limited and inconsistent data on the way in which early visual processing deficits are related to impaired emotional expression processing in this patient population. The research presented in this thesis assessed changes in ERPs to emotional expressions following cognitive behavioural therapy for voices (CBTv) in patients with schizophrenia who experience auditory hallucinations. The studies presented also examined ERPs evoked in response to spatial frequency filtered (SF-filtered) and unfiltered images of facial expressions and control objects in healthy controls and a homogenous sample of schizophrenia patients – those experiencing auditory verbal hallucinations. This was done to test certain hypotheses regarding the low-level genesis of face recognition difficulties in schizophrenia.

Relative to controls, patients with schizophrenia indicated blunted: 1) early-stage visual information processing to sad, angry and fearful facial expressions (as indexed by the amplitude of

the P100 ERP), 2) facial structural encoding to neutral, joyful, sad, angry and fearful facial expression (as indexed by the N170), and 3) higher-order decoding of all facial expressions (indexed by mean amplitude of the P300). Assessment of SF-filtered facial expressions found impaired early processing (i.e., P100) specific to low spatial frequency (LSF) filtered fearful facial expression and high spatial frequency (HSF) filtered neutral faces in patients with schizophrenia, which at later stages (i.e., N170 and P300) extended to all facial expressions and SF filtering conditions. Within-group comparisons showed that patients exhibited a different pattern of ERP modulation across facial expressions than controls for P100 and N170, but not for P300. The within-group comparisons also suggested a heightened response to LSF threatening information, relative to BSF conditions, in the patient group.

CBTv therapy did not change ERP amplitudes in response to facial expressions, but was associated with decreased latency in the P100. This improved processing speed was not reflected in later ERP components (i.e., N170 and P300).

These results indicate that earlier perceptual processing impairments are expression-specific and that behavioural and electrophysiological face-processing deficits in schizophrenia arise from early-stage deficits in visual processing. The finding of an improvement in visual processing speed to facial expressions following CBTv treatment provides the first demonstration of CBTv-induced changes to brain responses to facial expressions at an early neural processing stage.

PREFACE

Apart from Chapters 1 and 5, which comprise of the General Introduction and Discussion, respectively, this thesis consists of manuscripts that are in the process of being reviewed in peer-reviewed journals (Chapters 2 and 3) or are being prepared for submission (Chapter 4). The authorship of the manuscripts presented in Chapters 2 and 4 is as follows: Dhrasti Shah, Verner Knott, Ashley Baddeley, Hayler Bowers, Nicola Wright, Allen Labelle, and Charles Collin. The authorship of the manuscript presented in Chapter 3 is as follows: Dhrasti Shah, Verner Knott, Ashley Baddeley, Hayley Bowers, and Charles Collin.

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DEDICATIONS

This thesis work is dedicated to the memory of my grandparents as well as the patients who participated in this study. Thank you for your generous time and willingness to participate in this work.

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CHAPTER 1 : GENERAL INTRODUCTION

1.1 Overview of Thesis Aims

About 1% of Canadians suffer from schizophrenia (Public Health Agency of Canada), a psychotic disorder characterized by delusions and hallucinations, as well as deficits in affect, social skills, and motivation. Pharmacotherapies are the front-line treatment for schizophrenia. However, medications are not entirely effective and many patients remain treatment-resistant (Pilling et al., 2002a; Tarrier & Wykes, 2004; Zimmermann, Favrod, Trieu, & Pomini, 2005). These individuals' symptoms become persistent, resulting in impaired quality of life and a diminished cognitive capacity. This diminishes their ability to engage in a number of skills of daily living, such as interpreting the emotions and intentions of others. Difficulty with interpreting emotions is thought to arise from a broad range of social mental processes, one of which is recognizing the emotional expressions of faces (Green, Olivier, Crawley, Penn & Silverstein, 2005).

The ability to identify an emotion from a face is one of the most important elements of correctly processing social situations. Deficits in recognizing emotional facial expressions have been found to predict negative social outcomes in schizophrenia (Eimer, 2000). Studies show that patients with schizophrenia have processing impairments in identifying emotional expressions, but it is not clear whether these difficulties are related to early-stage visual processing impairments or to higher-order aspects of face recognition. Nor is it clear whether these deficits are limited to a specific set of emotional expressions versus being more global in nature (Whittaker, Deakin & Tomenson, 2001). Investigating the neural indices associated with

face processing, and the efficacy of treatment on facial expression identification, may offer further insights into this impairment, and possibly help with treatment planning.

Cognitive Behavioural Therapy (CBT) has proven effective as a complementary approach to pharmacotherapies for improving symptoms and reducing distress, especially in chronic or treatment-resistant cases (Kane, 1996; Lieberman et al., 2005; Pilling et al., 2002b; Tarrier & Wykes, 2004; Zimmermann et al., 2005). CBT may also be a promising approach for mitigating information processing difficulties and, by so doing, improving social cognition and daily functioning. Researchers have suggested that future CBT intervention studies should incorporate neurophysiological measures, such as functional imaging and event-related potentials, to explore any underlying physiological changes that may be associated with the intervention (Shergill, Murray & McGuire, 1998).

While there have been a number of studies using electrophysiological measures to evaluate treatment effects in schizophrenia (Korostenskaja & Kahkonen, 2009; Luckhaus, Fromman, Stroth, Brinkmeyer & Wolwer, 2013; Su, Cai, Wang & Shi, 2012), none have specifically looked at electrophysiological changes following CBT in patients with persistent and distressing positive symptom(s) of schizophrenia. The general aim of the work presented in this thesis was to explore the brain's electrical activity in patients with schizophrenia as they interpret facial expressions, as well as to monitor the efficacy of CBT in ameliorating this aspect of social cognition. Chapter 1 presents background material on previous work in this area. Following this, Chapters 2 to 4 present original research studies. The final chapter summarizes and analyses the results of the thesis work as a whole.

The purpose of the work presented in Chapter 2 was to assess event-related potentials (ERPs) elicited by the presentation of faces with emotional expressions in patients and healthy control participants. Comparisons were made with healthy individuals in order to assess whether ERPs associated with processing emotional facial expressions differentiate the two groups. The aim of work presented in Chapter 3 was to explore the underlying physiological mechanisms involved in impaired facial expression perception in schizophrenia. To this end, the spatial frequency content of facial images was manipulated. This allowed us to determine if impaired basic early visual processing is implicated in the emotional facial processing difficulties of patients with schizophrenia. The aim of the work presented in Chapter 4 was to determine whether ERPs elicited by facial expressions are altered in patients with schizophrenia following completion of CBT.

The study presented in Chapter 2 is an important contribution because it replicates previous work examining differences in ERP responses between schizophrenia patients and controls, but does so in a more homogeneous sample. The study presented in Chapter 3 constitutes an important contribution as only two previous studies have investigated ERP changes in response to spatial frequency manipulated facial expressions in patients with schizophrenia. The study presented in Chapter 4 constitutes an important original contribution because, unlike previous studies, we measured not only behavioural performance, but also event-related potentials, to evaluate CBT treatment effects. This allowed us to measure emotional facial processing deficits in patients with schizophrenia at a neurophysiological level, and to observe any changes that occurred as a result of cognitive behavioural therapy. This has not previously been done.

1.2 Social Cognition Deficits in Schizophrenia

Schizophrenia is a psychotic disorder characterized by delusions and hallucinations, thought disorders, disorganized speech, deficits in social skills, and impairments in motivation (APA, 2013; DSM-V). Persistent positive symptoms such as hallucinations and delusions are severely distressing and disruptive of daily functioning, including social functioning. These deficits are present prior to onset of psychosis (Miller et al., 1999), present in patients during their first episode, may persist despite antipsychotic treatment, and tend to remain in subsequent phases of the illness (Addington & Addington, 2000). This suggests that impairments in social functioning are premorbid features in schizophrenia and are present throughout the course of the disorder. Consequently, social dysfunction is a defining characteristic of schizophrenia, and one that has important implications for the course and outcome of the illness (Addington, Girard, Christensen, & Addington, 2010; Addington, Saeedi, & Addington, 2006a). Social functioning deficits in patients with schizophrenia are thought to arise from impairments in a broad range of social cognitive functions, one of which is in emotional facial recognition (Green et al., 2005). The following sections review the literature on emotional facial recognition in schizophrenia.

1.3 Facial Expression Processing in Schizophrenia

Emotional processing is one important component of social cognition that has been widely studied in schizophrenia. It includes the perception, recognition, expression, identification, and experience of emotions (Phillips & Seidman, 2008). Measures of emotional processing vary broadly and include ratings of emotions displayed on faces (Savla, Vella, Armstrong, Penn & Twamley, 2012) and how individuals manage, regulate, or facilitate emotions based on their responses to written or videotaped vignettes of people interacting.

Emotional perception, identification and recognition refer to the ability to accurately identify and name emotions expressed by others, primarily by means of facial expression.

Patients with schizophrenia have shown impairments in both face recognition and emotional expression recognition (Addington & Addington 1998; Archer, Hay & Young, 1992; Chen, Norton, Ongur & Heckers, 2008; Gur et al., 2002; Gur et al., 2007; Hall et al., 2004; Phillips & David 1995; Sachs, Steger-Wuchse, Dryspin-Exner, Gur & Katschnig, 2004; Streit et al., 2001; Whittaker et al., 2001). Those who show deficits in accurately recognizing emotional expressions are more likely to experience negative social outcomes (Eimer, 2000). Multiple studies have reported an impairment of emotional facial perception wherein patients with schizophrenia show poorer performance in identifying and recognizing emotional facial expressions from pictures (Couture, Penn, & Roberts, 2006; Khoury & Lecomte, 2012). Evidence from meta-analyses suggests a large magnitude of impairment in emotional facial perception in patients with schizophrenia compared with healthy controls. Effect sizes ranging between 0.85 and 1.03 have been found for emotional expression perception, identification and discrimination (Chan, Li, Cheung, & Gong, 2010; Kohler, Walker, Martin, Healey & Moberg, 2010; Savla et al., 2012).

Kohler et al (2010) reviewed 86 studies, published from 1970 to 2007, to examine emotional facial perception differences between patients with schizophrenia and healthy controls, as well as to identify any demographic, methodological or clinical moderators. The studies reviewed used photographic images of faces in various tasks to examine emotional expression perception, identification and differentiation. Kohler et al.'s (2010) analyses revealed performance deficits in patients with schizophrenia, with effect sizes similar for studies examining identification and differentiation. Analysis of the overall sample (i.e., collapsed

across facial expression identification and differentiation studies) revealed a large effect size ($d = 0.91$), which was moderated by illness-related factors (current hospitalization, age of illness onset, clinical symptoms and antipsychotic treatment) and demographic factors (patient age and gender in controls). Savla et al (2012) conducted a meta-analysis of 112 studies of social cognition in patients with schizophrenia, published between 1980 and 2011. They found that patients with schizophrenia performed worse than healthy controls across all domains of social cognition, with large effect sizes for emotional perception ($d = 0.89$) and emotional processing ($d = 0.88$). Furthermore, greater deficits in emotional perception were associated with longer illness durations.

In summary, findings from two meta-analyses (Kohler et al., 2010; Savla et al., 2012) have demonstrated impaired ability to identify and recognize emotional expressions in patients with schizophrenia. These deficits impair social functioning and are crucial predictors of clinical outcome (Addington, Saeedi & Addington, 2006b; Couture et al., 2006; Kee, Green, Mintz, & Brekke, 2003; Pinkham, Penn, Perkins, Graham, & Siegel, 2007).

Although facial expression processing deficits have been repeatedly found in patients with schizophrenia, the precise nature of these impairments and the mechanisms underlying them continue to be debated. For instance, there is debate, with evidence supporting both views, regarding whether impairments in processing emotional information observed in patients are secondary to a generalized impairment in visual processing of faces, or reflective of a specific deficit in emotional perception (Barkhof, de Sonnevile, Meijer, & de Haan, 2015; Chan et al., 2010; Goghari, Sponheim & MacDonald, 2010; Johnston, Devir & Karayanidis, 2006; Schneider et al., 2006). Others have also proposed that face processing and facial expression

processing impairments in patients may be part of a generalized cognitive and sensory problem (Addington & Addington, 1998; Sach et al., 2004).

Studies supporting the generalized face deficit hypothesis suggest that deficits in processing facial expressions are part of a broader impairment involving face detection and identification, as well as age and gender judgments. Many of these studies have used Benton's Facial Recognition Test (Benton et al., 1978) as a control task to explore potential face recognition problems that might contribute to deficits in emotional expression processing in patients with schizophrenia (Addington & Addington, 1998; Mueser, Penn, Blanchard & Bellack, 1996). Recent reviews of face recognition in schizophrenia show that most studies reported a general deficit in face processing (see Bortolon, Capdevielle & Raffard, 2015 and Darke, Peterman, Park, Sundram & Carter, 2013 for reviews) with greater impairment observed when the demands of attention or memory are high. This last finding suggest that deficits observed with Benton's Facial Recognition Test and tasks involving non-emotional face processing may be better explained by more general cognitive (i.e., memory, attention) and visuospatial attention impairments (Baudouin, Martin, Tiberghien, Verlut & Franck, 2002) than by problems specific to face or facial expression processing.

In contrast, however, others have reported a specific emotional expression recognition deficit in schizophrenia (Schneider et al., 2006; Barkhof, de Sonnevile, Meijer, & de Haan, 2015; Goghari et al., 2013; Penn, Combs, Ritchie, Francis, Cassisi, & Morris, 2000; Kosmidis et al., 2007). For example Schneider et al. (2006) conducted a study where participants completed two cognitive control tasks and four conditions of an emotional discrimination task, one condition for each emotion as the target. Specifically, for the emotional discrimination tasks, patients with schizophrenia and healthy controls viewed faces and had to decide whether the

presented face was showing the target emotion for that condition (happiness, sadness, anger or fear) or any other emotion. For the two cognitive tasks, participants had to: 1) judge the age of the person in the image; and 2) indicate whether a face was viewed previously in testing. The authors found that patients with schizophrenia were impaired on all three tasks, but the largest deficit was on the emotional discrimination task. The authors conducted an analysis on the false positive errors from the emotional discrimination tasks and found greater false positives in patients regardless of the emotion. Specifically, the patients falsely identified happiness, sadness, fear and anger when it was absent (Schneider et al. 2006). These results indicate that when patients with schizophrenia attempt to select the target emotion, they misread that emotion even when it was not present (Schneider et al. 2006).

Penn et al. (2000) explored face and emotional expression processing in patients with schizophrenia compared to healthy controls. They used tasks involving emotional perception, face perception, and non-social perception. The authors found that patients with schizophrenia had specific emotional processing impairments, which remained after controlling for performance on the non-social perception task. Similarly, a recent study compared performance of patients with schizophrenia and healthy controls on emotional expression categorization, face identification, and abstract pattern recognition tasks (Barkhof et al., 2015). This study found patients with schizophrenia to be slower and less accurate than healthy controls in recognizing emotional expressions, as well as in determining the identity of the face. However, there was smaller deficit in processing non-social abstract information than emotional information. This supports the view that patients are impaired more in processing facial information compared to non-social information. Additionally, the findings showed patients to be slower at performing the emotional expression categorization task compared to the face identification task. This lends

support to the idea that deficits in emotional expression recognition cannot fully be accounted for by processing involved in face identity recognition (Barkhof et al., 2015; Penn et al., 2000; van Rijn et al., 2011) or impairments in general cognitive abilities.

Within studies that have examined deficits in emotion expression processing in schizophrenia, there is evidence of a general deficit that encompasses all emotions (Kee et al., 2003; Silver, Bilker & Goodman, 2009; Silver & Shlomo, 2001) but also of a more specific deficit in the processing of negative facial expressions (Huang, Hsiao, Hwu & Howng, 2013; Kohler et al., 2003; Lee, Lee, Kweon, Lee & Lee, 2010; Silver, Shloma, Turner & Gur, 2002). Consequently, it remains unclear whether these impairments apply to all emotional categories or only a subset. In several studies, patients with schizophrenia have shown impaired recognition of anger (Goghari & Sponhein, 2013), sadness, fear, and disgust but normal performance in recognition of happy faces (Bediou et al., 2005; Edwards et al., 2001; Lee et al., 2010; Silver et al., 2002). Conversely, other studies showed that patients have difficulty recognizing both positive and negative emotional expressions (Hall et al., 2004; Johnston et al., 2006; Kucharska-Pietura, David, Masiak, & Phillips, 2005; Laroi, Fonteneau, Mourad, & Raballo, 2010).

Deficits specific to negative expressions are believed to be due to either a cognitively mediated avoidance of negative stimuli, or to abnormal neuronal processing in brain regions specifically sub-serving negative emotional recognition (Mandal, Pandey, & Prasad, 1998; Phillips et al., 1999; Vuilleumier & Pourtois, 2007). The former view, known as the social-cognitive theory, posits that patients with schizophrenia develop the negative-emotion recognition deficit in an attempt to withdraw from social interactions and to avoid exposure to arousing stimuli (Mandal et al., 1998; Walker, Marwit & Emory, 1980). Over time this avoidance is thought to affect the patients' ability to recognize and interpret social cues (Walker

et al., 1980). Support for the social-cognitive theory can be seen in studies that have shown worse performance in recognizing negative expressions (i.e., when processing sadness, anger, disgust, and fear) in patients with schizophrenia compared to healthy controls (Comparelli et al., 2014; Martin, Baudouin, Tiberghien & Franck, 2005).

Imaging studies have shown the amygdala to be activated by viewing of emotional facial expressions (Derntl, et al., 2009), with a greater association in response to negative expressions, especially fear (Fusar-Poli, et al., 2009; Phan, Wager, Taylor & Liberzon, 2002; Winston, Strange, O'Doherty & Dolan, 2002) and sadness (Adolphs, Tranel, Damasio & Damasio, 1995; Wang, McCarthy, Song, & Labar, 2005). However, a meta-analysis reported that in addition to fearful and sad faces, happy faces also activate the amygdala, whereas angry and disgusted faces show no effect on this brain region (Fusar-Poli et al., 2009). Structural (Wright et al., 2000) and functional abnormalities of the amygdala in relation to emotional recognition have been documented in patients with schizophrenia as well as those with a very high risk of developing the condition (Aleman & Kahn, 2005, Gur, 2002; Holt et al. 2006; Pantelis et al., 2003). These abnormalities may underlie the dysfunction in emotional facial processing reported in patients. The presented findings provide support for the hypothesis of a distinctive impairment in the recognition of emotion (particularly negative emotions) in patients with schizophrenia (Aleman & Kahn, 2005; Amminger et al., 2012).

Overall, several hypotheses aim to explain emotional expression recognition deficits observed in patients with schizophrenia. There is evidence supporting: 1) A general impairment in visual processing of faces (Schneider et al., 2006; Goghari et al., 2010; Chan et al., 2010), 2) a specific deficit in emotional expression processing (Bediou et al., 2005; Gur et al., 2007) and 3) a more global cognitive and sensory problem (Butler et al., 2009; Johnston, Stojanov, Devir, &

Shall, 2005; Turetsky et al., 2007) which would encompass both faces and non-face objects. Further research is required to determine the underlying mechanisms related to emotional expression recognition deficits in this patient population. The research presented in this thesis is an attempt to do just that. In particular, our interest was in applying ERP measurements to explore when in the stages of visual information processing the impairment in this population is first observed. In addition, this study attempted to determine whether impairments observed with emotional expression processing extend to non-face stimuli (i.e. chair images).

1.4 An Overview of Event-Related Potentials (ERPs)

Event-related potentials provide direct and non-invasive measurements of electrical activity in the brain. They are recorded through the scalp at the time of a response, leading to excellent temporal resolution (Woodman, 2010). ERPs' temporal resolution allows for measurement of brain activity from one millisecond to the next. Given that many aspects of attention and perception appear to occur on a scale of milliseconds or even smaller, ERPs allow researchers to observe the sequence of perceptual and cognitive operations as they unfold during a trial (Picton et al., 2000).

Event-related potentials result from averaging time-sequences of electroencephalogram (EEG) data that is time-locked to an event, such as the presentation of a stimulus or the execution of a manual response. ERPs are embedded in the EEG signals and their extraction requires averaging of raw EEG data across many repetitions of the same type of trials (as well as other signal cleaning measures). When averaged in this way, an ERP waveform/peak is unmasked with a positive (P) or negative (N) deflection. ERPs can be thought of as scalp-recorded measure that occur in anticipation of and/or in response to stimuli (typically external).

There are several means of classifying ERPs. Firstly, they can be classified according to the type of stimulus that elicited them (e.g., auditory, visual, somatosensory ERPs). Secondly, ERPs can be categorized according to their latency following stimulus presentation. By arbitrary convention, short-latency ERPs are defined as occurring within 100 ms of the onset of the evoking stimulus. Long-latency ERPs emerge at >250 ms following stimulus onset. Finally, ERPs are grouped into *exogenous* and *endogenous* components. Exogenous components are elicited during the sensory stages of stimulus processing and are highly determined by stimulus characteristics. The amplitudes and latencies of exogenous components are determined by the physical properties of the external eliciting event and are considered to be insensitive to psychological manipulations (Picton et al., 2000). Exogenous components tend to be stable, unconscious, and automatic. They are not greatly influenced by cognitive processes or states. In contrast, endogenous ERP components are indicators of information processing (Picton et al., 2000), and reflect the interaction between the significance of the stimulus and the manner in which the participant processes it (Fabiani, Stadler & Wessels, 2000). Endogenous components index later cortical processing stages and are less dependent on stimulus characteristics. In fact, even the absence of a stimulus (i.e., violation of expectancy) can sometimes evoke endogenous components (Picton et al., 2000). Endogenous components are more variable than exogenous ones, and are influenced by factors such as attention, stimulus relevancy and resources required for stimulus processing (i.e., cognitive processes).

1.4.1 Neural Correlates of Emotional Facial Processing

Measurement of ERPs have excellent temporal resolution, allowing for investigation of the time-course of the information-processing cascade from early to later processing stages with millisecond resolution (Luck et al., 2011). They can thus be helpful in understanding the time

course and mechanisms underlying face processing. The initial stages of face and emotional expression recognition are thought by some to involve structural encoding of a face-specific configuration, which is then followed by the recognition of a familiar face; thereafter, the emotional information in the stimulus is processed (Bruce & Young, 1986). In contrast, others have assumed that facial and emotional recognition are parallel but interrelated processes (Holmes, Vuilleumier & Eimer, 2003; Pourtois, Schwartz, Seghier, Lazeyras, & Vuilleumier, 2006). Accordingly, a disruption in one of these processes in patients with schizophrenia would not necessarily impair the other. Electrophysiological studies of face recognition have revealed a number of ERP components associated with face recognition that can be used to investigate the time-course and stages of face processing. In general, three components are considered to be related to emotional expression processing: P100, N170, and P300 (Campanella, Montedoro, Streel Verbanck & Rosier, 2006; Jung, Kim, Kim, Im & Lee, 2012; Kim, Lee & Im, 2013; Lee, Kim, Kim & Bae, 2010; Rozenkrants & Polich, 2008; Turetsky et al., 2007; Wynn, Lee, Horan & Green, 2008). The P100 is one of the earliest components thought to reflect initial visual processing. The N170 component is thought to represent the earliest stage of facial structure encoding (Herrmann, Ehlis, Ellgring & Fallgatter, 2005). Finally, the P300 component is believed to reflect the affect encoding stage in processing emotions (An et al., 2003). The following sections discuss these three ERP components and summarize findings regarding ERP responses during face processing in schizophrenia.

1.4.2 The P100 Component and Emotional Facial Processing

Different facial expressions modulate early (<170 ms post stimulus) ERP components, suggesting that affect detection may precede face identification (Eimer & Holmes, 2007). The P100 is sourced from ventral extrastriate visual areas and is sensitive to processing of low-level

visual information (i.e., contrast, luminosity, and spatial frequency) (Nakashima et al., 2008b; Rossion & Jacques, 2008). Measured over the posterior (occipital) cortex at ~100 ms following onset of stimulus, the P100 is believed to reflect global processing and the assessment of early-stage visual information (Luck et al., 1994; Santesso et al., 2008). Recent literature suggests that the P100 is also modulated during face processing (Earls, Curran & Mittal, 2015). Several studies have reported larger amplitude P100 response to faces than objects (Allison, Puce, & McCarthy, 1999; Herrmann et al., 2005), however, these findings are not consistently observed (Rousselet, Husk, Bennet & Sekuler, 2005; Rousselet, Mace, Thorpe & Fabre-Thorpe, 2007). Others have also suggested that the P100 may be involved in preliminary processing occurring prior to face-encoding processing, indexed by the N170 (Jemel, Schuller, Cheref-Khan, Goffaux, Crommelinck & Bruyer, 2003). One concern is that the authors of some of these studies have not reported whether they have adequately controlled for the physical characteristics of their stimuli, meaning that the results could simply be due to differences in image contrast or brightness.

The P100, thought to index preconscious attention allocation, also appears to be modulated by emotional expression and intensity (Lee, Gosselin, Wynn & Green, 2011; Pizzagalli et al., 2002; Turetsky et al., 2007; Turetsky et al., 2008; Utama, Takemoto, Koike & Nakamura, 2009). For example, smaller amplitudes in response to sad expressions (Turetsky et al., 2008) and larger amplitudes (Pourtois, Dan, Grandjean, Sander & Vuilleumier, 2005; Rellecke, Sommer & Schacht, 2012) and shortened latency to fearful facial expressions (Lee et al., 2010) have been reported. Conversely, others have reported a general effect on the P100 of expressive versus neutral faces (Batty & Taylor, 2003) or have found no effect of emotional expressions (Degabriele, Lagopoulos & Malhi, 2011; Eimer & Holmes, 2007). Of note is that

P100 modulation by emotional expressions has been found even when the later N170 is not modulated (Pourtois, Grandjean, Sander & Vuilleumier, 2004; Pourtois et al., 2005). This suggests that the pathways for the early processing of emotional content, reflected in the P100, and the later structural encoding of facial features, reflected in the N170, are dissociable (Pourtois et al., 2004; 2005; Vuilleumier et al., 2007).

1.4.3 The N170: Face-Selective Component and Emotional Facial Processing

Source localization studies suggest that face processing elicits activation of the fusiform gyrus (FFG; Esslen, Pascual-Marqui, Hell, Kochi & Lehmann, 2004). The FFG is implicated in coding static face features and in identifying a stimulus as a face. There is also evidence to suggest that FFG activity can be modulated by facial expressions, especially negative ones (Fox, Mathews, Calder & Yiend, 2007). The N170, a posterior temporal negative peak occurring ~170 ms following the presentation of a visual stimulus, is thought to reflect early visual processing responsible for constructing a representation of the human face. In other words, the N170 is believed to reflect the earliest stage of facial structure encoding or identification of a face (Cauquil, Edmonds & Taylor, 2000; Eimer & Holmes, 2002; Jemel et al., 2003; Jemel, Coutya, Langer & Roy, 2009; Vuilleumier & Pourtois, 2007). The FFG is likely the source generator of N170 ERP (Eryilmaz, Duru, Parlak, Ademoglu & Demiralp, 2007).

The N170 is regarded as being 'face-selective' because non-face stimuli elicit smaller N170 amplitudes and longer latencies. The N170 has repeatedly been shown to be larger for faces than for houses, cars, and other objects (Goffaux, Gauthier, Rossion, 2003a; Rossion et al., 2000). Further, evidence has shown that irregularity of facial presentation (e.g., upside-down faces) increases its latency, which is an index of cortical processing speed, suggesting the specificity of the N170 component to faces (Jemel et al., 2003; Jemel et al., 2009; McCarthy,

Puce, Belger & Allison, 1999). However, the face-selective nature of the N170 has been questioned. For instance, Thierry, Martin, Downing and Pegna (2007) showed that larger N170 amplitudes to faces were found only when all facial stimuli shared a basic structure (perceptual variance) and the perceptual variance of non-face stimuli differed. In contrast, when the perceptual variance was the same for face and non-face stimuli, no N170 amplitude differences were observed. Note, however, that Thierry et al.'s (2007) findings have themselves been questioned (Rossion & Jacques, 2008) on two main grounds: 1) methodological flaws in their experiment, specifically with respect to choice of electrode to measure the N170 (they chose to measure the N170 at the medial occipital and parietal electrodes versus the well-documented choices of measuring at lateral posterior electrodes) and 2) the notion that the N170 is no longer face-sensitive when the perceptual variance is controlled for is inconsistent with existing data (Rossion & Jacques, 2008). Previous researchers took great care to ensure that face and non-face stimuli were equated for size, location, and viewpoint (Rossion & Jacques, 2008). This suggests that the N170 is sensitive to high-level visual (configural and feature) information, reflecting structural encoding of facial features (Rossion & Jacques, 2008).

While there is strong evidence that the N170 reflects some aspects of face processing, uncertainty exists as to whether this ERP component is altered by facial expressions. A substantial body of literature, with healthy controls, supports the notion that the amplitude and latency of the N170 is modulated by facial expression (Ashley, Vuilleumier & Swick, 2004; Eimer, Holmes & McGlone, 2003; Holmes et al., 2003; Ramos-Loyo, Gonzalez-Garrido, Santesso et al., 2008). Conversely, other research suggests that it is not (Eimer & Holmes, 2002; Holmes, Winston & Eimer, 2005; Obayashi et al., 2009). For instance, increased emotional intensities (Sprengelmeyer & Jentsch, 2006), and expressions of fear and anger, elicited larger

N170 amplitudes compared to expressions of surprise or neutral faces (Batty & Taylor, 2003; Eger, Jedynak, Iwaki & Skrandies, 2003; Stekelenburg & de Gelder, 2004). Conversely, others have found the N170 to be larger to joyful versus neutral and sad faces (Jaworska et al., 2010; Krombholz, Schaefer & Boucsein, 2007). Further confusing the issue are findings that positive affective stimuli can modulate the N170 relative to negative ones. For example, Pizzagalli et al. (2002) found that faces that were rated as most likable elicited greater activity in the FFG compared to less likable ones. Additionally, Batty and Taylor (2003) found that positive emotional expressions evoked earlier N170 responses than negative emotions. Thus, it may be that the N170's amplitude increases with greater intensity of emotions (Sprengelmeyer & Jentzsch, 2006), while N170 latencies are shortest to positive expression.

The lack of clarity regarding the N170's modulation by emotional expressions has raised suggestions that it may instead index non-specific configural and attentional effects related to encoding structural facial cues, rather than emotional processing per se (Ashley et al., 2004; Ioannides et al., 2000; Vuilleumier & Pourtois, 2007). Other researchers have suggested that the N170 may not be modulated by emotion at all and that the inconsistent findings are simply due to differences in referencing montages across studies (Rellecke, Sommers & Schact, 2013). Specifically, Rellecke et al. (2013) found less pronounced N170 amplitudes in response to facial expressions when ERPs were referenced to mastoids than when average reference was used. However, a recent meta-analysis examined the inconsistencies regarding the N170's modulation by emotional expressions (Hinojosa, Mercado & Carretie, 2015). These authors found different N170 amplitudes in response to neutral faces compared to emotional faces, with anger, fear and happy faces eliciting the largest N170 amplitudes (Hinojosa et al., 2015). Consequently, the authors argue that the N170 may reflect structural encoding of faces, as well as processing of

both basic-level and high-level facial features (i.e., facial expression, identity; Hinojosa et al., 2015). Furthermore, they found the N170 to show significant effects of facial expressions whatever the placement of the reference electrode. However, the N170 amplitudes were stronger when the common average reference was employed, supporting Rellecke et al.'s (2013) claims regarding the importance of the reference electrode(s) location. The physics (size, brightness, contrast of stimulus) of the stimulus set has been suggested to account for the inconsistencies observed with the N170 in response to emotional expressions (Blau, Maurer, Tottenham & McCandliss, 2007). The stimuli used in the present studies were equated for size, luminance, and visual contrast in an attempt to control for irrelevant sources of variance.

1.4.4 The P300 ERP Component and Emotional Facial Processing

The P300, occurring approximately 300 ms following onset of stimulus, is modulated by affect in tasks thought to involve higher levels of cognitive processing, such as those reflecting stimulus evaluation and selection (Campanella et al., 2002; Miltner et al., 2005). The P300's amplitude and latency are thought to reflect conscious attention allocation and stimulus evaluation speed, respectively. It is hypothesized to reflect the affect encoding stage (i.e., further evaluation of information related to affective valence of a face) in the processing of emotions (Luo et al., 2010). As with other ERP components, findings regarding the effects of facial expression on the P300 are mixed. Emotionally expressive face stimuli have been found to elicit larger P300 amplitudes than neutral ones (Campanella et al., 2002). Some studies have found larger P300 amplitude to fearful or happy faces (Liddell, Williams, Rathjen, Shevrin & Gordon, 2004; Luo et al., 2010; Williams, Palmer, Liddell, Song, & Gordon, 2006), whereas others reported no P300 changes to expressions (Balconi & Luchiari, 2006). The finding of larger P300 to fearful facial expression suggests that signals of potential danger enhance ongoing

stimulus elaboration and evaluation. However, overall it is difficult to come to firm conclusions from the existing data due to contradictory findings.

1.5 ERP Correlates of Emotional Facial Processing in Schizophrenia

Deficits in P100 component in patients with schizophrenia have been observed with non-face stimuli (Butler et al., 2007; Doniger, Foxe, Murray, Higgins & Javitt, 2002; Haenschel et al., 2007; Schechter et al., 2005; Yeap et al., 2006), but results are mixed with regard to processing facial expressions. Some studies show normal processing at the P100 stage (Bediou et al., 2007; Herrmann et al., 2005; Jung et al., 2012; Lee et al., 2010; Turetsky et al., 2007; Wynn et al., 2008), while others show P100 amplitude deficits (Caharel et al., 2007; Campanella et al., 2006). Furthermore, longer P100 latencies in patients (Wynn et al., 2008) have been shown, and other studies have demonstrated longer latencies specifically to faces with happy expression in female patients with schizophrenia compared to female healthy controls (Lee et al., 2010). In a recent meta-analysis on early face processing in schizophrenia, smaller P100 amplitudes in patients relative to controls ($d = 0.41$; Earls et al., 2015) were reported. In an exploratory analysis accompanying the meta-analysis, schizophrenia patients relative to controls elicited smaller P100 amplitudes in response to neutral ($d = 0.32$) and happy ($d = 0.21$) facial expressions, but showed no difference in response to fearful faces ($d = 0.09$; Earls, 2015). The authors interpreted these findings to suggest that impairments in emotional facial processing may occur at different stages depending on the emotion being viewed. Specifically, they proposed that processing deficits in neutral and positive face categories begin at an earlier visual processing stage, whereas impairment in processing of negative expression may be affected at later processing stages, such as those indexed by the N170 (Earls et al., 2015). Of note is that the meta-analysis did not include studies with other negative expressions, such as sadness and anger.

A number of studies have found smaller N170 amplitude to faces in patients with schizophrenia, relative to healthy controls, at least for some experimental conditions or selected contrasts (Bediou et al., 2007; Caharel et al., 2007; Jung et al., 2012; Kirihara et al., 2012; Lee et al., 2010; Lynn & Salisbury, 2008; Turetsky et al., 2007), while others have shown intact N170 amplitudes (Akbarfahimi, Tehrani-Doost & Ghassemi, 2013; Komlósi et al., 2013; Lee et al., 2007; Ramos-Loyo et al., 2009; Wynn et al., 2008). Lee et al. (2010) and Jung et al. (2012) found significantly smaller N170 amplitudes to happy and fearful facial expressions in schizophrenia patients compared with healthy controls. A recent meta-analysis (McCleery et al., 2015) provided evidence for moderate impairment (effect size: 0.49) of N170 amplitude in patients with schizophrenia. The N170 effects were similar for tasks requiring participants to respond to emotional judgments of facial stimuli compared with non-emotional tasks. Most of the studies included in the meta-analysis did not report ERP amplitudes for individual emotional categories; therefore, the authors were not able to examine the potential impact of any specific emotional expression on the N170. Results from the meta-analysis support the idea that there is a reduction of the N170's amplitude in patients with schizophrenia and suggest that the large behavioural deficits observed for emotional expression recognition arise from an underlying neural impairment (McCleery et al., 2015).

The findings that show impaired N170 suggest that patients may be less efficient at encoding facial features. Correlations between smaller N170 amplitude to faces and lower Global Assessment of Functioning (Obayashi et al., 2009) and Social Functioning Scale (Tsunoda et al., 2012) scores in patients with schizophrenia have also been observed. This suggests that the more profound the symptoms of schizophrenia, the more impaired a patient will be in face processing. Similarly, Campanella et al. (2006) found a significant positive

correlation between positive symptoms and smaller N170 amplitude in response to emotional faces. However, they found no correlation between N170 reduction and negative symptoms, nor between positive and negative symptoms and amplitudes of other ERP components (P100, P300, N400).

Findings regarding the effects of facial expression on the P300 are mixed. In neurotypical individuals, emotionally expressive face stimuli have been found to elicit larger P300 amplitudes than neutral stimuli (Campanella et al., 2002; Miltner et al., 2005) and some studies have found larger P300 amplitude specifically to fearful or happy faces in contrast to neutral ones (Liddell et al., 2004; Luo et al., 2010; Williams et al., 2006). However, others have reported no P300 changes in response to facial expression variations (Balconi et al., 2006). The finding of an enhanced P300 to fearful facial expressions suggests that signals of potential danger enhance ongoing stimulus elaboration and evaluation.

Only two studies have examined the effect of facial expression on the P300 in individuals with schizophrenia. One reported larger P300 amplitudes to negative expressions than to positive ones in healthy controls, whereas the opposite pattern was found for patients with schizophrenia (An et al., 2003). The other reported significantly smaller P300 amplitudes to all emotional expressions in patients with schizophrenia compared to healthy controls (Turetsky et al., 2008).

Differential response in the 300-450 ms range between patients with schizophrenia and healthy controls (Turetsky et al., 2008) has been found to be mediated by symptom presentation (Mori et al., 2013). For instance, some studies have found that a P300 amplitude reduction in response to simple visual and auditory stimuli is related to positive symptoms (Kutas, McCarthy & Donchin, 1997) or negative ones (Strik, Dierks & Maurer., 1993; Mori et al., 2013). However,

others have examined this relationship specifically in emotional processing paradigms and report no or limited correlations between P300 amplitude reduction and symptom presentation (Wölwer et al., 2012). A recent study reported positive symptoms to be correlated with prolonged, long latency activation to fearful faces. However, others have suggested that the emotional facial recognition deficits in patients with schizophrenia are secondary to effects of broader cognitive deficits in visual face processing (Johnston et al., 2005). Consistent with this view, N170 ERP deficits have been found in patients with schizophrenia but no affect-modulated recognition deficits have been observed in the time frame of 180-250 ms (Herrmann, Reif, Jabs, Jacob, & Fallgatter, 2006). Additionally, smaller P300 amplitude to emotional expressions in patients with schizophrenia was found to be correlated with reductions in the early N170 response (Turetsky et al. 2008). These researchers suggest that the disturbances in the higher order evaluative processes (evidenced by the P300) may be a consequence of the earlier disruption in the sensory encoding of facial stimuli.

1.5.1 Facial Processing in Schizophrenia: Summary and Research Aims

Patients with schizophrenia show a deficit in emotional facial expression processing as reflected in multiple ERP components, including the P100, N170, and P300. There is no consensus as to whether the deficit in processing occurs during the course of earlier visual and face processing (<200 ms) or later higher-order cognitive processing (>200 ms). Nor is it clear as to whether the impairment observed is specific to faces or extends to non-face stimuli. In addition, it is unclear whether the deficit applies to neutral faces, emotional facial expressions, or only specific emotional expressions, such as negative ones. The work presented in Chapter 2 replicated previous studies while including a wider range of emotional facial expressions, thus allowing comparisons of ERP responses between neutral faces and several common emotional

categories: sadness, anger, joyful, fear. An additional goal of the study was to examine a more homogeneous sample of patients with schizophrenia, specifically those with auditory hallucinations. The present study only included individuals with auditory hallucinations in order to determine if similar ERP findings are observed in this more specific case. Researchers have shown that the negative impacts of experiencing auditory hallucinations are not limited to the auditory modality, but also extend to impairments in visual processing as well (Bruder et al., 2011; van Lutterveld, Sommer & Ford, 2011), including face processing (Kayser et al., 2012). The findings from this study should inform our understanding of the course of emotional facial processing deficits in patients with schizophrenia and whether there are any emotional category specific deficits in this population. This study was deemed a critical step for future research assessing role of stimulus characteristic manipulation on face and emotional processing and the impact of cognitive behavioural therapy on neural correlates of emotional facial processing.

1.6 Visual Pathways

A number of studies have shown impairments in higher-level cognitive functions, such as facial emotional perception, in patients with schizophrenia (Addington & Addington, 1998; Kerr & Neale, 1993; Morris, Weickert & Loughland, 2009). Basic early-stage visual capacities, such as the ability to discriminate the orientation of luminance gratings or detect contrast and motion (Butler, Silverstein & Dakin, 2008; Chen, Palafox & Nakayama, 1999; Slaghuis, 1998) have also been observed to be impaired in this population. Several studies have found that impaired emotional expression recognition is associated with impaired basic visual processing in schizophrenia (Caharel et al., 2007; Kosmidis et al., 2007; Norton, McBain, Holt, Ongur & Chen, 2009; Turetsky et al., 2007; Wynn et al., 2008). However, the way in which these early visual processing deficits are related to impaired emotional facial processing is unclear. One

approach to elucidating the relationship between low-level visual analysis and emotional facial processing is to examine the effects of modulating signals in one domain (i.e., basic visual attributes) on the other domain (i.e., emotional processing). In part, the ability to process emotional facial expressions relies on the analysis of basic visual content, such as visuospatial information at various scales (Deruelle, Rondan, Salle-Collemiche, Bastard-Rosset & Da Fonseca, 2008). Accordingly, in Chapter 3 (Study 2) we manipulated the spatial frequency content of facial expression stimuli to assess how this would affect emotional recognition. This in turn allowed us to investigate the mechanisms involved in the impaired emotional facial processing that were found in Chapter 2 (Study 1).

Visual images are processed by the brain via functional units or pathways that are tuned to specific information in the image (De Valois & De Valois, 1990). There are two major pathways in the visual system, the magnocellular (M) and the parvocellular (P) (Bassi & Lehmkuhle, 1990; Breitmeyer & Williams 1990; Tobimatsu & Celesia, 2006). The M pathway is composed of large, rapidly-adapting cells with large receptive fields. It therefore carries information with low spatial and high temporal resolution. Conversely, the P pathway is composed of smaller cells with slower adaptation speeds and smaller receptive fields. It therefore carries information with relatively low temporal and high spatial resolution.

The M and P pathways project separately from the retina to layers 1-2 and 3-6 of the lateral geniculate nucleus (LGN) of the thalamus, respectively, then to separate layers of the primary visual cortex (V1). From there, the M-pathway projections are conveyed primarily to the dorsal visual stream (within the parieto-occipital cortex) and then project back to cortical area V1. They are thought to be involved in motion processing. The P-pathway projects mainly

to the ventral visual stream (within the temporo-occipital cortex) and is involved primarily in object recognition and colour processing.

The M and P pathways are differentiated functionally and, accordingly, process different aspects of visual information. For instance, they carry information regarding different levels of detail in an image, a parameter that can be quantified in terms of spatial frequency (SF) (Tobimatsu et al., 2008). The visual system breaks down the variations of luminance across the retina amongst distinct neural populations representing luminance modulations over spatial regions of different sizes (i.e., different spatial frequencies). SF refers to the frequency with which variations in luminance occur on the retina. Fine details in the visual scene consist of changes across small distances on the retina and therefore consist of high spatial frequency information. The P-pathway is sensitive to high-spatial frequency (HSF) information (i.e., local or featural detailed information; Goffaux & Rossion, 2006; Sergent, 1994; Shulman & Wilson, 1987). The P pathway is more slowly conducting and is sensitive to slower temporal frequencies (Livingstone & Hubel, 1988; Tobimatsu & Celesia, 2006). The primary function of the P/ventral pathway is identification and object recognition (i.e., “what” pathway) because of its ability to transmit finely-detailed information (Derrington & Lennie, 1984; Kaplan, 1991; Tootell, Silverman, Hamilton, Switkes, & De Valois, 1988). In contrast, large elements of a scene consist of changes across larger distances on the retina and therefore consist of low spatial frequencies. The M-pathway is sensitive to low-spatial frequency (LSF) information (i.e., coarse information). The M-pathway is rapid conducting, sensitive to high temporal frequencies and is thought to play a role in guiding eye-movements (Livingstone & Hubel, 1988; Tobimatsu & Celesia, 2006). One function of the M/dorsal pathway, also referred to as the “where” pathway,

is to orient attention to the appearance or presence of stimuli, as it helps in processing motion, location, and spatial relationships among stimuli (Schwartz, Tomlin, Evans, & Ross, 2001).

1.7 Contribution of Spatial Frequency to Visual Processing

As mentioned above, the parvocellular visual pathway is slower to respond than the magnocellular pathway. Based on observations that suggest the visual system processes information at different spatial scales separately, a “frame and fill” model of object recognition (aka coarse-to-fine or global-to-local analysis) has been proposed (Bar, 2003; Calderone et al., 2013; McSorley & Findlay, 2002; Parker, Lishman & Hughes, 1996). Both the M- and P-pathways play a role in this model of visual object recognition, in which LSF information is rapidly projected first to the prefrontal cortex via the dorsal (M) pathway, and then back to the ventral visual areas, to join slower projections of high resolution information, arriving via the ventral (P) pathway (Bar et al., 2006a; Kveraga, Boshya & Bar, 2007; Laycock et al., 2007). Accordingly, the initial, global scene is extracted by the M-pathway, which facilitates processing in the later ventral stream areas associated with object recognition (Kveraga et al., 2007). Bar and colleagues (2006a) have found, using MEG and fMRI techniques, that stimuli biased toward the magnocellular pathways (i.e., images filtered to contain only low SFs), increased activity in connections between the striate/extrastriate cortices and orbito-frontal cortices (OFC), the latter being an area associated with object and emotion perception. They also found increased communication between the OFC and the fusiform gyrus (FFG), a ventral object recognition area highly associated with face processing (Kanwisher & Yovel, 2006). Conversely, stimuli biased towards the parvocellular pathways (i.e., images filtered to contain only high SFs) produced less prefrontal cortex activity and more ventral stream activity and activated a pathway from occipital visual cortex to FFG (Bar et al., 2006a; Kveraga et al., 2007).

Subsequent outputs from the M- and P- pathways typically meet in higher-level regions, including the fusiform gyrus, and orbitofrontal cortex (Bar et al., 2006a; Rotshtein, Vuilleumier, Winston, Driver & Dolan, 2007; Vuilleumier, Armony, Driver & Dolan, 2003). Researchers have suggested that information from LSF and HSF bandwidths may be integrated at these sites, producing a neural representation of the face to guide subsequent recognition (Eger, Schyns & Kleinschmidt, 2004; Rotshtein et al., 2007). Taken together, these data suggest that fast M-projections link early dorsal, frontal and later ventral areas and may play a role in connecting networks for face and emotional processing (Bar et al., 2006a; Kverage et al., 2007).

1.8 Spatial Frequency and Face Processing

Face processing is an important function for humans, so it is important to understand the perceptual processes and the underlying physiological mechanism involved in it. Researchers have shown great interest in examining the factors that influence face processing, such as task demands (Ruiz-Soler & Beltran, 2006; Schyns, 1998). There are a variety of ways to study face processing. For example, researchers in this area have used the following tasks in their quest to understand the mechanisms involved in face processing: categorizing faces versus objects, identifying a face at the individual level (i.e., "what is that person's identity?"), indicating the gender of a face, categorizing expressive versus non-expressive faces, and pinpointing expression of faces (Collin, Therrien, Campbell & Hamm, 2012; Goffaux et al., 2003a; Goffaux, Jemel, Jacques, Rossion & Schyns, 2003b; Ruiz-Soler & Beltran, 2006; Schyns, Bonnar & Gosselin, 2002). In addition to task demands, researchers have been interested in determining the role of low-level visual information in face processing, including the role of the various SF ranges.

A review by Ruiz-Soler and Beltran (2006) suggests that the role of different SFs is modulated by the individual's visual task, and that the role played by specific SFs in different tasks is not fully understood. In some detection tasks (for example, detecting a face in an image, or gender categorization), LSFs (2-8 cycles per face) have been shown to be sufficient in performing this task (Goffaux, 2009; Ruiz-Soler & Beltran 2006; Schyns et al., 2002). The middle band of frequencies, between 8 to 16 or 5 to 20 cycles per face, have been reported to be most useful for individual identification of faces (Collin, Liu, Troje, McMullen & Chaudhuri, 2004; Collin et al., 2012; Gold, Bennett & Sekuler, 1999; Näsänen, 1999; Tanskanen, Näsänen, Montez, Päälyssaho & Hari, 2005). Finally, fine-tuned analysis of local details is based on HSF, and seems to be important in tasks such as expression categorization (Schyns & Oliva, 1999).

A number of studies have also noted the importance of holistic processing—i.e., integrated processing of facial features such that the face is processed as a gestalt—for face identification (e.g., Badcock, Whitworth, Badcock & Lovegrove, 1990; Lamb & Yund, 1993; Shulman, Sullivan, Gish & Sakoda, 1986; Shulman & Wilson, 1987). Researchers also suggest that face identification relies on configural processing, which involves computing spatial relations among inner face features (eyes, nose, mouth), relative to each other and relative to the face contour (see Maurer, Le Grand & Mondloch, 2002 for review). Results from behavioural studies suggest that holistic processing of faces relies on relatively low spatial frequencies (LSFs) more than on HSFs (Badcock et al., 1990; Goffaux, Hault, Michel, Vuong & Rossion, 2005). However, this has been debated because Watier, Collin and Boutet (2010) found that low-pass and high-pass spatial frequency thresholds are the same for configural and featural processing of faces, suggesting that there are no particular SFs for configural processing (See also Boutet, Collin & Faubert, 2003; Collin, Rainville, Watier & Boutet, 2014). Other studies

have suggested that HSFs are more important for featural processing, which is related to analyzing the appearance of isolated facial features such as the brow, eyes, nose, mouth, etc. (Shulman & Wilson, 1987).

Previous findings suggest that face processing may rely on a combination of features, configurations and gestalt representations and task demands, at different levels and stages of face analysis, and thus both LSF and HSF scales may be used during face perception. Overall it is agreed that most of the relevant information for face identification is conveyed by middle spatial frequencies, from about 8-16 cycles/face (Collin et al., 2012, 2014; Costen, Parker & Craw, 1994; Fiorentini et al., 1983; Morrison & Schyns, 2001; Nasanen, 1999). However, emotional expression recognition relies more on low SF information than middle and high SF information, although this may be task dependent (Aguado, Serrano-Pedraza, Rodriguez & Roman, 2010; Kumar & Srinivasan, 2011; Vuilleumier et al., 2003).

1.8.1 Spatial Frequency and Emotional Recognition/Processing: Behavioural Data

Studies suggest that spatial frequency is relevant not only to face identification, but also to the identification and categorization of facial expressions (e.g., Bar, Neta & Linz, 2006; Kumar & Srinivasan, 2011; Schyns & Oliva, 1999). Specifically, emotional information processed under short, unintentional, or even non-conscious presentation conditions critically relies on LSFs (Johnson, 2005; Tamietto & De Gelder, 2010; Vuilleumier et al., 2003).

Behavioural evidence stems, for example, from Bar, Neta & Linz (2006b). The authors presented neutral faces for 39 ms and 1700 ms (followed by a mask) and asked participants to rate each face according to the perceived threat. To clarify, the images presented were of individuals who were instructed to show a neutral expression, but these nevertheless exhibited

residual traces of facial expressions (or at least what can be interpreted as expressions). The authors found that during the rapid presentation condition, the features used to detect threat in a face were primarily conveyed by and were more dependent on LSFs (<8 cycles/face) versus HSFs (>24 cycles/face), whereas in the longer presentation condition no difference was observed in detection of threat between LSF and HSF images (Bar et al., 2006b).

Holmes, Green and Vuilleumier (2005) conducted a series of experiments using a spatial cueing paradigm (dot probe task) with LSF (< 2 cycles/degree of visual angle) and HSF (>8 cycles/degree of visual angle) filtered faces as cues that they presented at varying durations (30, 100, 500 and 1000 ms). Participants responded faster to targets replacing LSF fearful faces compared with LSF neutral faces, but only during the shorter stimulus duration (30 and 100ms). No difference in reaction time was observed for targets replacing HSF fearful versus HSF neutral faces during any of the stimulus presentation duration conditions.

These data (Holmes et al., 2005; Bar et al., 2006b) corroborate the notion that emotional information, specifically fear, is initially detected primarily via LSF information relative to HSF information. Furthermore, spatial cueing was only observed with short presentation, suggesting that LSF information is crucial for rapid extraction of emotional meaning, but might not contribute to information processing at later stages or with longer stimulus presentations (Holmes et al., 2005). These data are consistent with the view that LSFs, carried by the magnocellular pathway, are processed in the brain faster than HSFs (see Bar, 2003, for a review). The magnocellular pathway carries the LSF visual information and rapidly distributes it to fast-responding neural areas implicated in processing related to threat perception, such as the prefrontal cortex (Bar, 2003; Bar et al., 2006b) and the amygdala (Vuilleumier et al., 2003).

In summary, the Bar et al. (2006b) and Holmes et al. (2005) studies both suggest the importance of LSFs for rapid early processing of information about threats. However, it should be made clear that these studies do not provide similar evidence of the importance of LSFs when processing threatening faces that are presented for more sustained durations. Thus, the relevance of different SF bands in processing threat during longer presentation periods is unclear.

Previous evidence supports the role of LSF in processing threat information. Relatively fewer studies have focused on the role of spatial frequency content in identifying or categorizing non-threatening emotional content such as happy and sad expressions. As such, the role of LSF has been questioned with respect to emotional expressions that are non-threatening. For example, one study found low (<8 cycles/face) SF to be critical for identifying happy expressions and high SF (>32 cycles/face) to be more useful for identification of sad expressions (Kumar & Srinivasan, 2011). Of note is that the sample size of this study was small ($N=18$) and the authors did not report power statistics, making it difficult to evaluate the impact of the findings. Another study, with a larger sample size of 64 participants, reported greater correct responses at categorizing anger, fear and sadness expressions for the broad spatial frequency (BSF: unfiltered images) information relative to LSF (>8 cycles/face) and HSF (>32 cycles/face) information, but no difference in correct categorization rate between LSF and HSF filtered facial expressions (Wang, Eccleston & Keogh, 2015). The same study found better performance in categorizing neutral faces with BSF and HSF relative to LSF information and again no difference in performance was observed between HSF and LSF filtered neutral faces. Finally, they reported no performance difference between happy and surprised faces across SFs. These authors concluded that the contribution of LSF and HSF information in recognizing emotional

expressions depends on the type of expression and the task demands. They suggest that the lack of SF effects of emotional expressions may be a result of the longer stimulus duration of 300 ms. For example, increased exposure time correlates with improved performance with face from HSF information, but decreased performance with LSF faces (Bachmann, 1991).

A recent study examined the role of LSF (< 6 cycles/face) and HSF (>20 cycles/face) in a classification task with 24 emotional expressions. They too found no difference in emotion categorization based on SF manipulations and suggested that features specific to each emotional expression of a face may be represented by both LSF and HSF information (Jennings & Yu, 2017). The differences in LSF and HSF, or lack thereof, observed in previous studies should be interpreted with caution for a number of reasons. These include the limited (or unreported) power of the studies, the number of emotional states used in the study, spatial frequency cut-off variations, task demands, and the duration of stimulus presentation. These factors make cross-study comparisons challenging.

In summary, the behavioural data suggests the importance of LSF information for rapid threat processing, but findings are unclear with regards to the role of SF in processing non-threatening facial expressions, as well as threatening facial expressions that are presented for longer durations (Kumar & Srinivasan, 2011; Wang et al., 2011; Jennings & Yu, 2017).

1.8.2 Spatial Frequency Effects on Emotional Expression Processing in Schizophrenia: Behavioural Data

Impairment in the ability to identify or recognize faces and emotional expressions in patients with schizophrenia has been well documented (Kohler et al., 2010; Savla et al., 2012), although the neuronal aetiology remains unclear. Of particular interest to the current study presented in Chapter 3 (Study 2) was the impairment in emotional facial categorization. Two

theories are commonly proposed to explain this impairment. One posits that emotional facial recognition deficits in schizophrenia are a reflection of an inherent emotional processing problem specific to negative emotions and stemming from limbic structures (Bediou et al., 2005; Gur et al., 2007) or related to a more general deficit in perceiving faces (e.g. identity) (Chan et al., 2010). Evidence for the latter position comes from studies that have found similar levels of dysfunction in tasks involving emotional processing (e.g., facial expression recognition) and non-emotional processing (such as age or gender discrimination: Edwards, Jackson, and Pattison, 2002; Kerr & Neale, 1993; Kohler, Bilker, Hagendoorn, Gur, and Gur, 2000). These studies indicate that the deficits in emotional facial recognition observed in patients with schizophrenia reflect an impairment in early-stage visual processing of faces in general, rather than emotional expressions per se. The second theory suggests that the deficit is related to a more generalized cognitive incapacity, or even to a broad-based impairment in visual processing of faces (Butler et al., 2009; Johnston et al., 2006; Turetsky et al., 2007). Specifically, that a more general deficits in sensory processing might impact further stages of face processing (Darke et al., 2013).

A large body of research has found that patients with schizophrenia have specific visual impairments at an early stage of processing (Butler & Javett, 2005; Krishnan et al., 2005), especially with regard to the magnocellular stream (Butler et al., 2007; Butler & Javett, 2005; Butler et al., 2008; Norton et al., 2009). In addition, studies have shown an association between this M-pathway dysfunction and emotional identification impairments in patients with schizophrenia. These findings suggest that there is a sensory-level contribution to the observed impairment in emotional expression processing (Butler et al., 2009; Norton et al., 2009). These data suggest that deficit in the ability to process global configural information—which is carried

by LSFs and therefore primarily by the M pathway—may in turn interfere with facial expression perception and recognition observed in patients with schizophrenia (Laprévote, Oliva, Delerue, Thomas & Boucart, 2010; Silverstein et al., 2010; Turetsky et al., 2007), particularly with processing of negative/threatening expressions.

The findings discussed to this point suggest that patients with schizophrenia show impairment in processing LSFs (Martinez, Hillyard, Bickel, Dias, Butler et al., 2012). However, this finding is not universal. For instance, some studies with this patient group have reported a bias *towards* LSFs when processing faces and objects (Laprévote et al., 2013; Laprévote et al., 2010). These studies explored how LSFs (<8 cycles/face) and HSFs (>24 cycles/face) are integrated to form a complete representation of a face. This was done by measuring performance in a facial expression recognition task with hybrid faces (Laprévote et al., 2010). A hybrid face stimulus is one in which the LSF information comes from one face and the HSF information comes from another. This study did not show a deficit in LSF information processing. Rather, they found that patients more often used LSF, rather than HSF, information to recognize facial expressions at a glance, whereas they did not find this in the controls. Furthermore, findings showed that both patients and healthy controls performed the categorization task more accurately with HSF-only faces than with the LSF-only faces (Laprévote et al., 2010), and that there was no difference between patients and controls in performance using LSF-only faces. These findings suggest that both patients and controls use SFs in the same way and with the same efficacy.

Laprévote and colleagues (2010) suggest that the time course of processing of concurrently perceived LSF and HSF information is impaired in patients with schizophrenia. Possible explanations could be that LSF processing is over-persistent or that there is a

dysfunction in the mechanism of integrating HSF into LSF. Consequently, patients' may use more coarse visual information, which influences their difficulties with facial processing and social interactions.

The same group of researchers tested whether the LSF bias in patients is specific to faces or occurs with other visual objects. They found the LSF bias generalized to other objects (Laprévote et al., 2013), suggesting that any difficulties with processing LSFs in faces and facial expressions are due to general visual impairments, not face-specific ones.

Along similar lines, a study by McBain, Norton and Chen (2010) suggests that excessive processing of LSF information is what leads to disruptions in higher-level visual tasks in schizophrenia. Specifically, they used an emotion perception task with LSF, HSF and BSF fearful and happy facial expressions and showed that patients were more likely, compared to controls, to perceive LSF information as more fearful than images with HSF and BSF. Furthermore, images with HSF were perceived as happier in the patient group. Others suggest that processing of all SFs to objects is impaired in patients with schizophrenia and is related to attentional dysfunction rather than visual deficits (Skottun & Skoyles, 2007).

In summary, there is a range of findings regarding impairments of SF processing in patients with schizophrenia, which could be attributed a number of factors: (1) stimuli presented (objects vs. faces), (2) task used and (3) the SF contrast filtered used. As such it is not clear whether SF impairments are general and apply to all objects and faces, to faces alone (or more profoundly), or to specific emotional expressions, such as threatening faces. We turn to electrophysiological data to clarify the role of SF in emotion recognition.

1.8.3 Spatial Frequency and Face Processing: Electrophysiological Investigations

In addition to examining patterns of behavioural data, researchers have used electrophysiological indices, such as the face-selective N170 ERP component, to investigate the effects of spatial scales on early stages of face perception. The N170 is thought to index face detection (Bentin, Allison, Puce, Perez & McCarthy, 1996; Harris & Nakayama, 2007; Itier, Latinus & Taylor, 2006; Rossion et al., 2000) or possibly the analysis of facial features (Bentin et al., 1996; Schyns, Jentzsch, Johnson, Schweinberger & Gosselin, 2003).

Studies investigating face processing with varying frequency scales have yielded relatively consistent results. Awasthi, Sowman, Friedman and Williams (2013) used behavioural and magnetoencephalographic (MEG) data to explore the role of LSF (<8 cycles/face) and HSF (>25 cycles/face) information during a face and place categorization task. The researchers found faster reaction times to categorizing faces with LSF information, but more rapid categorization of places with HSF information. MEG results revealed an earlier M170 component, the magnetoencephalographic counterpart to the electroencephalographic N170, for LSF faces compared to HSF faces, and larger M170 amplitude for LSF faces than for LSF places. Similar results were observed in a study that compared N170 for spatially filtered images of faces and cars (Goffaux et al., 2003a). Another study that used a gender discrimination task found a larger N170-effect for faces with LSFs (<8 cycles/face) than for HSF (>16 cycles/face) faces (Goffaux, et al., 2003b). These results suggest that LSF facilitates rapid detection of a face as a face per se, and may encode global stimulus categorization. Finally, another study used a face detection task (face or not) and found that LSF (<8 cycles/face) faces elicited a greater N170-effect than HSF (>24 cycles/face) faces (Halit, De Haan, Schyns & Johnson, 2006). This study also found faster and more accurate detection of faces containing middle spatial frequency (8-16 cycles/face)

information compared with faces containing predominately LSF information or HSF. These findings show that participants perform better with images with middle spatial frequencies relative to images with high or low SF.

1.8.4 Spatial Frequency and Emotional Expression Processing: Electrophysiological Investigations

The previous section highlighted the behavioural findings corroborating the influence of LSFs in rapid detection of threatening stimuli, as well as the mixed findings regarding the role of LSFs in processing other emotional expressions (Bar, 2003; Bar et al., 2006b; Holmes et al., 2005; Johnson, 2005; Tamietto & de Gelder, 2010; Vuilleumier et al., 2003; Wanget al., 2015; Jennings & Yu, 2017). The present section reviews the limited electrophysiological findings that examine the influence of LSF and HSF (M- and P- pathways) on emotional expression processing. Electrophysiological studies have contributed to our understanding of the time course of emotional expression processing, but currently there is no consensus in the literature as to the stage at which emotion exerts its effect.

A number of studies have found that the P100 ERP component is modulated by emotional expression and intensity (Lee et al., 2011; Pizzagalli et al., 2002; Turetsky et al., 2007, 2008; Utama et al., 2009), while others have not (Caharel et al., 2007; Degabriele et al., 2011; Eimer & Holmes, 2007). Researchers have conducted studies trying to disentangle the effects of emotional expression on the P100 by using SF filtered facial expression stimuli. For example, Pourtois et al. (2005) presented either broadband faces (BSF; containing the normal full range of SFs), and LSF or HSF filtered faces to compare ERP responses to fearful and neutral facial expressions. After filtering for LSF (< 6 cycles per face) and HSF (> 24 cycles per face) information, faces were combined with their complementary SF content in upside-down

orientation to create hybrid faces (to control for the possible effects of low-level pictorial differences between LSF and HSF stimuli, such as total contrast energy). They found larger P100 amplitude in response to fearful versus neutral facial expressions in both the BSF and LSF conditions and no difference in P100 amplitude to HSF stimuli. Vlamings, Goffaux and Kemner (2009) found similar results to Pourtois et al. (2005) and corroborated previous findings, showing that in low-pass filtered (< 12 cycles per face), but not high-pass filtered (> 36 cycles per face) images, emotional stimuli (specifically fearful facial expressions) elicited larger P100 amplitudes compared with neutral facial expressions. These findings suggest that coarse-scale threat cues in facial expressions are preferentially extracted by the M-pathway and subsequently transmitted to dorsal extrastriate regions as early as 100 ms following stimulus presentation.

In addition to the P100, several studies have investigated the contribution of LSF and HSF to the N170 as it pertains to early facial expression processing (Holmes et al., 2005; Pourtois et al., 2005; Vlamings et al., 2009). Vlamings et al (2009) found that the N170 was larger and faster to fearful versus neutral facial expressions only during the LSF (< 12 cycles per face) condition and not during HSF (> 36 cycles per face) condition, suggesting the influence of LSFs in the early processing of threatening faces. Other studies did not find an expression effect to either HSF (> 26 & > 24 cycles per face) or LSF (< 6 cycles per face) facial expressions (Holmes et al., 2005; Pourtois et al., 2005). However, these studies included a smaller sample size of 13 and 14 participants, respectively).

Discrepancies in these findings may be due to a variety of reasons: First, the range of SFs defined as "high" or "low" is not consistent. For instance, some studies used definitions of < 6 and > 24 cycles per face, respectively, while others used < 12 and > 36 cycles per face, respectively. In addition, the studies vary in how contrast and luminance difference across

stimuli were controlled. Some studies equate contrast and luminance, while others do not (or do not report doing so). In some cases, contrast is equalized across SF filtering conditions. Because HSFs naturally have lower contrast in unfiltered images, this produces a situation that is difficult to compare to real-world face processing, where images are not equalized for contrast. Another factor that makes inter-study comparison difficult, and which may explain diverging results across experiments, is variations in task requirements. Schyns (1998), among others, has pointed out the importance of task demands in determining which SF ranges will be most useful for a task. Finally, studies often do not report power, and so null results are difficult to interpret.

In addition to the P100 and N170, ERP studies have examined the effects of facial expression on the P300 (Amrhein, Muhlberger, Pauli, & Wiedemann, 2004; Keil, Bradley, Hauk, Rockstroh, Elbert, & Lang, 2002; Polich, 2007; Schupp, Flaisch, Stockburger & Junghofer, 2006). This component is modulated by affect in tasks thought to involve higher levels of cognitive processing, such as those reflecting stimulus evaluation and selection (Campanella et al., 2002; Miltner et al., 2005). The positive parietal P300 amplitude and latency reflect conscious attention allocation and stimulus evaluation speed, respectively (Campanella et al., 2002; Miltner et al., 2005). Findings of the effects of facial expression on the P300 are mixed, where some have found larger P300 amplitude to fearful or happy faces compared to neutral faces (Liddell et al., 2004; Luo et al., 2010; Williams et al., 2006) and others have reported no P300 changes related to expression (Balconi & Lucchiari, 2005b). To our knowledge, Kim, Shim, Song, Im and Lee (2015) are the only authors who examined the influence of SF filtered emotional expressions in a sample of healthy controls and patients with schizophrenia. The authors found no difference in P300 amplitude or latency across the varying SF filtered emotional expressions.

In summary, the electrophysiological data support the behavioural data in suggesting that the LSF information in facial expressions, carried via the M-pathway, is preferentially used in rapid, early processing of face and emotional processing, especially with fearful facial expressions, as indexed by findings from studies reporting P100 effects (Pourtois et al. 2005; Vlamings et al., 2009). Findings of the role of SF in emotional processing at the N170 stage were mixed, with some studies showing a greater importance of LSF in threat detection and others showing no difference between LSF and HSF filtered emotional faces.

To this point we have primarily discussed research in healthy individuals. Next we turn to the implication of this area of research for patients with schizophrenia, who display impairment in face and emotional expression processing (Kohler et al., 2010; Savla et al., 2012).

1.8.5 Spatial Frequency and Face Processing: Electrophysiological Investigations in Schizophrenia

As previously discussed, in response to emotional expressions, healthy controls have shown modulations in ERP signals as early as 100 ms, as indexed by the P100 component. This early response is compatible with M-pathway involvement in rapid emotional processing. Patients with schizophrenia have shown both intact P100 amplitude to emotional expressions (Herrman et al., 2005; Johnston et al., 2005; Turetsky et al., 2007; Wynn et al., 2008), as well as a smaller P100 (Caharel et al., 2007; Campanella et al., 2006). Two ERP studies have used SF filtered facial images to investigate where (which visual pathway) and when emotional processing breaks down for patients with schizophrenia (Kim et al., 2015; Obayashi et al., 2009).

Obayashi et al. (2009) administered a passive viewing task involving LSF (<4 cycles/face), HSF (>30 cycles/face) and BSF manipulated images of happy, angry, fearful and

neutral facial expressions. They found that controls and patients showed different modulations of P100 amplitude by SF. Specifically, controls showed increased P100 amplitudes to LSF compared to BSF, but patients did not. Both groups showed larger amplitudes to BSF faces than HSF ones. In addition, they found different patterns of P100 latency modulation by SF in the two groups. These findings support the hypothesis that there is a problem with early M-pathway processing in patients (Obayashi et al., 2009). Neither controls nor patients showed modulations of accuracy in processing emotional faces as a result of SF manipulation.

Recently, Kim et al. (2015) found smaller P100 amplitude to LSF (<8 cycles/face) fearful facial expression in patients compared to healthy controls. Patients also elicited larger P100 amplitudes for BSF fearful faces compared to HSF (>24 cycles/face) and LSF fearful faces. In response to neutral faces, patients showed smaller P100 amplitude for HSF compared to BSF and LSF. These differences were not observed in healthy controls. Rather, the controls demonstrated larger in P100 amplitude to LSF fearful faces compared with HSF fearful faces and no difference in SF to neutral faces. The reduced P100 activation to both SF ranges is consistent with suggestions that patients show both magnocellular and parvocellular pathway deficiencies (Butler et al., 2001; Butler et al., 2005; Campanella et al., 2006).

The N170 in schizophrenia patients has been found to be reduced in amplitude in a number of studies investigating facial processing (Caharel et al., 2007; Johnston et al., 2005; Lynn & Salisbury, 2008; Turetsky et al., 2007). Unlike controls, N170 amplitude in patients was found to be insensitive to SF manipulation and emotional expression by Obayashi et al., (2009). Kim et al. (2015) found larger N170 amplitude to LSF compared to HSF images in patients; however, healthy controls instead showed stronger activation to BSF compared to HSF. The authors suggest that this indicates a compensatory effect associated with the observed

reduction in P100 amplitude to LSF stimuli (Kim et al., 2015). Thus the impairment in earlier (P100-indexed) visual processing carries forward at least as far as this N170 component.

Patients with schizophrenia have shown impairments in later affect-related (Streit et al., 2001; Turetsky et al., 2007; Wynn et al., 2008) ERP component such as the P300 (An et al., 2003; Turetsky et al., 2008). To our knowledge, only Kim et al. (2015) explored the P300 (in addition to the P100 and N170) with SF-manipulated facial images. They did not find any impairment in the P300, suggesting that the altered emotional recognition in patients with schizophrenia is more likely due to bottom-up effects involving earlier stages of visual processing rather than a top-down influences (Butler et al., 2007).

1.8.6 Special Frequency Manipulated Facial Processing in Schizophrenia: Summary and Research Aims

There is limited ERP work using SF-manipulated facial expressions to test which visual pathway influences the abnormal emotional recognition observed in patients with schizophrenia. Moreover, what data does exist is mixed. One study found controls to show augmented P100 amplitudes to LSF versus HSF and BSF faces and BSF versus HSF faces (i.e., $LSF > BSF > HSF$), whereas the patient group showed no increased P100 amplitudes between LSF and BSF faces (i.e., $LSF = BSF > HSF$; Obayashi et al., 2009). A more recent study found decreased P100 amplitudes in the patient group, indicating abnormalities in early visual processing in both LSF and HSF conditions. They also found significant emotion effects, with smaller P100 amplitude to LSF fearful faces and a trend towards decreased P100 amplitude to HSF neutral faces (Kim et al., 2014). Only one study found N170 amplitude effects to LSF faces, which the authors suggest to indicate a compensatory effect associated with an observed reduction in P100 amplitude to

the same stimuli (Kim et al., 2014). Finally, no SF effects were observed at a latter stage of processing, as indexed by the P300, in either study (Kim et al., 2007; Obayashi et al., 2009).

A central weakness of these two studies (Kim et al., 2007; Obayashi et al., 2009) is that they do not provide evidence for whether the impairments observed in the patient group are specific to faces or are more general. Obayashi et al., (2009) included a control object stimulus (house image) to confirm an N170 effect, specifically to determine whether subjects could discriminate the faces from objects, but they did so by using BSF images only. This leaves open the questions of whether SF manipulations influence both face and object discrimination in patient and control groups. Kim et al. (2015) included a control object (chair) in their task, but did not report any comparisons between chairs and faces. The work from chapter 3 used the emotional facial identification paradigm to clarify what occurs in the visual processing stream during emotional processing in patients with schizophrenia. The study included SF manipulated chair stimuli as controls. The use of facial expression and chair stimuli allowed for examination of whether any SF-based impairments observed in the patient group are specific to faces or generalized to objects.

1.9 Treatment of Schizophrenia: Auditory Hallucinations

Pharmacotherapies are the front-line treatment for attenuating positive symptoms and reducing the risk of relapse in patients with schizophrenia (SZ). However, these therapies are not 100% effective. Many patients remain symptomatic despite adequate doses of antipsychotic drugs (Kane, 1996; Lieberman et al., 2005). These patients become chronic, causing an impaired quality of life and a diminished cognitive capacity, leading to poor functional outcomes. Cognitive Behavioural Therapy (CBT) has been suggested as a complementary therapy to pharmacotherapies, specifically to target psychosis in treatment resistant cases (Pilling et al.,

2002; Tarrier & Wykes, 2004; Zimmermann et al., 2005). CBT may be a promising approach for improving information processing difficulties in schizophrenia, and by so doing, facilitating social cognition and daily functioning. However, the research to date lacks consistent methodologies and outcome measures, which might provide firmer support for the efficacy of CBT in patients with schizophrenia. Researchers have suggested that future CBT intervention studies should incorporate investigations of neurophysiological approaches such as functional imaging and event-related potentials to observe any underlying physiological changes that may occur as a result of the therapy (Shergill et al., 1998).

1.10 Auditory Verbal Hallucinations and Early Visual Processing Impairments

Auditory hallucinations are a common characteristic of schizophrenia. Indeed, over 60% of individuals diagnosed with schizophrenia experience hallucinations over the course of their illness (Andreasen & Flaum, 1991; Flaum & Andreasen, 1991). Auditory hallucinations are defined as a “sensory perception that has a compelling sense of reality, but which occurs without external stimulation of the sensory organ” (American Psychiatric Association, 1994, p.767).

Patient with schizophrenia usually report high levels of distress in response to auditory hallucinations (Birchwood & Chadwick, 1997; van der Gaag, Hageman & Birchwood, 2003). The cognitive model of voice hearing proposes that the distress is related to idiosyncratic beliefs or cognitive appraisals involving such factors as control, power, identity of voice, authority, and consequences of not complying with the voices. These beliefs/appraisals impact the individual’s emotional, behavioural, and somatic responses to the voice hearing experiences. In turn, emotional and behavioural responses influence cognitive appraisals about the voices. The experience of an auditory hallucination has been suggested to occur when an individual

misattributes some internal stimuli (e.g., unwanted intrusive thoughts), to an external source (Morrison & Haddock, 1997; Morrison, Haddock, & Tarrier, 1995).

Researchers have reported that patients who experience auditory hallucinations showed significantly poorer performance in a word serial position test than patients who did not, suggesting that experiencing auditory hallucinations interferes with processing in both auditory and visual modalities (Bruder et al., 2011; van Lutterveld et al., 2011). Kayser et al. (2012) examined whether patients' tendency to experience auditory hallucinations affects early visual processing. The authors found that patients who reported experiencing auditory hallucinations had substantially reduced N170 to faces compared to controls and nonhallucinators (Kayser et al., 2012), suggesting that the association between impaired auditory processing and hearing voices is not limited to the auditory modality but also extends to impairment in visual processing as well, and face processing in particular (Kayser et al., 2012). Thus patients with auditory hallucinations show increased distress over hearing the voices as well as experience impairments secondary to the positive symptoms (i.e., impaired early visual processing).

1.11 Cognitive Interventions for Auditory Verbal Hallucinations

Cognitive Behavioural Therapy is a recognized and effective treatment option for reducing symptoms across a variety of psychiatric disorders. Specialized cognitive behavioural approaches have been developed to decrease patient's distress associated with hallucinations and delusions (Haddock et al., 1998). Cognitive Behavioural Therapy for psychosis (CBTp), developed as a psychosocial treatment to reduce the distress of psychotic symptoms, is recommended as an adjunctive treatment for individuals who experience persistent auditory verbal hallucinations (NICE clinical guidelines; National Collaborating Centre for Mental Health, 2010). Multiple meta-analyses on the effectiveness of CBTp have evaluated treatment

effects on the frequency and severity of positive symptoms (Gould, Mueser, Bolton, Mays, & Goff, 2001; Lynch, Laws & McKenna, 2010; Lincoln et al., 2012; NICE, 2010; Rector & Beck, 2001; Pfammattter, Junghan, & Brenner, 2006; van der Gaag, Valmaggia & Smit, 2014; Wykes, Steel, Everitt & Tarrier, 2008; Zimmermann et al., 2005) and have found that CBTp demonstrates modest but significant positive impact in controlled studies (average effect around 0.35 - 0.40; Sivec & Montesano, 2012). The meta-analyses found that CBTp reduces positive symptoms (Gould et al., 2001; Pfammatter et al., 2006; Zimmermann et al., 2005), negative symptoms (Rector & Beck, 2001), and general psychopathology (Wykes et al., 2008; Sarin, Wallin & Widerlov, 2011). A recent meta-analysis examining the effects of CBTp in the treatment of outpatients who did not show a complete response to medication found an overall benefit of CBT for positive symptoms (Hedges' $g = .47$) and for general symptoms (Hedges' $g = .52$; Burns, Erickson, & Brenner, 2014). The outcome of this study suggests that patients with medication resistant psychosis (positive symptoms) may obtain more benefit from an adjunctive psychotherapy, such as CBTp, than from medication alone. A second recent meta-analysis has shown small beneficial effects of CBTp (Jauhar et al., 2014). However, this research has some limitations such as not including studies that targeted hallucinations. Its results should therefore be considered with caution.

Growing evidence in the field supports the use of CBT to specifically target auditory verbal hallucinations in treatment-resistant cases or as a complement to pharmacotherapy. However, individual CBT for voices is costly and demand typically exceeds available resources. Group therapy is cost effective, provides a place for patients to recognize that others experience similar problems, to feel less stigmatized, to feel accepted by other group members, and to improve their social functioning (Goodliffe, Hayward, Brown, Turton, & Dannahy, 2010;

Lecomte, Leclerc, Corbiere, Wykes, Wallace & Spridel, 2008; McLeod, Morris, Birchwood, & Dovey, 2007a). Three randomized controlled trials (RCTs) of group CBT for voices (CBTv) have been conducted. An RCT comparing group CBTv to treatment as usual (TAU) with a sample size of 85 outpatients found significant improvements in social functioning for up to 6 months after the end of group CBTv, as well as some improvement in self-esteem and effective coping strategies (Wykes et al., 2005). Another RCT demonstrated significant reduction in voice frequency and in perceived voice power, as well as a trend towards distress reduction (McLeod, Morris, Birchwood, & Dovey, 2007a,b). However, they did not conduct a follow-up test and there were no reports of independent allocation or blind assessors. Finally, a third RCT compared group CBTv to a treatment consisting of supportive therapy and found significant improvements in general symptoms and positive symptoms (Penn et al., 2009).

Three RCTs of group CBT for psychosis to target voices specifically have been conducted. Barrowclough et al. (2006) compared group CBT with interventions targeting distress around voices with TAU and found significant reduction in feelings of hopelessness and low self-esteem in the CBT group. However, this study did not report any difference between the treatment group and control group in symptoms, functioning, or relapse rate. Additionally, the researchers chose to use the PANSS rather than the PSYRATS to measure positive symptoms, even though the PSYRATS is more sensitive to change. The other two trials compared group CBT targeted at voices with psycho-education (Bechdolf et al., 2004) and social skills training and a waitlist group (Lecomte et al., 2008). These studies found significant reduction in the number of hospital admissions, improved medication compliance, significant improvements in overall symptomatology, active coping strategies, self-esteem and lower drop-

out rates in the CBT group relative to the control groups. Both studies showed improvements in positive symptoms in all treatment groups (Bechdolf et al. 2004; Lecomte et al., 2008).

In summary, an important mechanism of change from group CBT for voices, or CBT for psychosis with voices as a specific target, may be alteration of beliefs about voices. Altering the beliefs about voices reduces distress and thus enhances effective coping strategies and improves functioning (Ruddle, Mason & Wykes, 2011). Additionally, researchers also suggest that changing the relationship that patients have with their voices, the level of social activity and improving self-esteem may also be a recipe for improving outcomes (Ruddle et al., 2011).

Although there is some evidence supporting the effectiveness of group CBT for targeting voices (CBTv), the field lacks consistent methodologies, outcome measures and larger scale RCTs, which could provide further support for the efficacy as well as cost-effectiveness of group CBT for voices in treatment-resistant patients with schizophrenia. Researchers have recommended incorporating neurophysiological measures to monitor any underlying physiological changes following CBT for voices treatment (Shergill et al., 1998).

1.11.1 Neurophysiological Changes Following Cognitive Behavioural Therapy for Psychosis

Neuroimaging studies suggest that psychotherapy can lead to lasting structural neuroplastic changes in brain regions important for effective information processing (see Weingarten & Strauman, 2015 for review). Kumari et al. (2011) has examined neural changes following CBT treatment of psychosis. The authors examined functional brain changes following CBT for psychosis in patients with persistent and distressing positive symptoms of schizophrenia. Participants were required to complete a gender discrimination task with stimuli depicting facial emotions of fear, anger, happiness or neutrality. Following treatment, patients in

the CBTp group showed a decrease in activation of a network of regions (e.g., inferior frontal lobe, insula, thalamus, occipital lobe) during processing of angry and fearful facial expressions (Kumari et al., 2011). The authors suggested that their study was the first to provide evidence that CBTp attenuates brain responses to threatening stimuli. They also suggested that the treatment may assist with mediate symptom reduction by promoting the processing of threats in a less distressing way (Kumari et al., 2011). However, the authors did not mention the use of a healthy control group who were tested at baseline and compared with the pre- treatment data in the patient group. Additionally, no difference in FFG activation (where the N170 ERP is thought to be generated) from pre- to post- treatment was reported. The fMRI data is also difficult to relate to ERP findings, as the temporal resolution is much different (i.e., on the order of seconds for fMRI and milliseconds for ERP). Given the lack of a control group and no difference in brain activation in the area known to be important to face recognition, these results should be interpreted with caution. However, the aim of this study was not to test the efficacy of CBTp, but rather to observe changes in brain activity over the course of CBTp, and this was observed. Additional research exploring neurophysiological measures to monitor any underlying physiological changes following group CBT for patients with schizophrenia is required (Shergill et al., 1998).

1.11.2 Cognitive Behavioural Therapy for Voices: Summary and Study Aims

Cognitive behavioural therapy has been shown to be widely effective for reducing symptoms across a range of psychiatric disorders. Group CBT for schizophrenia has been shown to reduce overall symptoms, including distress associated with auditory hallucinations. Also, it has been shown to improve social functioning. Although there is evidence of CBTv's

effectiveness in schizophrenia patients, no researchers have investigated if CBTv affects the electrophysiological markers of schizophrenia.

Therefore, the work presented in Chapter 4 (Study 3) is the first study (to our knowledge) that has examined ERP changes that emerged following CBT for voices in patients with persistent and distressing auditory hallucinations. As discussed earlier, patients with schizophrenia show reduced ERP amplitudes in response to faces and faces depicting a variety of emotional expressions. For the patient population included in the work presented in Chapter 4, the primary positive symptom was auditory verbal hallucinations and, as such, the CBT was developed to target attribution to the voices and in turn reduce distress related to hearing voices and in turn improve functioning. However, as previously noted, this form of therapy has been shown to mitigate a range of symptoms of schizophrenia to some degree and should therefore aid in improving social cognition as measured by face and emotional expression processing. The aim of the work presented in Chapter 4 was to explore whether ERPs elicited by emotional facial processing were altered in patients with schizophrenia following completion of CBT. This work constitutes an important original contribution to the literature because, unlike previous studies, we used event-related potential components to measure emotional facial processing deficits in patients with schizophrenia. This allowed us to observe any underlying neurophysiological changes that may arise as a result of cognitive behavioural therapy.

Publication Status: The study is published in the International Journal of Psychophysiology.

CHAPTER 2 : STUDY 1

Impairments of Emotional Face Processing in Schizophrenia Patients:

Evidence from P100, N170 and P300 ERP Components in a Sample of Auditory Hallucinators

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Charles Collin

2.1 Abstract

Patients with schizophrenia show impaired face and emotional expression processing that may be due to early perceptual deficits or late impairments in higher-order emotional facial recognition. This study examined event-related potentials (ERPs) in 23 patients with schizophrenia who experience auditory hallucinations and 19 healthy controls. EEG activity was recorded from 32 scalp sites positioned according to the 10-10 placement system. Linked left and right electrodes at the mastoids served as the reference. The P100, N170 and P300 were measured during an emotional facial identification task, which included neutral, joyful, sad, angry and fearful facial expressions and non-face stimuli (chairs). P100 was measured at $O_{1/2}$ and $P_{7/8}$. N170 was measured at $P_{7/8}$. P300 was measured at P_z . Patients with schizophrenia were slower at identifying all facial expressions, including neutral ones. They also showed less positive P100 amplitude to sad, angry and fearful facial expressions. N170 amplitudes were smaller in patients in response to neutral, joyful, sad, angry, and fearful facial expression. Patients showed less positive P300 mean amplitudes to all facial expressions, including neutral ones. Within-group comparisons showed that patients exhibited a different pattern of ERP modulation across facial expressions than controls for P100 and N170, but not for P300. Our findings are compatible with the idea that behavioural and electrophysiological face-processing deficits in schizophrenia arise from early-stage deficits in visual processing.

Key Words: Schizophrenia, Face processing, Emotional processing, Electrophysiology

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Impairments of Emotional Face Processing in Schizophrenia Patients:

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2.2 Introduction

Schizophrenia is characterized by hallucinations and delusions, thought disorder, disorganized speech, and deficits in social skills (APA, 2013). Persistent, positive symptoms such as hallucinations and delusions are severely distressing and disruptive to daily functioning, including social functioning (Mier & Kirsch, 2015). Emotional processing, which is a domain of social cognition, has been studied extensively via emotional facial expression recognition (Green et al., 2005) and identification as well as auditory emotional recognition (Gold et al., 2012; Kantrowitz et al., 2015).

A range of research findings, including two meta-analyses, have demonstrated impairments in the ability to identify and recognize emotional facial expressions in patients with schizophrenia (Kohler et al., 2010; Savla et al., 2012), but it is not clear whether these difficulties are related to early visual processing impairments or to higher-order aspects of face recognition. It is also not clear whether these deficits are limited to a specific set of emotional facial expressions (Schneider et al., 2006; Chan et al., 2010; Johnston, Devir & Karayanidis, 2006; Bryson, Bell, Lysaker, 1997; Barkhof, de Sonnevile, Meijer, & de Haan, 2015a, b) or to a more generalized impairment in face identity recognition (Kerr & Neale, 1993; Salem et al., 1996; Addington & Addington, 1998; Sachs et al., 2004). Others have also proposed that impairments in processing face and emotional facial expressions observed in patients may be part of a more general cognitive and sensory problem (Addington & Addington, 1998; Sach et al., 2004). Regardless of whether emotional facial expression processing deficits represent a specific or generalized form of cognitive impairment in patients, studies have shown that emotion

processing deficits are a crucial predictor of clinical outcome and are uniquely related to clinical symptoms (Addington, Saeedi & Addington, 2006b; Couture et al., 2006; Kee, Green, Mintz, & Brekke, 2003; Kohler et al., 2010; Pinkham, Penn, Perkins, Graham, & Siegel, 2007; Silver, Shlomo, Turner, & Gur, 2002; Sachs et al., 2004).

2.2.1 Event Related Potentials and Emotional Facial Processing

Event-related potential (ERP) measurements have been used to understand the mechanisms underlying face processing. The excellent temporal resolution of ERP measurements allows for investigating the time-course of the information-processing cascade from early to late processing stages (Luck et al., 2011). The processing of emotional facial expressions may involve three stages with associated ERP components: the P100 (Campanella, Montedoro, Streel Verbanck & Rosier, 2006; Jung, Kim, Kim, Im & Lee, 2012; Lee, Kim, Kim & Bae, 2010; Turetsky, Kohler, Indersmitten, Bhati, Charbonnier, & Gur, 2007; Wynn et al., 2008), the N170 (Campanella, Montedoro, Streel Verbanck & Rosier, 2006; Jung, Kim, Kim, Im & Lee, 2012; Lee, Kim, Kim & Bae, 2010; Turetsky, Kohler, Indersmitten, Bhati, Charbonnier, & Gur, 2007; Wynn et al., 2008), and the P300 (Jung, Kim, Kim, Im & Lee, 2012; Lee, Kim, Kim & Bae, 2010; Turetsky et al., 2007).

Measured over the posterior (occipital) cortex, the P100 is believed to reflect early-stage visual information processing and index automatic attention allocation (Luck et al., 1994; Santesso et al., 2008). Several studies have reported larger P100 amplitude to faces than objects, and P100 modulation by emotional facial expressions (Lee, Gosselin, Wynn & Green, 2011; Pizzagalli et al., 2002; Turetsky et al., 2007; Turetsky et al., 2008; Utama, Takemoto, Koike & Nakamura, 2009).

The N170, a posterior temporal negative peak that is more prominent over the right hemisphere (Bentin et al. 1996; Fan et al., 2015; Dundas, Plaut, & Behrmann, 2014; Kovács, Zimmer, Volberg, Lavric & Rossion, 2013; Luo et al. 2010; Rossion et al. 2000; Rossion & Jacques, 2008), is thought to reflect early visual processing responsible for constructing a representation of the human face (Vuilleumier & Pourtois, 2007). In other words, the N170 is believed to reflect the earliest stage of facial structure encoding and/or face identification (Cauquil, Edmonds & Taylor, 2000; Eimer & Holmes, 2002; Vuilleumier et al., 2007). While a substantial body of literature supports the notion that the amplitude and latency of the N170 are modulated by emotional facial expressions (Ashley, Vuilleumier & Swick, 2004; Eimer, Holmes & McGlone, 2003; Holmes et al., 2003; Ramos-Loyo, Gonzalez-Garrido, Sanchez-Loyo, Medina & Basar-Eroglu, 2009; Santesso et al., 2008), other studies suggests that they do not (Eimer & Holmes, 2002; Holmes, Winston & Eimer, 2005; Obayashi et al., 2009). A recent meta-analysis examined the inconsistencies regarding the modulation of the N170 by emotional facial expressions (Hinojosa, Mercado & Carretie, 2015). These authors found different N170 amplitudes in response to neutral faces compared to emotional facial expressions – angry, fearful and happy faces elicited the largest N170 amplitudes (Hinojosa et al., 2015). The authors argued that the N170 may reflect the structural encoding of a face, as well as, be involved in processing information from both basic-level and high-level facial features (i.e., facial expression, identity; Hinojosa et al., 2015). The physical properties (e.g. size, brightness, contrast) of the stimulus set may account for inconsistencies observed with the N170 in response to emotional facial expressions (Blau, Maurer, Tottenham & McCandliss, 2007).

The positive parietal P300, which peaks about 300 ms following stimulus onset, is modulated by affect in tasks involving higher-level cognitive processes including stimulus

evaluation and selection (Campanella et al., 2002; Miltner et al., 2005). The P300 is also thought to reflect conscious attention allocation and stimulus evaluation speed (Polich, 2007). Findings regarding the effects of emotional facial expression on the P300 in typically developing participants are mixed – some studies report larger P300 amplitudes to emotional versus neutral stimuli (Campanella et al., 2002; Miltner et al., 2005) while others report larger P300 amplitudes to fearful (Liddell, Williams, Rathjen, Shevrin & Gordon, 2004; Luo et al., 2010; Williams, Palmer, Liddell, Song, & Gordon, 2006) or happy facial expressions (Luo et al., 2010) relative to neutral ones. Others studies find no P300 changes whatsoever to any expression (Balconi et al., 2006).

2.2.2 ERP Components of Emotional Facial Expression Processing in Patients with Schizophrenia

Deficits in the P100 component in patients with schizophrenia have been observed with non-face stimuli (Butler et al., 2007; Doniger, Foxe, Murray, Higgins & Javitt, 2002; Haenschel et al., 2007; Schechter et al., 2005; Yeap et al., 2006). However, results are mixed with regard to emotional facial expression processing. Some studies show normal processing at the P100 stage (Bediou et al., 2007; Herrmann et al., 2005; Jung et al., 2012; Lee et al., 2010; Turetsky et al., 2007; Wynn et al., 2008), but a recent meta-analysis reported smaller P100 amplitude to faces in patients relative to controls ($d = 0.41$; Earls et al., 2015). In an exploratory analysis accompanying the meta-analysis, schizophrenia patients exhibited smaller P100 amplitude in response to neutral ($d = 0.32$) and happy ($d = 0.21$) facial expression but showed no difference in response to fearful facial expression ($d = 0.09$; Earls, 2015) when compared to controls. The authors interpreted these findings as evidence that face-processing deficits in patients with schizophrenia begin at an earlier stage of processing than previously expected and that there is

some evidence that these deficits are emotion specific. The authors suggest that processing deficits may occur in earlier visual processing stages for faces with neutral or positive expressions but occur in later processing stages for fearful faces, such as that indexed by the N170 (Earls et al., 2015). Of note is that the meta-analysis did not include studies with other negative facial expressions such as sadness and anger, nor did it discuss specific symptom characteristics (i.e., positive symptoms, negative symptoms) of patients with schizophrenia and their possible relations to impairment in face processing. Furthermore, other studies show P100 amplitude deficits to faces irrespective of emotion (Caharel et al., 2007 [happy, disgust, and neutral]; Campanella et al., 2006 [i.e., happy, fearful, sad, and neutral]). The literature suggests less positive P100 amplitude to faces and emotional facial expressions but is inconsistent regarding deficits in the processing of specific emotions. Further exploration of impaired early visual processing with multiple emotion categories is required.

Many studies have found reductions in N170 amplitude to faces in patients with schizophrenia relative to healthy controls at least for some experimental conditions or selected contrasts (Bediou et al., 2007; Caharel et al., 2007; Jung et al., 2012; Kirihara et al., 2012; Lee et al., 2010; Lynn & Salisbury, 2008; Turetsky et al., 2007), but others have shown no corresponding reduction in N170 amplitude (Akbarfahimi, Tehrani-Doost & Ghassemi, 2013; Komlósi et al., 2013; Lee et al., 2007; Ramos-Loyo et al., 2009; Wynn et al., 2008). A recent meta-analysis (McCleery et al., 2015) provided evidence for moderate impairments (effect size: 0.49) with N170 amplitude in patients with schizophrenia. The N170 effects were similar for tasks requiring participants to respond to emotion judgments of facial expressions compared with non-affective tasks. Most studies included in the meta-analysis did not report ERP amplitudes for individual emotional facial-expression categories and were not able to examine any potential

impact of emotional facial expressions on N170. However, results from the meta-analysis suggest a reduction of the N170's amplitude for patients with schizophrenia and that this reduction reflects an impairment in the general encoding of facial features rather than an impairment specific to the encoding of emotion. Previous studies having reported less negative N170 amplitudes in patients with schizophrenia found the impairment irrespective of emotion (Bediou et al., 2007; Caharel et al., 2007; Jung et al., 2012; Kirihara et al., 2012; Lee et al., 2010; Lynn & Salisbury, 2008; Turetsky et al., 2007). These findings also suggest that the large behavioural deficits observed for emotional facial expression recognition arise from an underlying neural impairment. Further, the non-specificity of the deficit to an emotion suggests an impairment in general face processing rather than in emotion processing (McCleery et al., 2015). These findings of impairment in N170 suggest that patients may be less efficient at encoding facial features.

Two studies examined the effect of emotional facial expression on the P300 in individuals with schizophrenia. One reported larger P300 amplitudes to negative facial expressions than to positive ones in healthy controls whereas the opposite pattern was found for patients with schizophrenia (An et al., 2003). The other study reported significantly smaller P300 amplitudes to all emotional facial expressions in patients with schizophrenia compared to healthy controls (Turetsky et al., 2008).

A recent study reported that positive symptoms are correlated with prolonged, long-latency activation to fearful facial expressions (Komlosi, Csukly, Stefanics, Czigler, Bitter & Czobor, 2013). However, others have suggested that emotional expression-recognition deficits in schizophrenic patients are attributable to broader deficits in visual face processing (Johnston et al., 2005). Consistent with this view, N170 ERP deficits have been found in patients with

schizophrenia, but no emotional -modulated recognition deficits have been observed in the 180-250 ms time frame (Herrmann, Reif, Jabs, Jacob, & Fallgatter, 2006). Furthermore, P100 modulation by emotional facial expressions has been found even when the later N170 is not modulated by the same stimuli (Pourtois, Grandjean, Sander & Vuilleumier, 2004; Pourtois et al., 2005). This suggests that the mechanisms for the earlier processing of affective content (reflected in the P100) and the later structural encoding of facial features (reflected in the N170) are dissociable (Pourtois et al., 2004; 2005; Vuilleumier et al., 2007). Additionally, less positive P300 amplitude to emotional facial expressions in patients with schizophrenia was correlated with reductions in the earlier N170 response (Turetsky et al. 2008). These researchers suggest that the disturbances in the higher-order evaluative processes (evidenced by the P300) may be a consequence of earlier disruption in the sensory encoding of facial stimuli.

There is evidence that electrophysiological correlates of face and emotion processing may vary with the severity and nature of patient symptoms. Correlations between less negative N170 amplitude to faces and lower scores on the Global Assessment of Functioning (Obayashi et al., 2009) and Social Functioning Scale (Tsunoda et al., 2012) in patients with schizophrenia have also been observed. Campanella et al. (2006) found a significant positive correlation between positive symptoms and a decrease in N170 amplitude in response to emotional facial expressions, but no correlation between N170 reduction and negative symptoms nor between positive and negative symptoms and amplitudes of other ERP components (P100, P300, and N400).

2.2.3 The Present Study

Patients with schizophrenia show a deficit in emotional facial expression processing as reflected in multiple ERP components including the P100, N170, and P300. However, there is no

consensus as to whether the deficit in processing occurs during the course of early visual and face processing (<200 ms) or later higher-order cognitive processing (>200 ms). Furthermore, it is unclear whether neutral faces, emotional facial expressions, or only specific emotional expressions lead to impairments in processing.

Although many authors have used ERPs to examine face processing in patients with schizophrenia, only four studies have focused on the time course of face or emotional facial expression processing in the same sample (Jung et al., 2012; Lee et al., 2010; Turetsky et al., 2007; Wynn et al., 2007). One goal of the present study was to replicate these previous studies while including a wider range of emotional facial expressions in order to allow comparisons of ERP responses between neutral faces and some basic emotion categories, namely sadness, anger, joyful, fear. The present study also aimed to investigate whether impairments observed with P100, N170 and P300 components in patients with schizophrenia correlate with positive or negative symptoms, social cognition and global functioning. Given that early visual ERPs are influenced by low-level physical stimulus characteristics, we were careful to equalize the luminance and visual contrast of our images.

An additional goal of the present study was to examine a more homogeneous sample of patients with schizophrenia, specifically those with auditory hallucinations. Past studies on deficits in facial and emotional facial expression processing in patients with schizophrenia have typically included heterogeneous samples of patients with mixed symptoms presentations (e.g., individuals with concerns of hallucinations, delusions and/or negative symptoms). Heterogeneous samples introduce variability in the data and makes it difficult to know whether findings can be generalized to all forms of schizophrenia or only to those with specific symptomology. The present study included only individuals with auditory hallucinations to

determine if similar ERP findings are observed in this specific case. While the presence of auditory hallucinations may seem to be only superficially relevant to the study of face recognition, there is evidence that auditory hallucinations can affect visual processing. Studies have shown that the negative impacts of auditory hallucinations are not limited to the auditory modality but also extend to visual processing (Bruder et al., 2011; van Lutterveld, Sommer & Ford, 2011) including face processing (Kayser et al., 2012). Patients who experience auditory hallucinations perform more poorly on visual word serial-position tests than patients who do not (Bruder et al., 2011; van Lutterveld et al., 2011). Kayser et al. (2012) examined whether patient propensity to experience auditory hallucinations affects early visual processing and found that patients reporting auditory hallucinations had substantially less negative N170 amplitude for faces compared to controls and non-hallucinators.

Our last objective for the present study was to determine whether patients with schizophrenia exhibit a normal N170 effect – that is, a larger amplitude for face stimuli than non-face stimuli. To this end, our design included non-face control stimuli consisting of chair images. Chairs have been used in previous studies as a relatively homogeneous category whose members, like faces, are typically seen upright. Including this non-face condition also allowed us to examine whether the magnitude of the N170 effect varies with facial expression and to determine if the ERP group effects observed with neutral and emotional facial expressions are specific to faces or extend to non-face stimuli.

To summarize, the general aim of the study was to measure the brain's electrical activity in patients with schizophrenia during an emotional facial identification task. Based on our interpretations of the literature, we hypothesized that: 1) patients would have difficulty categorizing facial expressions relative to healthy controls, as evidenced by reduced accuracy

and longer response times, 2) patients would show smaller P100, N170 amplitude and P300 mean amplitude to neutral faces and emotional facial expressions compared to healthy controls, and 3) patients would show an emotion-specific P100, N170, and P300 modulation pattern that differs from that of healthy controls. Findings should inform our understanding of where during the course of emotional facial processing deficits occur in patients with schizophrenia and whether the deficit is specific to any one-emotion category in this population. The existing literature provides none to limited evidence of earlier or later P100, N170 and P300 latency in response to neutral and emotional facial expressions in patients with schizophrenia compared with healthy controls. As such, the present study did not formulate specific hypotheses regarding latency effects between the two groups.

2.3 Methods

2.3.1 Participants

We evaluated twenty-three patients (9 women, 14 men) with schizophrenia who were diagnosed by trained psychiatrist using the Structural Clinical Interview (SCID) for DSM-IV-TR and the Global Assessment of Functioning (GAF; DSM-IV-TR, 2000; Appendix A). All participants included in the study: (i) were recruited from the Outpatient Schizophrenia Program of the Royal Ottawa Mental Health Centre; (ii) were between the ages of 18-60 years; (iii) were clinically stable for at least the 3 month period prior to testing as indicated by the absence of significant changes in symptoms or medication; (iv) took one of the atypical antipsychotics as their primary medication; (v) reported no current history of drug/alcohol dependence, history of head injury resulting in loss of consciousness, diagnosis of epilepsy or other neurologic disorder, electroconvulsive therapy within the past year, significant medical illness, symptoms resulting in movement disorder that could affect ERP recordings, or abnormal audiometric assessment; and

(vi) reported a consistent history of auditory verbal hallucinations over the course of their illness and exhibited a score greater than 3 (reflecting mild or greater auditory/verbal hallucinatory experience) on the hallucination item of the PANSS Positive Symptom Scale and less than 65 on the total PANSS score (PANSS; Kay, Fiszbein, & Opler, 1987; Appendix B). This assessment was based on self-reported symptoms experienced over the past month, deviating from the standard administration of the PANSS, which typically reflects symptoms over the past week (Kay et al., 1987). Participants with impaired vision were required to correct their vision with glasses while undergoing the study assessments.

Nineteen adult healthy controls (HC: 8 women, 11 men) were interviewed by a trained investigator to ensure absence of: (i) current or past psychopathology, (ii) family history of schizophrenia in a first-degree relative; (iii) alcohol or drug abuse (assessed with an adaptation of the structured clinical interview, non-patient version [SCID-I/NP]; First, Spitzer, Gibbon, & Williams, 1996; Appendix C); and (iv) history of seizures or significant brain trauma or known anatomical brain lesion(s). HCs were matched to the patient group with regard to gender, age and education level. HCs completed the Beck Depression Inventory-II (BDI-II; Beck et al., 1996; Appendix D) and the Beck Anxiety Inventory (BAI; Beck, Epstein, Brown, & Steer, 1988; Appendix E). HCs were tested with the same battery as the patient group. A hearing test was also administered and those who exhibited a hearing loss of >30 dB SPL were excluded from study participation. No participants were excluded on basis of hearing loss criteria. The data for study 1 and Study 2 were collected with the same participants during the same session.

Table 1 includes control and patient group characteristics and demographics. There were no significant group differences in age or education level. Patients had a significantly greater number of depressive and anxiety symptoms as reflected in the BDI-II and BAI questionnaire

scores. Healthy controls produced a significantly higher percentage of correct responses on the Short Multichannel Version of the Profile of Nonverbal Sensitivity (MiniPONS) than patients, thereby confirming a higher-order social cognitive impairment in the patient group.

2.3.2 Session Procedures

Prior to testing, participants abstained from caffeine and nicotine (if smokers) for a minimum of 3 hours and abstained from alcohol and drugs (other than regular prescribed medication) from midnight. Upon arrival at the laboratory, all participants were administered a test to measure social cognition (MiniPONS; Rosenthal, Hall, DiMatteo, Rogers, & Archer, 1979). Patients were administered the Auditory Hallucinations subscale from the Psychotic Symptom Rating Scales (PSYRATS; Haddock, McCarron, Tarrier, & Faragher, 1999; Appendix F) to measure the severity of a number of dimensions of auditory hallucinations such as frequency, duration, location, loudness, amount and intensity of distress, amount and intensity of negative content, disruption, controllability and number of voices. Electrodes were applied to the participant's scalp and face, and EEG activity was recorded while completing the Emotional Facial Identification Task. The study was approved by the Royal Ottawa Mental Health Centre and University of Ottawa Social Science and Humanities Research Ethics Boards. Informed consent was obtained from all participants.

Table 1.

Patients with Schizophrenia and healthy control group characteristics & demographics (mean $\pm$ SD)

Measures	Schizophrenia (N=23)		Healthy Controls (N=19)		df	<i>t</i>	<i>p</i>
	Mean	S.D.	Mean	S.D.			
Age (years)	46.39	12.39	47.00	7.97	40	-0.19	0.85
Education Years	4.87	1.42	5.37	1.38	40	-1.15	0.26
BDI-II*	14.96	13.48	4.94	4.77	40	3.00	.005
BAI*	22.87	14.05	3.95	4.28	40	5.65	.000
MiniPONS (social cognition score)*	63.01%	1.78	76.55%	1.47	40	5.69	.000
Duration of illness (years)	21.0	9.92					
GAF	44.04	10.71					
PSYRATS Total	26.44	5.12					
PANNS							
Positive Scale	15.78	3.50					
Negative Scale	16.13	4.53					
General Psychopathology Scale	33.09	11.22					

BDI-II: Beck Depression Inventory-II; BAI: Beck Anxiety Inventory; PSYRATS: The Auditory Hallucinations subscale from the Psychotic Symptom Rating Scale; PANNS: Positive and Negative Syndrome Scale; Short Multichannel Version of the Profile of Nonverbal Sensitivity. * $p < .05$.

2.3.3 Experimental Conditions

Social cognition. The Short Multichannel Version of the Profile of Nonverbal Sensitivity (MiniPONS [Banziger, Scherer, Hall, & Rosenthal, 2011]) was used to assess social cognition, that is, the ability to recognize the communication of feelings, attitudes, and intentions from nonverbal expression in face, voice, gestures, and body postures. The MiniPONS correlates highly with the full version and has showed construct validity through significant correlations with other tests of emotive recognition ability (Banziger, Scherer, Hall, & Rosenthal, 2011). The shorter version of the PONS was used to account for the limited time during test sessions. 64 scenes of two-second video clips of a Caucasian female were used in the MiniPONS. Each scene contained (either singly or in combination) facial expressions, voice intonations, and bodily gestures. After watching each scene, participants were asked which of two labels (e.g. ‘talking to a child’ or ‘saying a prayer’) best described the scene. A practice session was administered with

3 scenes out of the other 64 scenes not previously showed to ensure participants understood the task. The percentage of correct responses was used as the primary dependent measure. The group difference in performance on the MiniPONS confirmed the previously documented higher-order social cognitive impairment in patients with schizophrenia (refer to Table 1).

2.3.4 Emotional Facial Identification Task.

Stimuli. Facial expression stimuli were derived from Gosselin, Kirouac, & Dore's (1995) database. The database included photographic faces displaying emotions expressed at three emotion intensities (20%, 50%, and 100%) by each actor. Expressions at 20% intensity were labeled as neutral because they were not reliably distinguished from neutral expressions (Orgeta & Phillip, 2008). The present study included sixteen photographic faces displaying four emotional expressions at 100% intensity (4 joyful, 4 angry, 4 fearful and 4 sad) and four photographic faces displaying expressions at 20% intensity (i.e., our neutral stimuli). The same four actors who depicted one of four emotional expressions depicted the neutral faces. Each facial expression used was displayed by 4 actors (2 females and 2 males). In addition to face stimuli, 4 different chair photographs were used as control stimuli.

The validity of the facial expressions used in the present study has been previously established (Gosselin et al., 1995). All photographs were digitized and converted to greyscale images that were then matched for luminance and contrast. Neck and backgrounds were cropped out and faces scaled into equal-height rectangles (513 pixels; Figure 2.1) such that faces spanned the full width of the rectangle. Spatial-frequency-by-energy functions of the images were not equalized.



Figure 2.1 Examples of the facial expression stimuli and chair stimuli used in the emotional facial identification task.

Emotional Facial Identification Task Procedures. Twenty photographic faces displaying one of five expressions (joy, anger, fear, sadness and neutrality) and four photographic chair images were presented individually on a 17-inch computer screen positioned in front of the seated participant (approximately 1 m away). Participants identified via key press which emotion was expressed by the stimulus. The task was administered in 4 blocks. Each emotional facial expression and chair image was presented 17 times in one block. Each block consisted of 102 trials (85 trials including faces and 17 trials including chairs¹) with 408 total trials per participant. Each grey-scale stimulus image was presented 68 times over the course of 4 blocks. As shown in Figure 2.2, each trial began with a fixation cross (200ms) that was followed by a face or chair stimulus (500 ms). Of the 408 total trials, 120 were selected as “active” trials whereby the stimulus (either a face or a chair) was followed by a response prompt asking the participant to identify via a key press which emotion was expressed by the stimulus. A blank screen appeared between trials (ITI = 800-1000 ms). Trial order was randomized with the constraint that active trials be equally distributed across facial expressions. On each trial, we

¹ Each facial expression was presented 68 times but this was divided across four different actors displaying the facial expression. As such, the same facial image was presented only 17 times. Still, we acknowledge that this number of repetitions has the potential to affect the results. To address this concern, we visually compared the ERP data for the first half of trials and the second half. No indications of differences in ERP patterns were observed.

recorded correct emotion identification (% accuracy) and response time (RT) to select an emotion during the active trials of the emotional facial identification task.

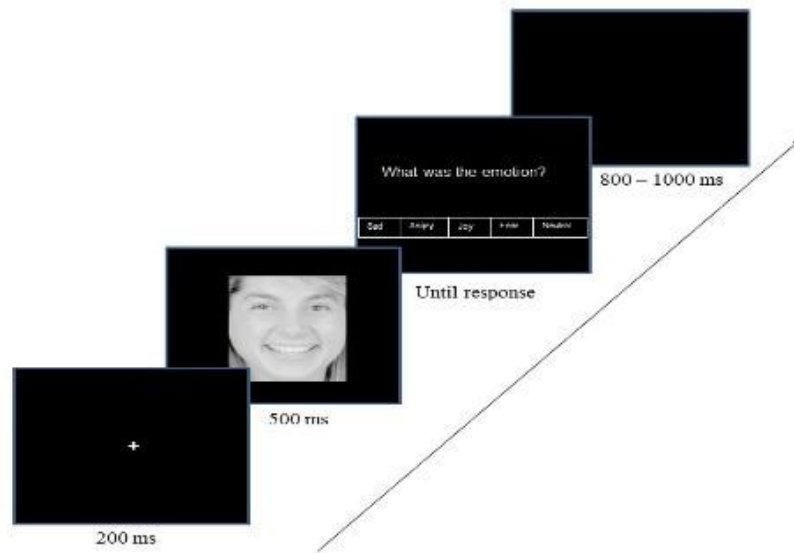


Figure 2.2 Schematic of emotional facial identification task used in the present study.

2.3.5 Electrophysiological Recordings and Data Reduction

During the emotional facial identification task, continuous EEG activity was recorded with a cap-embedded with Ag+/Ag+-Cl ring electrodes (EasyCap®, Herrsching-Breitbrunn, Germany) at 32 scalp sites positioned according to the 10-10 system of electrode placement. Additional electrodes were placed on the orbital ridges and external canthi of the eyes to monitor vertical and horizontal electrooculographic (EOG) activity and subsequently minimize contamination from eye movements and blinks. Linked electrodes positioned at the left and right mastoids served as references and a frontally positioned electrode served as the ground. Electrode impedances were kept below 5 K Ω and EEG activity was digitally sampled at 500 Hz (BrainVision Recorder®, Richardson, TX, USA). Electrical signals were amplified with a

bandwidth filter set at 0.1-70 Hz and stored on hard disk for subsequent off-line processing and analysis (BrainVision Analyzer2).

Off-line EEG data analysis was processed using BrainVision Analyzer 2 (BrainVision Analyzer®, Richardson, TX, USA). During off-line signal processing, analytical procedures were applied to the stored digitized recordings: (1) individual trials were bandpass-filtered between frequencies of 0.1-30.0 Hz; (2) an ocular-correction software algorithm (Gratton, Coles, & Donchin, 1983) was employed to correct for EOG recordings of eye movements/blinks; (3) data were segmented into epochs (100 ms prior to and 1500 ms after stimulus onset) for each facial expression and chair stimuli (epochs with active trials were pooled with those without responses); (4) segmented epochs with EEG voltages greater than $\pm 75\mu\text{V}$ were removed; (5) filtered epochs were baseline-corrected by subtracting averaged electrical activity 100 ms prior to stimulus onset, and (6) each stimulus type (angry, fearful, joyful, neutral, sad, and chair) was synchronized with a time stamp code entered into the EEG data. The codes were used to average epochs for specific stimuli per participant. No significant differences (stimuli: $F [5, 200] = < 1.0$, n.s.; group x stimuli: $F [5, 200] < 1.0$, n.s.) were observed in the number of trials that comprised the ERP averages for each stimulus and group. The mean numbers and range of accepted epochs were as follows: chair image (SCZ: 58.8 ± 8.7 ; range: 40-68]; HC: 61.1 ± 7.4 ; range: 42-68]); neutral face (SCZ: 58.6 ± 8.7 ; range: 41-68]; HC: 62.3 ± 6.7 ; range: 42-68]); joyful face (SCZ: 58.4 ± 8.9 ; range: 40-68]; HC: 61.2 ± 6.6 ; range: 46-68]); sad face (SCZ: 58.4 ± 8.9 ; range: 41-68]; HC: 61.0 ± 8.4 ; range: 40-68]); angry face (SCZ: 58.3 ± 9.0 ; range: 40-68]; HC: 61.0 ± 6.1 ; range: 49-68]); and fearful face (SCZ: 59.0 ± 8.3 ; range: 40-68]; HC: 61.4 ± 7.7 ; range: 40-68]). The signal-to-noise ratio, as measured by the Analyzer 2 default option during averaging epochs procedure, was similar for both groups and for chair and face stimuli (group: F

[1, 40] = 2.95, $p = 0.093$; stimuli: $F [1, 40] < 1.0$, n.s.; group x stimuli: ($F [1, 40] < 1.0$, n.s.). The signal-to-noise ratio computed by Analyzer 2 included pre-stimulus signal and noise variance vs. only post-stimulus onset variance.

2.3.6 ERP Analyses

ERPs were identified based on visual examination of grand-averaged waveforms and previous literature (Campanella, Montedoro, Streel Verbanck & Rosier, 2006; Jung, Kim, Kim, Im & Lee, 2012; Lee, Kim, Kim & Bae, 2010; Luo et al., 2010; Turetsky, Kohler, Indersmitten, Bhati, Charbonnier, & Gur, 2007; Wynn et al., 2008). The following components were identified for emotional facial expressions, neutral faces and chair stimuli: P100 peak (measured at $P_{7/8}$ and $O_{1/2}$; with maximum positive voltage within the time window of 80-130ms following stimulus onset), N170 peak (measured at $P_{7/8}$; with maximum negative voltage, within the time window of 140-230ms following stimulus onset), and P300 mean amplitude (measured at P_z with mean positive amplitude within the time window of 200-600 ms). All amplitudes and mean amplitudes were measured relative to mean pre-stimulus voltage levels. Visual inspection of the grand-averaged waveforms showed well-defined positive-going and negative-going peaks within the time-window of P100 and N170 component, respectively. As such, a peak amplitude measure was chosen because there was little ambiguity as to whether it accurately captured the component peak (Handy, 2005). Visual inspection of the grand-average waveforms of the P300 component revealed a less defined positive peak with no definitive point at which to measure peak amplitude. As such, it was preferable to take the mean amplitude measure that spanned the temporal breadth of the observed P300.

2.3.7 Statistical Analysis

Group differences in demographic and clinical information (e.g., MiniPONS data) were assessed with t-tests. Behavioural and ERP data were analyzed using planned contrasts (Rosenthal & Rosnow, 1985). In order to obtain the accuracy and response-time error terms for planned contrasts (Rosenthal & Rosnow, 1985), the data were subjected to mixed factorial ANOVAs with group (2 levels: schizophrenia patients and control group) as the between-subjects factor and emotion category (5 levels: fearful, joyful, sad, angry facial expressions, and neutral faces) as the within-subjects factor. In order to obtain the error terms for planned contrasts (Rosenthal & Rosnow, 1985) for ERP components, the data were subjected to mixed factorial ANOVAs. The P100 peak amplitude data measured over O_{1/2} and P_{7/8} were subjected to mixed factorial ANOVAs with group (2 levels: schizophrenia patient and control group) as the between-subject factor and hemisphere (2 levels: left, right), site (2 levels: occipital and parietal) and emotion category (5 levels: fearful, joyful, sad, angry facial expressions, and neutral faces) as the within-subjects factors. The ANOVA for N170 peak amplitude, measured over P_{7/8}, included group (2 levels: schizophrenia patient and control group) as the between-subject factor and hemisphere (2 levels: P7, P8) and emotion category (5 levels: fearful, joyful, sad, angry facial expressions, and neutral faces) as within-subjects factors. The ANOVA for P300 mean amplitude, measured over P_z, included group (2 levels: schizophrenia patient and control group) as the between-subject factor and emotion category (5 levels: fearful, joyful, sad, angry facial expressions, and neutral faces) as within-subjects factor. In order to determine if the ERP group effects observed with neutral and emotional facial expressions are specific to faces or extend to non-face stimuli, mixed factorial ANOVAs were conducted with group (2 levels: schizophrenia patient and control group) as the between-subject factor and stimulus type (2 levels: chair and faces [emotional expressions pooled together]), hemisphere (2 levels: left and right) for P100 and

N170, and site (2 levels: occipital and parietal) for P100 as within-subject factor. The ANOVA for P300 mean amplitude included group (2 levels: schizophrenia patient and control group) as the between-subject factor and stimulus type (2 levels: chair and faces [emotional expressions pooled together]) as within-subject factor.

In order to determine if patients with schizophrenia show ERP amplitude modulation across emotional facial expressions, within-subjects analyses for each group were conducted with emotion category (5 levels: neutral, fearful, joyful, sad, and angry), hemisphere (2 levels: left and right) for P100 and N170, and site (2 levels: occipital and parietal) for P100. Within-subjects analyses for P300 mean amplitude for each group included emotion category (5 levels: neutral, fearful, joyful, sad, and angry). Given that group sample sizes differed slightly, the harmonic mean between sample sizes across both groups was used in all contrast analyses (Rosenthal & Rosnow, 1985, p.17).

For each of our hypotheses and outcome measures (accuracy, RT, P100 and N170 amplitude and P300 mean amplitude), between six to twelve planned simple contrasts were performed. Considering that only a small number of planned contrasts were conducted relative to the total number of possible comparisons, the alpha level was not adjusted and remained at $\alpha = 0.05$ (Rosenthal & Rosnow, 1985, p. 45). Effect sizes for contrasts were measured using correlation coefficient r (Rosenthal & Rosnow, 1985, p. 10). The results of the contrast analyses are reported here and the ANOVA tables are presented in the Appendix G. We conducted a post-hoc power analysis using the “Repeated-Measures” function in G-power. Power calculated for two groups, six measures and with the smallest effect size observed in our study ($r = .32$), suggested a power of .80. Thus, power for observed effect size greater than $r = .32$ is in excess of .80.

The face-specific N170 effect was assessed with a mixed factorial ANOVA with group as the between-subjects factor and stimulus type (neutral face or chair) and hemisphere (left or right) as the within-subjects factor. Two-tailed Pearson correlations were conducted to correlate PSYRATS, GAF, PANNS – positive symptom, PANNS –negative symptom and MiniPONS scores with P100 and N170 amplitudes and P300 mean amplitude in response to facial expressions.

2.4 Results

2.4.1 Hypothesis 1: Do patients with schizophrenia have poorer accuracy and response times when identifying neutral faces and emotional faces compared to healthy controls?

Mean percentages of correct identification for each facial expression for both groups are shown in Figure 2.3. Planned contrast analysis showed that the patient group was significantly ($F [1, 40] = 5.32, p = 0.03, r = 0.34$) less accurate than control participants at identifying angry expressions. There was no difference between groups in accuracy for identifying neutral, joyful, sad, and fearful facial expressions².

² We conducted a post-hoc analysis to explore group differences for accurately identifying angry facial expressions. We conducted a repeated measure ANOVA within the patient group with the 4 error types (neutral, joyful, sad, and fearful) on incorrect responses to angry facial expressions. A main effect of error type was observed ($F [3, 66] = 3.362, p < .05$). Follow up contrasts revealed patients were less likely to select joyful facial (M = 1.6%, $p < .05$) expressions to identify angry facial expression than neutral (M = 8.2 %), sad (M = 8.8%), and fearful (M = 8.9%) facial expressions. Based on this data, it appears that the patient group confused angry facial expression with neutral, sad and fearful facial expression at the same rate.

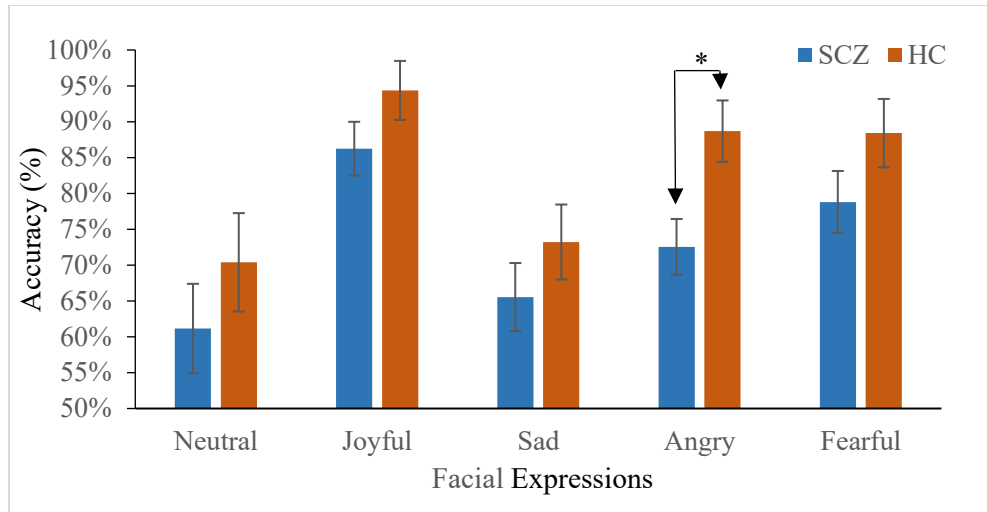


Figure 2.3 Mean ($\pm$ SE) values for percentage correct response (%) for patients with Schizophrenia (SCZ) and healthy controls (HC) groups in relation to facial expression condition.

Median reaction times (RT) for correct identification of each facial expression and group are shown in Figure 2.4. Planned contrast analyses showed significant group differences in RT for identifying all facial expressions: neutral ($F [1, 40] = 148.06, p < 0.001, r = 0.88$), joyful ($F [1, 40] = 128.33, p < 0.001, r = 0.87$), sad ($F [1, 40] = 80.02, p < 0.001, r = 0.82$), angry ($F [1, 40] = 60.91, p < 0.001, r = 0.78$) and fearful ($F [1, 40] = 42.84, p < 0.001, r = 0.72$).

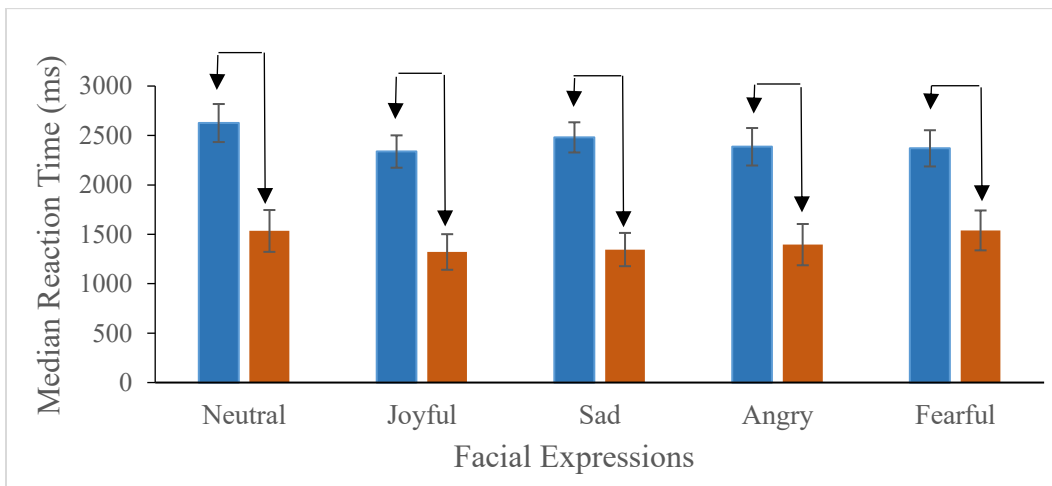


Figure 2.4 Median ($\pm$ SE) values for RTs (ms), for patients with Schizophrenia (SCZ) and healthy controls (HC) groups in relation to facial expression condition.

In summary, the patient group was slower at identifying all emotional facial expressions including neutral ones. The behavioural results showed that patients with schizophrenia were specifically less accurate at identifying angry expressions. However, visual examination (refer to Figure 2.3) of the data suggests that patients with schizophrenia have poorer performance for neutral, fearful, sad and joyful facial expressions, but the difference did not reach significance. Hence, based on the behavioural findings we cannot confirm that the patients have an impairment in specifically identifying negative expressions. The chance of such a consistent underperformance across 5 conditions if the two populations are equal is $1 / 2^5 = .0325$. Combined with the reaction time data, these findings suggest a pattern of general impairment in facial expression categorization for a range of expressions.

2.4.2 Hypothesis 2: Do patients with schizophrenia, compared to healthy controls, have impairments in processing non-face stimuli, neutral faces, and emotional facial expressions during early visual processing (P100), facial encoding (N170) and affect encoding (P300) stages, as evidenced by smaller amplitudes of ERPs?

P100 Amplitude

Planned contrast analyses of neutral and emotional facial expressions data found a significant group difference in P100 amplitude over the parietal sites (P_7 and P_8 pooled) in response to sad faces ($F [1, 40] = 9.93, p = 0.003, r = 0.45$) with the patient group having elicited smaller P100 amplitude compared to the control group. Significant group differences in P100 amplitudes over the occipital sites (O_1 and O_2 pooled) in response to sad ($F [1, 40] = 23.65, p < 0.001, r = 0.61$), angry ($F [1, 40] = 18.67, p < 0.001, r = 0.56$), and fearful ($F [1, 40] = 6.44, p = 0.02, r = 0.37$) and facial expressions were observed with the patient group having elicited smaller P100 amplitude compared to the control group. There was no difference between groups for P100 amplitudes in response to neutral and joyful facial expressions.

Planned contrast analyses of chair and face (emotional expressions pooled) data found significant larger P100 amplitudes in healthy control than patients over the parietal sites in response to chair stimuli ($F [1, 40] = 4.13, p = 0.05, r = 0.31$). Significant larger P100 amplitude in healthy controls than patients over the occipital sites in response to faces ($F [1, 40] = 6.91, p = 0.01, r = 0.38$) was observed. Mean P100 amplitudes for faces (emotion categories pooled), chair stimuli and both groups are shown in Table 2 and Figure 2.6.

N170 Amplitude

N170 Face/Chair Discrimination. A repeated measures 2x2x2 ANOVA with group (SCZ or HC), stimulus type (chair vs. neutral faces), and hemisphere (P_7 vs. P_8 electrodes) as factors was conducted to test for the N170 effect (Bentin et al. 1996; Fan et al., 2015; Dundas, Plaut, & Behrmann, 2014; Kovács, Zimmer, Volberg, Lavric & Rossion, 2013; Luo et al. 2010; Rossion et al. 2000; Rossion & Jacques, 2008) in N170 peak amplitude (see Appendix I for ANOVA tables). This analysis showed a significant main effect of stimulus type ($F [1, 40] = 35.60, p < 0.001$) with neutral faces ($M = -2.99 \mu V, SD \pm 2.5$) eliciting larger N170 amplitudes compared to chair stimuli ($M = -1.33 \mu V, SD \pm 2.1$) for both groups. The more negative N170 amplitude for neutral faces suggests that both groups showed a face-specific N170 amplitude effect (Cauquil, Edmonds & Taylor, 2000; Dundas et al. 2015; Eimer & Holmes, 2002; Fan et al. 2015; Kovács et al. 2013; Luo et al. 2010; Rossion et al. 2003; Sagiv and Bentin 2001; Vuilleumier & Pourtois, 2007). There was no significant interaction between group and stimulus type, thereby suggesting that the size of the N170 effect was similar in the two groups.

The mixed factorial ANOVA for N170 amplitude also found a significant main effect ($F [1, 40] = 6.09, p = 0.02$) of hemisphere (Appendix I), with larger amplitudes found over the right hemisphere ($M = -3.9, SD \pm 0.89$) compared to the left ($M = -2.5, SD \pm 0.67$). Given that the

N170 is typically more pronounced over the right hemisphere (Bentin et al. 1996; Fan et al. 2015; Dundas et al. 2015; Kovács et al. 2013; Luo et al. 2010; Rossion et al. 2003; Sagiv and Bentin 2001) and the significant main effect of hemisphere (also observed in grand-average waveforms presented in Figure 2.6 and topographic maps presented in Figure 2.5), further analyses of the N170 presented here focused on that location (P₈). Planned contrast analyses found significant group differences in N170 amplitudes in response to all emotion categories: neutral faces ($F [1, 40] = 4.42, p = 0.04, r = 0.32$), joyful faces ($F [1, 40] = 50.17, p < 0.001, r = 0.75$), sad faces ($F [1, 40] = 19.28, p < 0.001, r = 0.57$), angry faces ($F [1, 40] = 41.41, p < 0.001, r = 0.71$) and fearful faces ($F [1, 40] = 26.05, p < 0.001, r = 0.63$). The patient group showed smaller N170 amplitudes than the control group in all cases.

Planned contrast analyses of chair and face (i.e., pooled across emotional expression) data found significant group differences in N170 amplitudes in response to chair stimuli ($F [1, 40] = 6.34, p = 0.02, r = 0.37$) and faces ($F [1, 40] = 6.95, p = 0.01, r = 0.38$). Mean N170 amplitude for faces (emotional category pooled), chair stimulus and group are shown in Table 2 and Figure 2.6.

Table 2.

Mean amplitudes (μV) of P100, N170, and P300 segments and respective standard deviation of emotional category (facial expression, neutral faces and chair stimuli) and group. The amplitudes of P100 are averaged across hemisphere.

	Neutral	Joyful	Sad	Angry	Fearful	Faces	Chair
P100 (μV), P ₇ , P ₈							
SCZ	4.68 (2.09)	4.66 (1.92)	4.08 (2.26)*	4.58 (2.51)	4.53 (2.00)	4.50 (2.06)	4.21 (1.96)*
HC	4.69 (3.44)	4.72 (3.31)	4.93 (3.77)	4.83 (3.58)	4.88 (3.39)	4.81 (3.46)	4.79 (2.91)
P100 (μV), O ₁ , O ₂							
SCZ	4.59 (2.65)	4.47 (2.17)	4.29 (2.57)*	4.40 (2.93)*	4.31 (2.23)*	4.41 (2.39)*	3.99 (2.40)
HC	5.03 (4.81)	4.58 (4.09)	5.62 (5.07)	5.57 (4.99)	5.00 (4.25)	5.16 (4.60)	3.73 (3.58)
N170 (μV), P ₈							
SCZ	-2.96 (2.61)*	-3.16 (2.57)*	-3.46 (2.81)*	-3.10 (2.81)*	-2.99 (2.19)*	-3.15 (2.36)*	-1.04 (1.76)*
HC	-4.38 (3.62)	-5.09 (3.53)	-4.65 (3.65)	-4.95 (3.65)	-4.39 (3.64)	-4.69 (3.47)	-2.52 (2.79)
P100-N170 (μV), P ₈							
SCZ	7.92 (3.60)*	8.19 (3.13)*	7.92 (3.85)*	8.10 (3.26)*	8.08 (3.59)*	8.04 (3.31)*	5.30 (2.21)*
HC	9.28 (5.81)	10.16 (6.09)	10.07 (5.71)	9.94 (6.32)	9.65 (5.26)	9.82 (5.75)	7.72 (4.00)
P300 (μV)							
SCZ	2.30 (2.29)*	2.11 (2.78)*	2.93 (2.70)*	2.76 (2.25)*	3.13 (3.04)*	2.64 (2.46)*	0.65 (2.93)*
HC	4.32 (2.84)	4.08 (2.95)	4.99 (2.91)	4.87 (2.46)	4.90 (3.08)	4.63 (2.69)	2.71 (2.88)

* $p < .05$

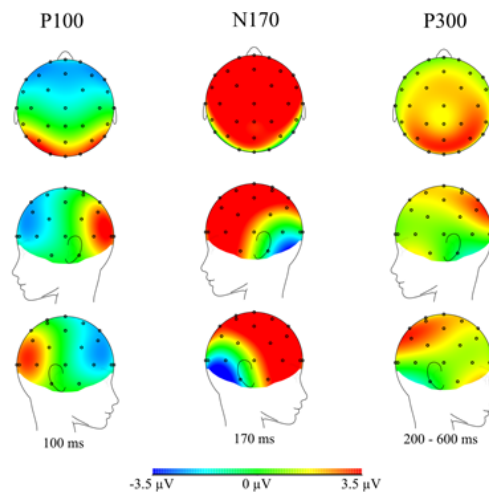


Figure 2.5 Scalp topographies of P100, N170 and P300 component in all participants (both healthy controls and patients with schizophrenia) and pooled across all emotional categories and chair images.

P100-N170 Difference

Figure 2.6 and 2.7 show grand averaged P100 and N170 waveforms of faces by group. In order to account for the unstable baseline observed in the control group (see Figure 6 and 7), P100-N170 peak-to-peak differences were calculated (Table 2). Planned contrast analyses found significant group differences in P100-N170 amplitude in response to all emotion categories: neutral faces ($F [1, 40] = 10.45, p = 0.002, r = 0.45$), joyful faces ($F [1, 40] = 21.72, p < 0.001, r = 0.59$); sad faces ($F [1, 40] = 26.09, p < 0.001, r = 0.63$); angry faces ($F [1, 40] = 18.94, p < 0.001, r = 0.57$), and fearful faces ($F [1, 40] = 13.78, p < 0.001, r = 0.51$). Patients with schizophrenia showed smaller P100-N170 differences than control participants in all cases. These findings are similar to those observed for N170 amplitudes and mitigate concerns regarding the effects of the unstable baseline on our findings.

Planned contrast analyses of chair and faces (emotional expressions pooled) data found significant group differences in P100-N170 amplitude in response to chair stimuli ($F [1, 40] = 14.07, p < 0.001, r = 0.51$) and faces ($F [1, 40] = 7.61, p = 0.009, r = 0.40$).

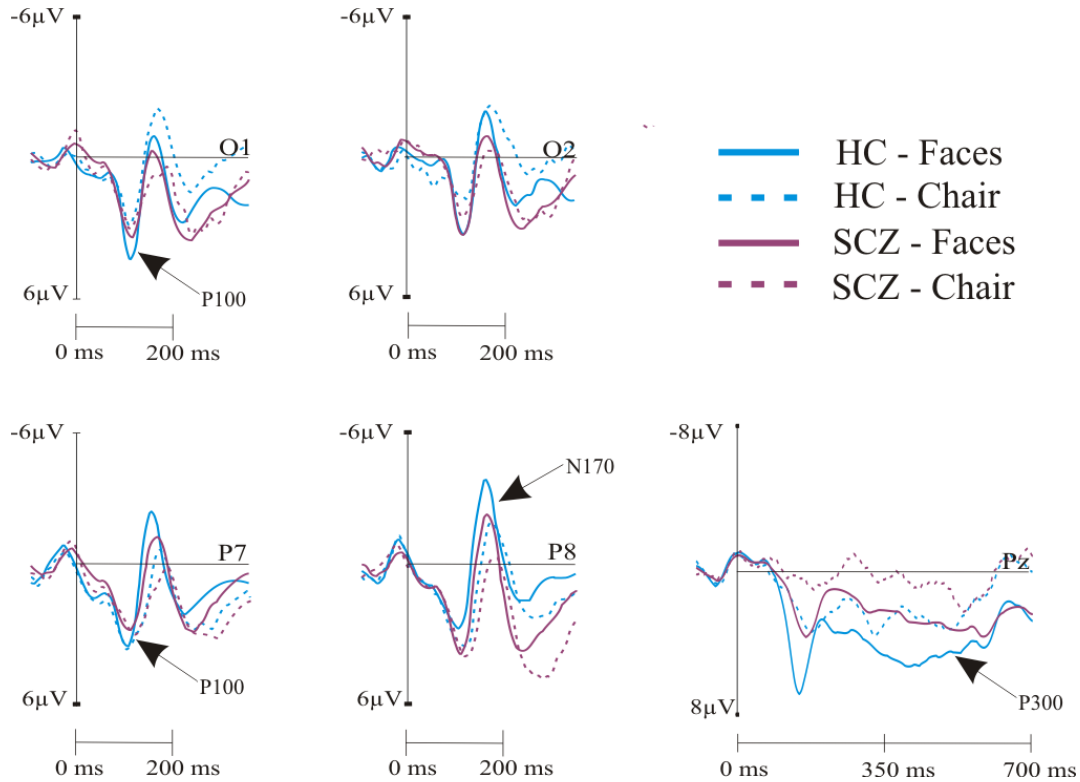


Figure 2.6. ERP results for healthy controls (HC) and patients with schizophrenia (SZ). These include grand-averaged P100 and N170 ERP waveforms in response to the chair stimuli and faces (emotional categories pooled) over occipital and parietal sites as well as P300 mean *amplitude* waveform over Pz.

P300 Mean Amplitude

Mean P300 amplitude for faces (emotion categories pooled) and groups are shown in Table 2 and Figure 2.6. Planned contrast analyses found a significant group difference in P300 mean amplitude in response to all emotion categories: neutral faces ($F [1, 40] = 36.24, p < 0.001, r = 0.68$), joyful faces ($F [1, 40] = 34.59, p < 0.001, r = 0.68$), sad faces ($F [1, 40] = 37.35, p < 0.001, r = 0.69$), angry faces ($F [1, 40] = 39.53, p < 0.001, r = 0.71$), and fearful faces ($F [1, 40] = 27.53, p < 0.001, r = 0.64$). The patient group showed smaller mean amplitude than the control group in all cases.

Planned contrast analyses of chair and faces (emotional expressions pooled) data found significant group differences in P300 mean amplitude in response to chair stimuli ($F [1, 40] = 27.58, p < 0.001, r = 0.64$) and faces ($F [1, 40] = 25.50 p < 0.001, r = 0.62$).

Summary Regarding Hypothesis 2

Relative to the control group, patients showed less positive early P100 amplitudes to specific facial expressions (sad, anger and fearful). During the structural encoding stage, patients showed less negative N170 amplitudes to all facial expressions. Disrupted processing of neutral and emotional facial expressions in the patient group was also observed at later stages of processing, as reflected in the P300 mean amplitude. Impaired processing of specific emotional expressions (sad, angry and fearful) was observed as early as during the P100 stage of processing whereas deficits in neutral face processing were first observed during the N170 stage. Deficits in processing of non-face stimuli (chair images) was observed across P100, N170 and P300. Overall, these findings imply a general deficit in visual processing in patients with schizophrenia. They are not compatible with the suggestion of a more profound deficit for faces than for other visual objects, nor do they provide evidence for particular difficulties with emotional facial expressions as compared with neutral ones.

2.4.3 Hypothesis 3: Unlike the control participants, we anticipate that patients with schizophrenia will show similar P100, N170 amplitudes or P300 mean amplitudes to neutral faces relative to emotional facial expressions.

In order to determine if patients with schizophrenia show ERP amplitude modulations across emotional versus neutral facial expressions, within-subjects contrast analyses for each group were conducted.

P100 Amplitude

Planned contrast analyses within the patient group found smaller P100 amplitudes over parietal sites in response to sad facial expressions compared to neutral faces ($F [1, 22] = 8.10, p = 0.009, r = 0.52$) and the other three facial expressions: joyful: $F [1, 22] = 7.44, p = 0.01, r = 0.50$; angry: $F [1, 22] = 5.53, p = 0.03, r = 0.45$; and fearful: $F [1, 22] = 4.64, p = 0.04, r = 0.42$. Within the control group, similar P100 amplitudes to all facial expressions were observed over the parietal sites. Significantly larger P100 amplitudes were observed over occipital sites for sad ($F [1, 18] = 12.49, p = 0.002, r = 0.64$) and angry ($F [1, 18] = 10.61, p = 0.004, r = 0.61$) facial expressions compared to neutral faces. A complex pattern of differences emerged when comparing emotional expressions to one another. Specifically, we observed larger P100 amplitudes for sad and angry compared to fearful faces (($F [1, 18] = 13.83, p = 0.002, r = 0.66$); ($F [1, 18] = 11.85, p = 0.003, r = 0.63$), respectively) and joyful faces (($F [1, 18] = 38.97, p < .001, r = 0.83$); ($F [1, 18] = 35.60, p < .001, r = 0.81$), respectively). There was also a larger P100 for fearful and neutral face compared to joyful ones (($F [1, 18] = 6.37, p = 0.02, r = 0.51$); ($F [1, 18] = 7.34, p = 0.01, r = 0.54$), respectively).

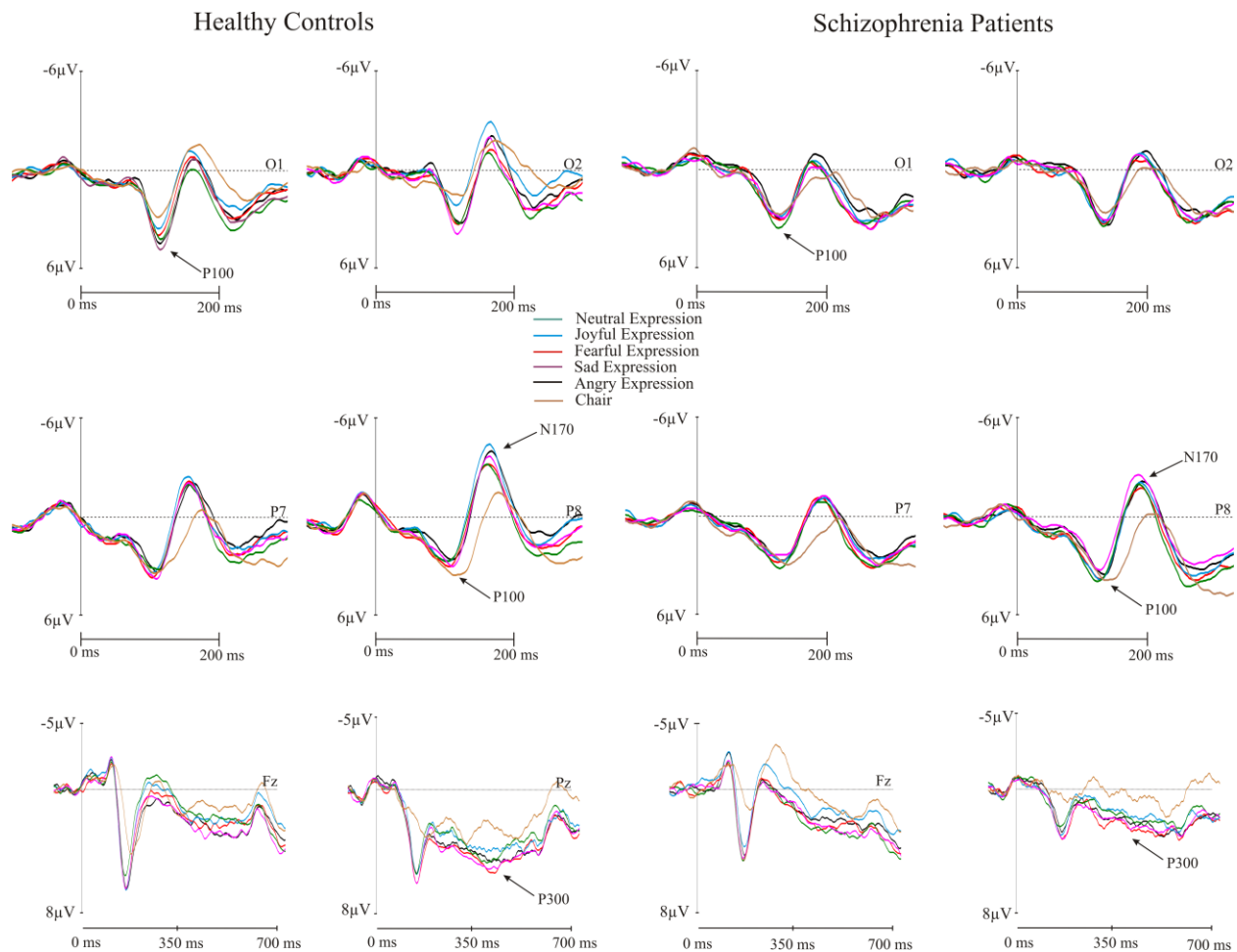


Figure 2.7 ERP results for healthy controls (HC) and patients with schizophrenia (SZ). These include grand-averaged P100 and N170 ERP waveforms in response to the chair stimuli, neutral faces and four emotional facial expressions over occipital and parietal sites as well as P300 mean amplitude waveform over Fz and Pz.

N170 Amplitude

Planned contrast analyses found no significant N170 amplitude differences in the patient group across any of the facial expressions.

Within the control group, a significantly larger N170 amplitude was found in response to joyful compared to neutral ($F [1, 18] = 7.43, p = 0.01, r = 0.54$) and fearful ($F [1, 18] = 7.34, p = 0.01, r = 0.54$) facial expressions. The control group showed significantly larger N170 amplitude in response for angry compared to neutral ($F [1, 18] = 4.76, p = 0.04, r = 0.46$) and fearful ($F [1,$

18] = 4.69, $p = 0.04$, $r = 0.45$) facial expression. The grand-average waveforms of the P100 and N170 ERP pattern of the two groups across emotional facial expressions are shown in Figure 7.

P100-N170 Difference

Due to previously noted concerns regarding an unstable baseline in the control group (see Figure 2.6), we decided to analyse amplitude differences between P100 and N170. Planned contrasts within the patient group found no P100-N170 amplitude differences in response to any of the emotional facial expressions. Within the control group, a larger P100-N170 was observed for joyful ($F [1, 18] = 5.26$, $p = 0.03$, $r = 0.48$) and sad ($F [1, 18] = 4.42$, $p = 0.05$, $r = 0.44$) facial expressions as compared to neutral ones. This pattern of larger amplitude to joyful compared to neutral was similar to that observed with the N170 data uncorrected for P100 amplitude.

P300 Mean Amplitude

Means for P300 mean-amplitude across emotional expressions are shown for the two groups in Figure 2.7. Planned contrasts for the patient group showed significant differences in P300 mean amplitude in response to emotional facial expressions compared to neutral faces. Neutral faces elicited smaller P300 mean amplitude compared to sad ($F [1, 22] = 4.43$, $p = 0.05$, $r = 0.41$) and fearful ($F [1, 22] = 7.69$, $p = 0.01$, $r = 0.51$) facial expressions. Joyful faces elicited smaller mean amplitude compared to sad ($F [1, 22] = 7.44$, $p = 0.01$, $r = 0.50$), angry ($F [1, 22] = 4.58$, $p = 0.003$, $r = 0.42$) and fearful ($F [1, 22] = 11.53$, $p < 0.05$, $r = 0.59$) faces. The control group showed a similar pattern of P300 mean-amplitude differences - neutral faces elicited significantly smaller P300 mean amplitude compared to sad ($F [1, 18] = 4.57$, $p = 0.05$, $r = 0.45$) and smaller P300 mean amplitude in response to joyful facial expression compared to sad ($F [1,$

18] = 8.36, $p = 0.01$, $r = 0.56$), angry ($F [1, 18] = 6.32$, $p = 0.02$, $r = 0.51$)), and fearful ($F [1, 18] = 6.78$, $p = 0.02$, $r = 0.52$) facial expressions.

Summary Regarding Hypothesis 3

The patient group showed a smaller P100 amplitude in response to sad facial expressions relative to other facial expressions and neutral faces; in contrast, the control group showed a smaller P100 amplitude in response to neutral compared to joyful, sad and angry facial expressions. The control group also showed larger P100 amplitudes to sad and angry faces compared to fearful and joyful one and larger P100 amplitude to fearful faces compared to joyful ones. During later stages of information processing, both groups showed similar modulation of P300 across emotional expressions.

Correlation Findings

Correlations were calculated between the psychometric measures, including the PANSS for positive and negative symptoms, PSYRATS scores, GAF scores, and MiniPONS performance scores, and ERP outcomes, including mean P100 and N170 amplitude and P300 mean amplitude for each emotional facial expression, as well as averaged across the five expressions. No significant correlations were observed between symptom measures, social cognition performance measures and the ERP components.

2.5 Discussion

In the present study, we compared the electrical brain activity of patients with schizophrenia with that of healthy controls during an emotional facial identification task. One aim of the present study was to replicate previous findings on face and emotional facial expression processing in patients. This was done by comparing ERP responses elicited by neutral faces to those elicited by four emotional expressions: sadness, anger, joy, fear.

In contrast to several previous studies wherein individuals with various forms of schizophrenia were tested, we only evaluated patients diagnosed with auditory hallucinations. By removing a source of variability in our data in this way, we were able to produce more narrowly focused findings. Another benefit of our design is that we included a non-face control condition that allowed us to determine whether impairments observed with facial expressions extend to non-face stimuli. To our knowledge, this is the first electrophysiological study to investigate the time course of emotional facial processing—including basic visual processing of faces (using the P100), facial feature encoding (using the N170) and higher-order affect encoding and stimulus processing (using the P300)—in a homogenous sample of patients with schizophrenia.

The present study provides support for previous research in which significant accuracy and response-time differences were found between patients with schizophrenia and healthy controls engaged in processing emotional and non-emotional faces. Similarly, we showed between-group differences in both earlier and later electrophysiological indices of processing for all three of our stimulus categories. Critically, however, we uncovered additional between-group differences using within-group analyses. Within-group analyses showed that healthy controls began producing different responses across facial expressions in the early stages of processing whereas patients only exhibited this modulation in later stages of processing. While there were a number of significant differences between groups, we also found similarities. For instance, both groups showed a significant N170 effect whereby larger N170 amplitudes were found for faces than chairs.

In line with reports from previous studies (Barkhof et al., 2015b; Kohler et al., 2010), we found that patients were behaviourally slower than healthy controls in identifying neutral faces

and emotional facial expressions. A pattern of deficits in identifying negative facial expression has been previously reported in patients with schizophrenia (Marwick & Hall, 2008; Chan et al., 2010; Kohler et al., 2010). In the present study, fearful and sad faces did not elicit significant group differences in accuracy, but angry faces did. However, visual examination (refer to Figure 3) of the data suggests that patients with schizophrenia have poorer performance across all emotion categories. Hence, based on behavioural findings, we cannot confirm that the patients have an impairment specifically in identifying negative expressions.

The present study showed less positive early P100 amplitudes in patients with schizophrenia to negative facial expressions (sad, angry and fearful). Deficits in early visual processing in patients with schizophrenia, as indexed by the P100, have been reported (Earls et al., 2015). This suggests that deficits in face processing in patients may begin at an earlier sensory level, proceed to later structural encoding levels-- as indexed by the N170-- and subsequently to higher-order processing deficits. Further, emotion specific P100 deficits in patients have been observed, although there is no clear consensus regarding which specific emotional expression categories are affected (An et al., 2003; Earls et al., 2015; Campanella et al., 2006; Caharel et al., 2007; Lee et al., 2010; Wynn et al., 2008). In a recent meta-analysis, schizophrenia patients showed smaller P100 amplitudes relative to controls in response to neutral ($d = 0.32$) and happy ($d = 0.21$) facial expressions but showed no difference in response to fearful faces ($d = 0.09$; Earls et al., 2015). Earls et al. (2015) suggested that early face processing may only be impaired when viewing neutral and positive facial expressions and may remain intact when viewing negative ones (i.e., fearful expression). Our findings support this idea, but the results are contrary to Earls et al. (2015)'s suggestion of the specific emotional category being neutral and positive. One explanation for our failure to find the same emotion specificity

deficit at P100 as Earls et al. (2015) could hinge on the homogeneity of our patient sample (i.e., auditory hallucinators). Indeed, findings in the current study could be limited to this one population. Methodological and stimulus characteristic differences (e.g. paradigm requirements, emotional vs. non- emotional stimuli, contrast, luminosity and colour of stimuli: Nakashima et al., 2008; Rossion & Jacques, 2008) may have also contributed to the different pattern of P100 findings in the present study from those of other studies (Earls et al., 2015).

Several studies have shown a modulation of the P100 by emotional facial expressions (Bediou et al., 2007; Campanella et al., 2006; Lee et al., 2011; Pizzagalli et al., 2002; Turetsky et al., 2008; Utama et al., 2009) in healthy controls. Taking into account P100 group differences and the effects of emotional category observed within controls (neutral faces < joyful, sad and angry), we suggest that processing of faces and their affective content may begin during this early stage of visual information processing and that this is disturbed in the patient population (Luck et al., 1994; Earls et al., 2015). Findings from the present study are in agreement with earlier studies and meta-analyses showing early-stage visual impairments not only for faces but also for specific facial expressions (An et al., 2003; Earls et al., 2015; Campanella et al., 2006; Caharel et al., 2007; Lee et al., 2010; Wynn et al., 2008).

In the current study, we found that all facial expressions (including neutral ones) elicited less negative N170 amplitudes in schizophrenia patients than in controls. Our results are in line with previous reports of N170 deficits in patients with schizophrenia engaged in processing neutral and emotional facial expressions (Bediou et al., 2007; Caharel et al., 2007; Jung et al., 2012; Kirihaara et al., 2012; Lee et al., 2010; Lynn & Salisbury, 2008; McCleery et al., 2015; Turetsky et al., 2007). We also found disrupted processing of neutral and facial expressions in the patient group when we compared P100-N170 differences across groups.

Patients with schizophrenia showed none to very little P100-N170 and N170 modulation by emotional expression whereas the control group exhibited significant P100-N170 and N170 amplitude differences between neutral, joyful, angry and fearful facial expressions. This absence of “specific emotional category” effects suggests a lower sensitivity to emotional stimuli in patients at this stage of processing. The N170 is thought to reflect face-specific structural encoding (Cauquil, Edmonds & Taylor, 2000; Eimer & Holmes, 2002; Vuilleumier & Pourtois, 2007), and our results therefore could be interpreted as reflecting a fundamental deficit of the structural encoding and perceptual integration of facial features in patients with schizophrenia. The results of the present study also suggest that this N170 deficit in the patient group could be attributed to the altered in earlier visual processing as indexed by a smaller P100. The smaller N170 amplitude in patients with schizophrenia was preceded by smaller P100 amplitudes to negative facial expressions. This again suggests that the deficit in face processing in patients with schizophrenia begins at the P100 stage and may be attributable to an earlier dysfunction of visual processing (Campanella et al., 2006; Foxe, Murray, & Javitt, 2005). Further, the specific emotion category impairment during the P100 stages and the absence of specific emotion category impairment during the N170 stage provides support for altered emotion processing in the schizophrenia patient population occurring at different stages depending on the type of emotion (Earls et al., 2015).

As with earlier ERP components, our P300 mean-amplitude results showed significant deficits in patients with schizophrenia, thereby suggesting disruption in higher order processing of visual stimuli. These results replicate previous reports of decreased activity in patients with schizophrenia (An et al., 2003; Turetsky et al., 2007) but not reports of varying activity in response to varying emotional expressions (Campanella et al., 2004; Turetsky et al., 2007).

Rather, patients showed less positive P300 activity to all facial expressions, including neutral ones. Our P300 findings are similar to what was found by Turetsky et al. (2007). However, in contrast to the present study, Turetsky and colleagues (2007) found a high correlation between less positive P300 amplitudes and less negative early N170 amplitudes in patients. They suggested that the higher-order disturbance (as indexed by P300) was a secondary consequence of disruptions in early visual processing (as indexed by P100) and early encoding of facial stimuli (indexed by N170). The present study found no such correlations between ERP amplitudes in response to any of the stimuli. The impaired P300 mean amplitude to all facial expressions is similar to the impaired response time and identification accuracy pattern observed. The impaired P300 and performance findings consistent with findings from Turetsky and colleagues (2007) who reported that task performance is significantly related to P300 amplitudes. The present study did not find correlation between P300 mean-amplitude and performance measures.

Both groups of participants showed modulation of P300 mean-amplitude across facial expressions – an effect that was not observed for the earlier sensory and perceptual ERP component (P100 and N170, respectively). The more positive mean amplitudes elicited by sad and fearful facial expressions relative to neutral ones suggests that signals of potential danger may enhance ongoing stimulus elaboration and evaluation and that negative facial expressions induce greater engagement of affect encoding, as indexed by P300. The P300 findings in the control group are consistent with An et al. (2003) who found similar patterns of P300 responses to negative facial expressions in controls. However, the same group reported smaller P300 amplitudes to negative emotional expressions than to positive ones in the patient group. Although the present study showed disturbance of affect encoding in the patient group relative to

controls across all facial expressions, the within-group findings do not indicate a more profound disturbance in processing for any given facial expression compared to any other.

The exact nature of face and facial expression processing deficit seen in patients with schizophrenia has been debated in the literature: Is the deficit specific to emotional facial expressions, is it part of an impairment in visual processing of facial information, or is it a basic visual processing impairment? The present study included non-face stimuli, neutral faces and faces expressing four distinct emotional facial categories to determine whether ERP deficits are observed across all conditions. We found early P100, N170, P1-N170 peak-amplitude differences and a P300 mean-amplitude impairment to chair stimuli and faces (emotional expressions pooled) in patients with schizophrenia relative to controls. Like for faces in general (emotional expression pooled), the disruption of processing for chair stimuli in the patient group began in the early P100 stage and extended to the P300 stage. When comparing processing of chairs and faces, the results suggests that impairments observed for P100 and later processing may not be specific to face or and may instead reflect a general impairment of visual processing. However, behavioural data from the present study cannot corroborate these claims because the relevant accuracy and reaction-time measures could not be obtained for chair stimuli. It should also be noted that the P100 deficit for chair stimuli was observed over parietal sites whereas the P100 deficit for faces was observed over occipital sites. Future research could investigate whether face, facial expression, and non-face object processing deficits are specific to early visual processing by including a behavioural task involving measures relevant to all emotional categories and chair stimulus.

Strengths and Limitations

While we replicated a number of previous findings and added to existing literature suggesting that deficits in face processing in patients with schizophrenia begin at an earlier perceptual stage of process, limitations of the study should also be noted. We did not find correlations between PANSS symptoms scores and ERP amplitudes. This is perhaps because our sample was more homogenous (i.e., patients who experienced hallucinations) than in previous studies whose samples included patients with prominent delusions, negative symptoms, and otherwise more heterogenous manifestations of schizophrenia (Campanella et al., 2006; Turetsky et al., 2007; Kayser et al., 2012).

Importantly, our sample included patients primarily with auditory hallucinations. Kayser et al. (2012) suggested that the underlying dysfunctional process involved in the experience of auditory hallucinations may also impair or interfere with processing of visual stimulus categorization. Impairment may begin at 150 ms and coincide with stimulus categorization. Specifically, the Kayser et al. (2012) study revealed that auditory hallucinators exhibit significantly less negative N1 amplitude to words and faces compared to healthy controls whereas non-hallucinators showed preserved N1. Findings from Kayser et al. (2012) suggest that the N170 and P300 visual impairments observed in the present study may be symptom specific or that it may be more profound in patients who experience auditory hallucinations relative to those who do not. In future work, it will be important to compare different forms of schizophrenia to determine if electrophysiological findings vary across symptoms of schizophrenia, and if patients without hallucinations show similar impairments to those observed in the present study during earlier P100 and later N170 and P300 stages.

Unlike previous studies that investigated gender effects in processing facial expressions in the patient population (Lee et al., 2010), we did not include gender as factor in our design.

Including gender as a factor would have decreased our statistical power due to small sample size and, given the small number of female participants, would have resulted in very uneven cell sizes. In future work, it will be important to explore gender effects on emotional facial processing in patients with schizophrenia.

Another concern that must be considered in interpreting our findings is the potential effect of the disproportionate number of face stimuli compared to chair stimuli. The greater number of face compared with chair stimuli may have had an effect on N170 amplitudes by generating greater variability for face stimuli than for chair stimuli. Indeed, it has been suggested that the N170 effect – whereby one sees larger amplitudes for faces than for objects – is an artefact of the lower degree of stimulus variability in faces than in typical control objects (Thierry et al., 2007). However, Rossion et al. (2008) has largely discounted these ideas by pointing out several methodological errors in the Thierry et al (2007) study and by providing data contradicting theirs. The present study attempted to equalize variability across stimulus types by using four distinct chair stimuli (i.e., the same number of distinct face identities used to present each emotional expression). Nevertheless, five times as many face images were shown as chair images in the experiment overall. While this difference in frequency of presentation may have had an effect, our findings of a significant N170 advantage is compatible with previous findings (Bentin et al. 1996; Fan et al., 2015; Dundas, Plaut, & Behrmann, 2014; Kovács, Zimmer, Volberg, Lavric & Rossion, 2013; Rossion et al., 2008). Regarding our own data, any concerns regarding such differences are lessened by the fact that we find substantively the same results whether collapsing across facial expressions (thus equalizing the effective number of face and chair trials) or not.

Conclusion

The central aims of this study were to determine if patients with schizophrenia exhibit altered behavioural and electrophysiological responses to emotional facial expressions. We aimed to replicate previous reports of impaired P100, N170 and P300 in response to facial expressions and non-face stimuli. While previous studies have examined this question (Bediou et al., 2007; Caharel et al., 2007; Jung et al., 2012; Kirihaara et al., 2012; Lee et al., 2010; Lynn & Salisbury, 2008; McCleery et al., 2015; Turetsky et al., 2007), ours is one of few studies to measure and analyse a range of ERPs from earlier visual processing (P100), through facial structural encoding (N170) to higher-order decoding of emotions (P300). In addition, our study is one of the few to examine a gamut of emotional expressions in comparison to a non-face control object. Finally, our study sample was more homogeneous than previous ones, including only those with a narrowly-defined form of schizophrenia.

The findings from the present study did replicate previous studies in a number of ways. First, we supported previous studies showing deficits in behavioural performance measures in patients with schizophrenia in both emotional and non- emotional faces (Barkhof et al., 2015b; Kohler et al., 2010). Second, in line with findings from the meta-analysis by Earls et al (2015), the present study showed less positive early P100 amplitudes in patients to emotional facial expressions. Thus, we provided equivocal support for the suggestion that patients show P100 deficits to specific emotional expressions or set of expressions (Earls et al., 2015). Third, we replicated previous reports of N170 deficits in patients with schizophrenia during processing of neutral and emotional facial expressions (Bediou et al., 2007; Caharel et al., 2007; Jung et al., 2012; Kirihaara et al., 2012; Lee et al., 2010; Lynn & Salisbury, 2008; McCleery et al., 2015; Turetsky et al., 2007) and less positive P300 mean amplitude to all facial expressions (Turetsky et al., 2008). These findings add to existing literature that suggests the deficit in face processing

in patients with schizophrenia begins with an earlier dysfunction of visual processing (Campanella et al., 2006; Foxe, Murray, & Javitt, 2005). Finally, the present study replicated impaired P100 and N170 amplitudes to non-face stimuli (Butler et al., 2007; Doniger, Foxe, Murray, Higgins & Javitt, 2002; Haenschel et al., 2007; Schechter et al., 2005; Yeap et al., 2006). Impairments observed with neutral faces, emotional facial expressions and non-face stimuli add to existing ERP literature suggesting generalized face processing impairments (Campanella et al., 2006; Caharel et al., 2007; Turetsky et al., 2007; Lynn & Salisbury, 2008; Ibáñez et al., 2012) or general impairment of visual processing.

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CHAPTER 3 : STUDY 2

ERP Evidence of Impaired Early Visual Processing in Schizophrenia During Categorization of Spatial Frequency-Filtered Emotional Facial Expressions

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3.1 Abstract

Objectives: The role of low-level visual information in face perception, in particular the role of different spatial frequency (SF) ranges in emotional expression recognition, was investigated in patients with schizophrenia. **Methods:** We examined event-related potentials (ERPs) in 23 patients with schizophrenia and 19 healthy controls. The P100, N170 and P300 were measured during an emotional expression categorization task, which included spatially-filtered images of neutral, joyful, sad, angry and fearful facial expressions, as well as non-face control stimuli (chairs). **Results:** The patients showed smaller P100 amplitudes to high-spatial frequency (HSF) filtered neutral faces, broadband spatial frequency (BSF) sad and angry faces, and low spatial frequency filtered (LSF) sad and fearful faces. Patients also showed smaller N170 amplitudes and P300 mean activity in response to all facial expressions for all three SF conditions. **Conclusions:** Our data suggests impaired early processing specific to LSF filtered fearful facial expression and HSF filtered neutral faces in patients with schizophrenia, which at later stages (i.e., N170 and P300) extend to all facial expressions and SF filtering conditions. The within-group comparisons suggested a heightened response to LSF threatening information, relative to BSF conditions, in the patient group. **Significance:** The results imply that patients may not use spatial frequency information, specifically LSFs, for processing threatening information in the same manner as controls.

Key words: Schizophrenia patients; event-related potentials; emotion processing; spatial frequency

Highlights:

- Patients showed impairments in P100 to specific emotions and spatial frequency ranges.
- A general emotional expression processing impairment was observed for N170 and P300.
- Patients showed heightened responses to low-spatial frequency vs. to broadband images.

ERP Evidence of Impaired Early Visual Processing in Schizophrenia During Categorization of Spatial Frequency-Filtered Emotional Facial Expressions

3.2 Introduction

Impairment in the ability to identify or recognize faces and emotional expressions in patients with schizophrenia has been well documented (Kohler et al., 2010; Savla et al., 2012), although the neuronal aetiology remains unclear. Impaired emotional facial recognition has been associated with impaired visual processing in schizophrenia (Caharel et al., 2007; Kosmidis et al., 2007; Norton, McBain, Holt, Ongur & Chen, 2009; Turetsky et al., 2007; Wynn et al., 2008). However, the way in which these early visual processing deficits are related to impaired emotional expression processing is unclear.

Researchers have investigated the role of low-level visual information in face processing, including the role of the various spatial frequency ranges (Ruiz-Soler & Betran, 2006) in emotional expression processing. Two major parallel pathways have been identified whereby such visual information is transferred from retina to the visual cortex: the magnocellular pathway (M-pathway) and the parvocellular (P-pathway) pathway (Bassi & Lehmkuhle, 1990; Breitmeyer & Williams 1990; Tobimatsu & Celesia, 2006). The pathways carry information regarding different levels of detail in an image, a parameter that can be quantified in terms of spatial frequency (SF) (Tobimatsu et al., 2008). The M-pathway is sensitive to low-spatial frequencies (LSF), which carry information about large elements of a scene that consist of gradual changes in luminance across large distances on the retina. The P- pathway is sensitive to high-spatial frequencies (HSF) (Goffaux & Rossion, 2006), which carry information about fine details in the visual scene that consist of sharp changes in luminance across small distances on the retina.

Emotional information processed during short, unintentional, or non-conscious presentation conditions critically relies on LSFs (Johnson, 2005; Tameitto & De Gelder, 2010). Specifically, LSF-filtered faces were found to be more threatening and detected faster than HSF-filtered ones (Bar, 2003; Bar et al., 2006b; Holmes, et al., 2005; Tamietto & de Gelder, 2010; Vuilleumier et al., 2003) at short presentation durations. Patients with schizophrenia have impairments in processing LSF information in (Butler & Javett, 2005; Krishnan et al., 2005) objects, faces and simple stimuli (Butler et al., 2005; Calderone et al., 2013; Martinez et al., 2008; O'Donnell et al., 2002; Martinez et al., 2012; Silverstein et al., 2010), implying problems with the M-pathway (Butler et al., 2007; Butler & Javett, 2005; Butler et al., 2008; Norton et al., 2009). Researchers have suggested that deficits in the ability to process global configural information—which is carried by LSFs and therefore primarily by the M pathway—may in turn interfere with emotional expression perception and recognition in patients with schizophrenia (Lapr v te et al., 2010; Silverstein et al., 2010; Turetsky et al., 2007). However, findings of impaired processing of LSFs (Martinez et al., 2012) are not seen consistently across the literature. For instance, some studies of this patient group have reported a bias *towards* LSFs when processing faces and objects (Lapr v te et al., 2013; Lapr v te et al., 2010). Patients were found to more often use LSF, rather than HSF, information to recognize facial expression at a glance, whereas this was not found in controls. The same group of researchers found the LSF bias generalized to other objects (Lapr v te et al., 2013), suggesting that any difficulties with processing LSFs in faces and facial expressions are due to general visual impairments, not face-specific ones. Along similar lines, a study by McBain, Norton and Chen (2010) suggests that excessive processing of LSF information is what leads to disruptions in higher-level visual tasks in schizophrenia. Specifically, they used an emotion perception task with LSF, HSF and BSF

fearful and happy facial expressions and showed that patients were more likely, compared to controls, to perceive LSF information as more fearful than images with HSF and BSF.

Electrophysiological indices have been used to investigate the effects of spatial scales on early stages of face and emotion processing. ERP studies with healthy controls support the behavioural data in suggesting that the LSF information in emotional expressions, carried via the M-pathway, is preferentially used in rapid, early processing of face and emotional expression processing (Holmes et al., 2005), especially with fearful facial expressions, as indexed by findings from studies reporting P100 effects (Pourtois, et al., 2005; Vlamings et al., 2009). Findings of the role of SF in emotional expression processing at the N170 stage are mixed, with some studies showing greater importance of LSF (Vlamings et al., 2009) in threat detection and others showing no difference in processing between LSF and HSF filtered emotional expressions (Holmes et al., 2005; Pourtois et al., 2005).

Two ERP studies have used SF filtered facial images to investigate where (which visual pathway) and when emotional expression processing breaks down for patients with schizophrenia (Kim et al., 2015; Obayashi et al., 2009). One study found controls to show augmented P100 amplitudes to LSF versus HSF and BSF faces, as well as to BSF faces versus HSF ones (i.e., $LSF > BSF > HSF$), whereas the patient group showed no increased P100 amplitudes between LSF and BSF faces (i.e., $LSF = BSF > HSF$; Obayashi et al., 2009). The more recent study found smaller P100 amplitudes in the patient group, indicating abnormalities in early visual processing, in both LSF and HSF conditions. They also found significant emotion effects, with smaller P100 amplitudes to LSF fearful faces, as well as a trend towards reduced P100 amplitudes in response to HSF neutral faces (Kim et al., 2015). Kim et al. (2015) also found N170 amplitude effects to LSF faces, and is the only study to have done so (Obayashi et

al., 2009, found no effects of SF filtering on N170). The authors suggest that this indicates a compensatory effect associated with the observed reduction in P100 amplitude to LSF stimuli (Kim et al., 2015). Finally, no SF effects were observed at later stages of processing, as indexed by the P300, in either study (Kim et al., 2015; Obayashi et al., 2009). This suggests that the altered emotional facial recognition found in patients results from bottom-up effects at a relatively earlier stage of visual processing (Butler et al., 2007; Kim et al., 2007; Obayashi et al., 2009).

In summary, there is limited ERP work using SF-manipulated facial expressions to test which visual pathway influences the abnormal emotion recognition observed in patients with schizophrenia. Moreover, what data does exist is mixed. Neither of the two previous ERP studies (Kim et al., 2015; Obayashi et al., 2009) provided evidence for whether the impairments observed in the patient group are specific to faces or are more general. This is because they did not include analysis of a non-face control object. Thus, they leave open the question of whether SF manipulations have the same influences on both face and object discrimination in patient and control groups.

The relationship between visual pathway deficits and altered facial and emotional expression recognition in patients with schizophrenia is still unclear. Further, it is unclear whether any SF-based impairments observed in this patient group are specific to faces or whether they generalize to objects. The present study examined ERPs to determine:

(1) Whether patients with schizophrenia showed smaller P100 amplitudes, N170 amplitudes, P300 mean activity levels, and poorer accuracy in response to LSF/HSF pictures of faces during an emotional expression categorization task.

(2) Whether any of these impairments was more profound for processing of LSF filtered threatening faces.

(3) Whether any of these impairments was specific to faces or was also observed with non-face stimuli (pictures of chairs).

(4) Whether patients with schizophrenia show different ERP responses than healthy controls to threatening facial expressions in LSF, HSF, and BSF filtering conditions.

We hypothesized that the patient group would show a more profound impairment relative to controls in the processing of LSF filtered faces than HSF or BSF ones. We anticipated that this would be reflected in reduced accuracy scores, as well as smaller amplitudes and longer latencies for P100 and N170 components. We also expected that this impairment to be most profound for LSF threatening faces (i.e., those with fearful and angry expressions) relative to BSF and HSF threatening faces. In accordance with the findings of previous studies (Kim et al., 2015; Obayashi et al., 2009), we anticipated that the patient group would exhibit impairment in M-pathway processing of faces, and that this earlier P100 and N170 deficit would not carry through to the later P300 component.

Regarding SF effects on responses to threatening face stimuli, we anticipated that the patient group would show reduced early visual processing of LSF threatening faces relative to BSF and HSF ones, as indexed by smaller and longer P100 and N170 amplitudes and latencies. Conversely, we expected, based on past work (Kim et al., 2015; Obayashi et al., 2009), that healthy controls would show larger and shorter P100 and N170 amplitudes and latencies to LSF threatening faces relative to BSF and HSF filtered threatening faces.

3.3 Methods

3.3.1 Participants

Twenty-three patients (14 men) between the ages 18 and 60 years diagnosed with schizophrenia (SCZ) were included in the study. Patients' psychiatric symptoms were evaluated with Positive and Negative Syndrome Scale (PANSS; Kay et al.1987) and the Global Assessment of Functioning (GAF; DSM-IV-TR, 2000). Patients tested: (1) were clinically stable; (2) exhibited a score greater than 3 on the hallucination item of the PANSS Positive Symptom Scale and less than 65 on the total PANSS score; (3) reported no current drug/alcohol dependence (nor history of same), no history of head injury, no diagnosis of epilepsy or other neurologic disorder, and no exposure to electroconvulsive therapy within the past year; and (4) were taking stable atypical antipsychotic medications.

Nineteen healthy controls (HC; 11 men) aged 18-60 years were recruited and matched to the patient group according to gender, age and education level. HC were screened for absence of: psychopathology, alcohol or drug abuse, history of seizures or significant brain trauma, known anatomical brain lesion(s), and presence of schizophrenia history in a first-degree relative. Participants with refractive error were required to correct their vision with glasses while undergoing the study assessments. The study was approved by the *Royal Ottawa Mental Health Centre Ethics Board* and the *University of Ottawa Social Science and Humanities Research Ethics Board*; informed written consent was obtained from participants. Table 1 shows a summary of demographic factors. The data for study 1 and Study 2 were collected with the same participants during the same session.

Table 1

Patients with schizophrenia and healthy control group characteristics & demographics

Measures	Schizophrenia (N=23)		Healthy Controls (N=19)		df	<i>t</i>	<i>p</i>
	Mean	S.D.	Mean	S.D.			
Age (years)	46.39	12.39	47.00	7.97	40	-0.19	0.85
Education Years	4.87	1.42	5.37	1.38	40	-1.15	0.26
BDI-II*	14.96	13.48	4.94	4.77	40	3.00	.005
BAI*	22.87	14.05	3.95	4.28	40	5.65	.000
Duration of illness (years)	21.0	9.92					
GAF	44.04	10.71					
PSYRATS Total	26.44	5.12					
PANNS							
Positive Scale	15.78	3.50					
Negative Scale	16.13	4.53					
General Psychopathology Scale	33.09	11.22					

BDI-II: Beck Depression Inventory-II; BAI: Beck Anxiety Inventory; PSYRATS: The Auditory Hallucinations subscale from the Psychotic Symptom Rating Scale; PANNS: Positive and Negative Syndrome Scale; Short Multichannel Version of the Profile of Nonverbal Sensitivity. * $p < .05$.

3.3.2 Stimuli

Facial expression stimuli were derived from Gosselin, Kirouac, and Dore (1995)'s database. Within the image database from which we drew our stimuli, three intensities of each emotion were presented: 20%, 50%, and 100%. We used the expressions presented at 20% intensity from each emotion as neutral. This was done for two reasons: First, previous research has shown that emotional expressions at this intensity cannot be distinguished from one another and are thus judged as neutral (Orgeta & Phillips, 2008). Second, previous research has shown that 0% intensity images, which are ostensibly neutral, are in fact more likely to be confused with negative expressions (Palermo & Cloheart, 2004).

The present study included sixteen photographic faces displaying four emotive expressions at 100% intensity (4 joyful, 4 angry, 4 fearful and 4 sad) and four photographic faces displaying expressions at 20% intensity (i.e., our neutral stimuli). The same four actors who depicted one of four emotive expressions depicted the neutral faces. Each facial expression used

was displayed by 4 actors (2 females and 2 males). In addition to face stimuli, 4 different chair photographs were used as control stimuli.

The validity of the facial expression stimuli and their intensity levels has been established by previous work (Gosselin et al., 1995). For the purposes of the present study, all photographs were converted to gray-scale images, which were then matched for luminance and RMS contrast. Neck, ears, and background were cropped out by trimming the image to a rectangle containing just the face. Images were adjusted to have the same height (513 pixels) and their aspect ratio was unaltered.

Unfiltered gray-scale photographs were used as the broadband spatial frequency (BSF) stimuli. Low spatial frequency (LSF) and high spatial frequency (HSF) stimuli were created by digital image processing techniques, using MATLAB. Specifically, the face stimuli were Fourier transformed, and the transform was multiplied by 2-dimensional circularly-symmetric Butterworth filter of order 5. The LSF stimuli were generated with a low-pass filter that had a half-maximum cut-off frequency of 8 cycles/face width. The HSF stimuli were created with a high-pass filter whose cut-off was 24 cycles/face width. In addition to face stimuli, 4 different chair photographs were used as control stimuli. These were HSF and LSF filtered in the same manner as the faces (Figure 3.1).

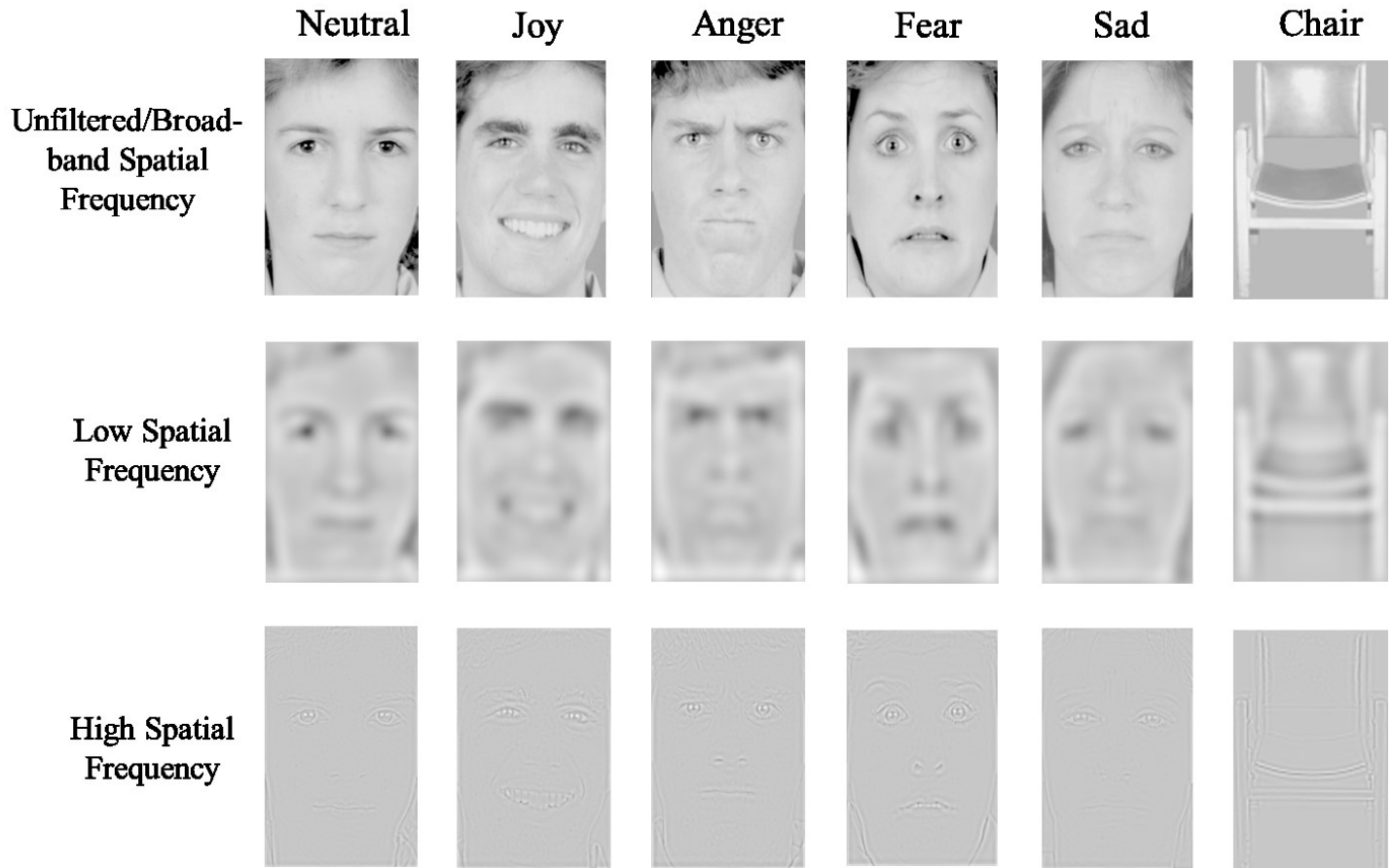


Figure 3.1 Examples of the facial expression stimuli and chair stimuli used in the emotional expression categorization task

3.3.3 Experimental Procedure and Emotional Expression Categorization Task

During the task, all participants were seated in a comfortable chair and viewed stimuli presented on a 17-inch computer screen positioned approximately 1 m in front of the seated participant in a dark room. The stimuli consisted of 20 BSF, 20 LSF, and 20 HSF grey-scale pictures of joyful, angry, fearful, sad, and neutral faces, as well as 12 chair stimuli (4 BSF, 4 LSF, and 4 HSF). Each of the 72 images was presented 17 times, for a total of 1224 trials. The trials were presented in random order and were split over 4 blocks of 306 trials each. A break of 30 minutes was given between blocks 2 and 3. All stimuli were presented in random order within each block.

Each trial began with a fixation cross (200 ms), followed by a face or chair stimulus (500 ms). For 360 of the trials (i.e., 20 trials for each of the 6 stimulus type conditions by 3 SF filtering conditions), the face or chair stimulus was followed by a response prompt asking the participant to identify the emotion being expressed via a key press. A blank screen appeared between trials (ITI = 800-1000 ms). Trial order was completely randomized, with the constraint that an equal proportion of trials requiring a response appear for each of the 18 conditions (i.e., 6 stimulus types by 3 SF filtering levels). The emotion category chosen by the subjects on each trial, and their response time (RT) to select that category, were recorded automatically. Recognition accuracy served as the key outcome variable on this task. As there were 5 possible responses, which could increase the manual response latency and its variance, RT was not examined.

3.3.4 Electrophysiological Recording and Data Reduction

The electroencephalograms (EEG) were recorded with a 32 channel easy cap (EasyCap®, Herrsching-Breitbrunn, Germany) using a 10-10 system (Chatrian et al., 1985) of electrode placement. Electrodes placed on the supra-orbital ridges and external canthi of the eyes monitored vertical and horizontal electro-oculographic (EOG) activity. A frontally positioned electrode served as the ground. Electrode impedances were kept below 5 K Ω and EEG activity was digitally sampled at 500 Hz (BrainVision Recorder®, Richardson, TX, USA). The electrical signals were amplified with a bandwidth filter set at 0.1-70 Hz and stored on hard disk for subsequent off-line processing and analysis (BrainVision Recorder®, Richardson, TX, USA).

During off-line signal processing, analytical procedures were applied to the stored digitized recordings. EEG was re-referenced to the average of the left and right mastoid (TP_{9/10}). Pre-processing included filtering at 0.1-30 Hz, eye movement correction, segmentation into

epochs 100 ms prior to the stimulus to 1500 ms after the stimulus, artefact removal (voltages greater than $\pm 75\mu\text{V}$ were removed) and baseline correction by subtracting averaged electrical activity 100 ms prior to stimulus onset. Finally, codes synchronized with stimulus delivery were used to average epochs associated with specific stimuli (i.e., angry, fearful, joyful, sad, and neutral faces, as well as chairs) for each participant.

3.3.5 ERP Analyses

ERPs were identified based on visual examination of grand-averaged waveforms and previous literature (Pourtois, Grandjean, Sander & Vuilleumier, 2004; Pourtois et al., 2005; Vuilleumier et al., 2007). The following components were identified for all stimuli: P100 (measured at $\text{P}_{7/8}$ and $\text{O}_{1/2}$; with maximum positive voltage within the time window of 80-130 ms following stimulus onset), N170 (measured at $\text{P}_{7/8}$; with maximum negative voltage within the time window of 140-230 ms following stimulus onset), and P300 (measured at P_z with mean positive activity within the time window of 200-600 ms). All amplitudes and mean activity values were measured relative to mean pre-stimulus voltage levels. Peak latencies of the P100 and N170 (i.e., time to reach maximum voltage) were assessed relative to stimulus onset.

3.3.6 Statistical Analyses

Group differences in demographic and clinical information were assessed with independent samples 2-tailed t-tests. Behavioural and ERP data were analyzed using planned contrasts to test our specific defined hypotheses (Rosenthal & Rosnow, 1985). In order to obtain the error terms for planned contrasts on accuracy results, the data were subjected to a mixed factorial ANOVA (Rosenthal & Rosnow, 1985). The accuracy measure ANOVA included group (patients and healthy controls) as the between subjects factor and facial expression (fearful,

joyful, sad, angry and neutral³) and spatial frequency (BSF, LSF, and HSF) as within-subjects factors.

Planned contrasts were performed to examine group differences in electrophysiological responses to stimuli in the different SF and emotional expression conditions. In order to obtain the error terms for these planned contrasts (Rosenthal & Rosnow, 1985), the P100, N170 and P300 data were subjected to mixed factorial ANOVAs with group (patients and healthy controls) as the between-subject factor and stimulus type (fearful, joyful, sad, angry and neutral faces, and chair images), hemisphere (right, left) and spatial frequency (BSF, LSF, HSF) as within-subject factors. Separate ANOVAs were conducted for amplitude and latency data. The P100 amplitude and latency ANOVAs included an additional between-subject factor of site (parietal vs. occipital), whereas the ANOVA for P300 did not include the hemisphere or site factors. In order to determine if patients with schizophrenia show ERP amplitude and latency modulation across facial expressions, within-subjects analyses for each group were conducted, with factors being stimulus type (neutral, fearful, joyful, sad, angry facial expressions), hemisphere (for P100 and N170), and site (for P100). The omnibus error terms of the series of within-subjects ANOVAs were used to conduct within-subjects contrasts (Rosenthal & Rosnow, 1985). The face-specific N170 effect was assessed with a repeated measures ANOVA having group as a between-subjects factor and stimulus type (neutral face or chair) and hemisphere (left or right) as within-subjects factors.

Given that group sample sizes differ slightly, the harmonic mean between sample sizes across both groups was used in all contrast analyses (Rosenthal & Rosnow, 1985, p.17). For each

³ Accuracy data for chair stimuli was not included in this analysis. The participants were requested to identify the emotion expressed, also for the chair, making the behavioural responses for the chair stimuli otherwise meaningless. As such, they were not included in the analysis.

of our hypotheses and outcome measures, between twelve to thirty-six planned simple contrasts were performed. Considering the number of planned contrasts conducted relative to the total number of possible comparisons, the alpha level was adjusted to between $\alpha = 0.001$ and 0.004 depending on the outcome measure and hypothesis (Rosenthal & Rosnow, 1985, p. 45). Effect sizes for contrasts were measured as r (Rosenthal & Rosnow, 1985, p. 45). Strength of impairment was determined by comparing effect size of group differences for facial expression across all three SFs. Specifically, criteria for gauging the size of effects was done according to Cohen (1988). According to Cohen (1988), an effect size between $r = 0.10$ and 0.29 qualifies as small, one between $r = 0.30$ and 0.49 qualifies as medium, and one equivalent to or larger than $r = 0.50$ qualifies as large.

3.4 Results

3.4.1 Hypothesis 1: Patients with Schizophrenia Will Show an Impairment of Early Visual Processing of Faces Related to M-pathway Dysfunction

Based on previous work (Butler et al., 2007; Butler & Javett, 2005; Butler et al., 2008; Butler et al., 2012; Norton et al., 2009), we hypothesized that patients would show impairment in emotional expression categorization arising from deficits in M-pathway function. Because this pathway is sensitive to low spatial frequencies, we anticipated that the patient group would show a more profound impairment relative to controls in the processing of LSF filtered facial expressions than HSF or BSF ones. We expected this to be reflected in reduced accuracy scores, as well as smaller amplitudes and longer latencies for P100 and N170 components. Based on Kim et al. (2015)'s work showing deficits in the processing of threatening faces, we further hypothesized that this impairment in patients relative to controls would be most profound for LSF fearful and angry faces relative to BSF and HSF ones. In addition, based on Kim et al.

(2015) and Obayashi et al. (2009)’s work, we expected that no LSF or HSF impairment would be observed in the patient group at later stages of processing (P300).

Group differences in response to LSF, HSF, and BSF filtered chair stimuli were analyzed to explore whether any impairments observed with facial expressions were also seen with non-face stimuli. Table 2 presents accuracy scores, P100 and N170 amplitudes, and P300 mean activity observed in response to all stimulus types (i.e., joyful, sad, angry, fearful and neutral facial expressions, as well as chairs) and spatial filtering conditions.

Emotional expression categorization accuracy scores

Given the number of conducted contrasts ($N=15$) of accuracy scores, a Bonferroni corrected $\alpha = .003$ was used to identify significant group differences. Planned contrast analyses showed that, compared to control participants, the patient group was significantly less accurate at identifying angry facial expressions in all three SF conditions: BSF ($F [1, 40] = 22.59, p < 0.001, r = 0.60$), LSF ($F [1, 40] = 13.17, p < 0.001, r = 0.48$) and HSF ($F [1, 40] = 14.20, p < 0.001, r = 0.51$). Patients also showed impaired accuracy in identifying fearful and joyful facial expressions that were LSF filtered (fearful: $F [1, 40] = 14.67, p < 0.001, r = 0.52$; joyful: $F [1, 40] = 31.57, p < 0.001, r = 0.66$) and HSF filtered (fearful: $F [1, 40] = 18.03, p < 0.001, r = 0.56$; joyful: $F [1, 40] = 14.80, p < 0.001, r = 0.52$) as well as sad facial expressions in the LSF condition only ($F [1, 40] = 17.45, p < 0.001, r = 0.55$). The largest impairment was observed for LSF joyful facial expressions, although all effect sizes were in the high range. There was no evidence of a more profound impairment in patients for LSF neutral or threatening faces.

Table 2.

Mean percentage (%) accuracy, P100 and N170 amplitudes and mean activity (μV) of P300 segments and respective standard deviations of each spatial frequency filtered facial expressions and chair stimuli for both groups (SCZ: patients with schizophrenia; HC: healthy controls).

Shaded cells indicate significant group differences.

Condition	SF	P100 Amplitude (μV), O1, O2		N170 Amplitude (μV), P8		P300 Mean Activity (μV)		Accuracy (%)	
		SCZ	HC	SCZ	HC	SCZ	HC	SCZ	HC
Neutral	BSF	4.59	5.03	-2.96	-4.38	2.27	4.32	61.15	70.39
		(2.59)	(4.68)	(2.61)	(3.62)	(2.30)	(2.84)	(32.12)	(26.99)
	LSF	4.65	5.39	-2.50	-4.09	2.07	4.69	47.04	51.80
		(2.63)	(3.87)	(2.27)	(3.37)	(2.68)	(2.04)	(26.09)	(25.73)
	HSF	2.94	4.07	-1.57	-3.59	2.57	4.43	50.48	56.08
		(2.41)	(3.61)	(2.13)	(3.52)	(2.64)	(1.94)	(24.13)	(23.74)
Joyful	BSF	4.47	4.58	-3.16	-5.09	2.10	4.09	86.24	94.36
		(2.12)	(3.98)	(2.56)	(3.53)	(2.78)	(2.94)	(17.76)	(18.17)
	LSF	4.86	5.24	-2.46	-4.47	2.72	4.53	72.36	91.44
		(2.83)	(4.20)	(2.39)	(3.82)	(2.69)	(2.11)	(25.34)	(19.50)
	HSF	3.53	3.43	-0.76	-3.74	2.32	4.62	74.09	92.56
		(2.06)	(3.13)	(2.29)	(3.48)	(2.58)	(2.52)	(27.05)	(19.40)
Sad	BSF	4.29	5.62	-3.46	-4.65	2.94	4.99	65.54	73.22
		(2.51)	(4.94)	(2.81)	(3.65)	(2.70)	(2.91)	(21.38)	(24.41)
	LSF	4.85	5.76	-2.46	-4.36	2.37	4.79	45.95	60.14
		(2.70)	(4.42)	(2.73)	(3.19)	(2.43)	(2.01)	(22.86)	(25.88)
	HSF	3.29	4.23	-1.13	-3.80	2.68	4.99	38.83	50.06
		(2.24)	(3.79)	(2.20)	(3.53)	(2.53)	(2.06)	(23.06)	(29.69)
Angry	BSF	4.40	5.57	-3.19	-4.95	2.78	4.87	72.54	88.68
		(2.86)	(4.87)	(2.19)	(3.64)	(2.26)	(2.46)	(21.52)	(14.42)
	LSF	5.38	5.52	-2.07	-3.91	2.63	4.64	49.88	62.20
		(2.85)	(4.60)	(2.21)	(3.43)	(2.43)	(2.33)	(26.12)	(21.03)
	HSF	3.39	3.51	-0.65	-4.02	2.94	4.73	44.22	62.32
		(2.45)	(3.11)	(2.70)	(3.35)	(2.44)	(2.66)	(25.31)	(18.10)
Fearful	BSF	4.31	5.00	-2.99	-4.39	3.04	4.90	78.79	88.41
		(2.18)	(4.14)	(2.61)	(3.64)	(3.07)	(3.08)	(22.60)	(18.33)
	LSF	4.18	5.28	-2.54	-4.10	2.64	5.24	37.33	50.33
		(3.39)	(4.16)	(2.02)	(3.52)	(2.69)	(2.46)	(29.31)	(22.05)
	HSF	3.14	4.07	-1.42	-3.87	2.67	4.79	48.02	68.41
		(2.12)	(3.51)	(2.05)	(3.69)	(2.63)	(2.44)	(35.59)	(20.20)
Chair	BSF	3.99	3.73	-1.04	-2.52	0.68	2.71		
		(2.34)	(3.49)	(1.76)	(2.79)	(2.94)	(2.88)		
	LSF	4.40	5.00	-0.63	-3.19	1.18	3.49		
		(2.65)	(4.05)	(1.76)	(2.75)	(2.12)	(2.56)		
	HSF	3.51	4.10	0.32	-0.87	1.07	3.37		
		(2.11)	(3.11)	(2.52)	(2.03)	(2.27)	(2.36)		

P100 amplitude and latency

Figure 3.2 shows P100 amplitude values for both groups for all stimulus categories and SF filtering conditions. Given the number of conducted contrasts ($N = 36$), a Bonferroni corrected $\alpha = .001$ was used to identify significant group differences. The planned contrast analyses found significant group differences in P100 amplitude over the parietal sites (P_7 and P_8 pooled) in response to BSF filtered sad faces ($F [1, 40] = 14.44, p < 0.001, r = 0.52$), where the patient group elicited smaller P100 amplitude compared to the control group. In addition, significant group differences were found in P100 amplitude over the occipital sites (O_1 and O_2 pooled) in response to HSF filtered neutral faces ($F [1, 40] = 12.73, p < 0.001, r = 0.49$), BSF filtered sad ($F [1, 40] = 34.42, p < 0.001, r = 0.68$) and angry ($F [1, 40] = 27.16, p < 0.001, r = 0.64$) faces and LSF filtered sad ($F [1, 40] = 16.31, p < 0.001, r = 0.54$) and fearful ($F [1, 40] = 23.69, p < 0.001, r = 0.61$) faces. No group differences were observed for HSF and BSF fearful faces, suggesting greater impairment of LSF threatening faces, specifically fearful expressions, than HSF and BSF filtered ones.

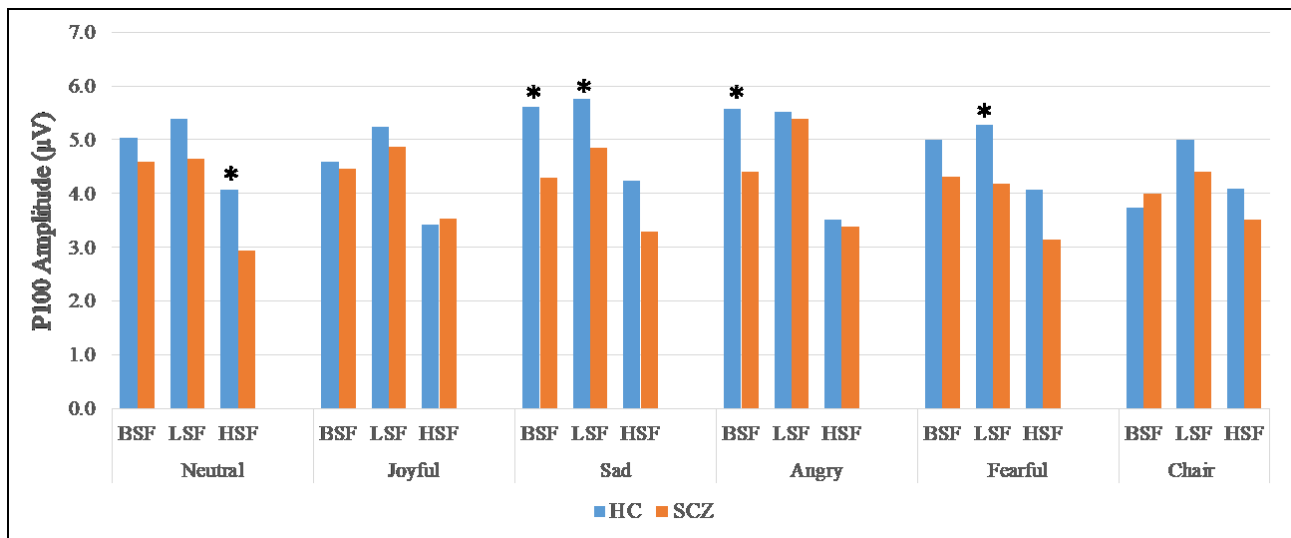


Figure 3.2 P100 amplitude comparison between groups across facial expressions and chair stimuli. P100 measured over occipital sites (O_1 and O_2 pooled). Asterisk signifies significant difference between groups.

Group differences in P100 amplitude over the parietal and occipital sites for chair stimuli were not observed, suggesting that the deficit observed with emotional expression is specific to faces. The planned contrast analyses for P100 latency over the parietal and occipital sites found no significant group differences for any of the stimulus categories or SF filtering conditions.

N170 amplitude and latency

N170 Face/Chair Discrimination. To test for group differences in the N170 effect (Rossion & Jacques, 2008), whereby faces are expected to elicit a larger amplitude than non-face stimuli, a repeated measures ANOVA was conducted. This showed a significant main effect of stimulus type ($F [1, 40] = 35.60, p < 0.001$), where neutral faces ($M = -2.99 \mu V, SD \pm 2.5$) elicited larger N170 amplitude compared with chair stimuli ($M = -1.33 \mu V, SD \pm 2.1$) for both groups. The increased N170 amplitude for neutral faces suggests that both groups show a face-selective N170 amplitude effect (Cauquil, Edmonds & Taylor, 2000; Dundas et al. 2015; Eimer & Holmes, 2007; Fan et al. 2015; Kovács et al. 2013; Luo et al. 2010; Rossion et al. 2003; Sagiv and Bentin 2001; Vuilleumier & Pourtois, 2007). The group x stimulus type interaction effect was not significant ($F [1, 40] = 0.18, p = 0.67$), and there was therefore no evidence from this analysis that the size of the N170 effect varied between groups.

Figure 3.3 shows N170 amplitude values for both groups for facial expressions and non-face chair stimuli. The N170 is typically more pronounced over the right hemisphere (Bentin et al. 1996; Fan et al. 2015; Dundas et al. 2015; Kovács et al. 2013; Luo et al. 2010; Rossion et al. 2003; Sagiv and Bentin 2001) and therefore the N170 analyses presented here focused on that location (P_8). Several planned contrasts were conducted to test whether patients with schizophrenia showed a deficit in facial encoding to specific spatial frequency filters. Given the

number of conducted contrasts (N=18), a Bonferroni corrected $\alpha = .002$ was used to identify significant group differences.

Planned contrast analyses were conducted to test for N170 amplitude and latency impairments to threatening faces across the three SF filtering conditions. These showed that, compared to the control group, the patient group had significantly smaller ($p < 0.001$) N170 amplitude to neutral, sad, joyful, fearful and angry facial expressions for all three SF conditions. Table 3 shows the F values and related information for group difference for all facial expression and SF conditions. The largest impairment was observed for HSF angry faces, followed by HSF joyful faces, although all the effect sizes were in the high range. Planned contrasts for chair stimuli showed smaller N170 amplitudes in patients relative to controls for all three SF conditions: BSF ($F [1, 40] = 35.90, p < 0.001, r = 0.68$), LSF ($F [1, 40] = 108.30, p < 0.001, r = 0.85$) and HSF ($F [1, 40] = 11.64, p < 0.002, r = 0.47$). The greatest impairment was observed for LSF chair stimuli. The analyses for N170 latency showed no group differences in any of the stimulus or SF filtering conditions.

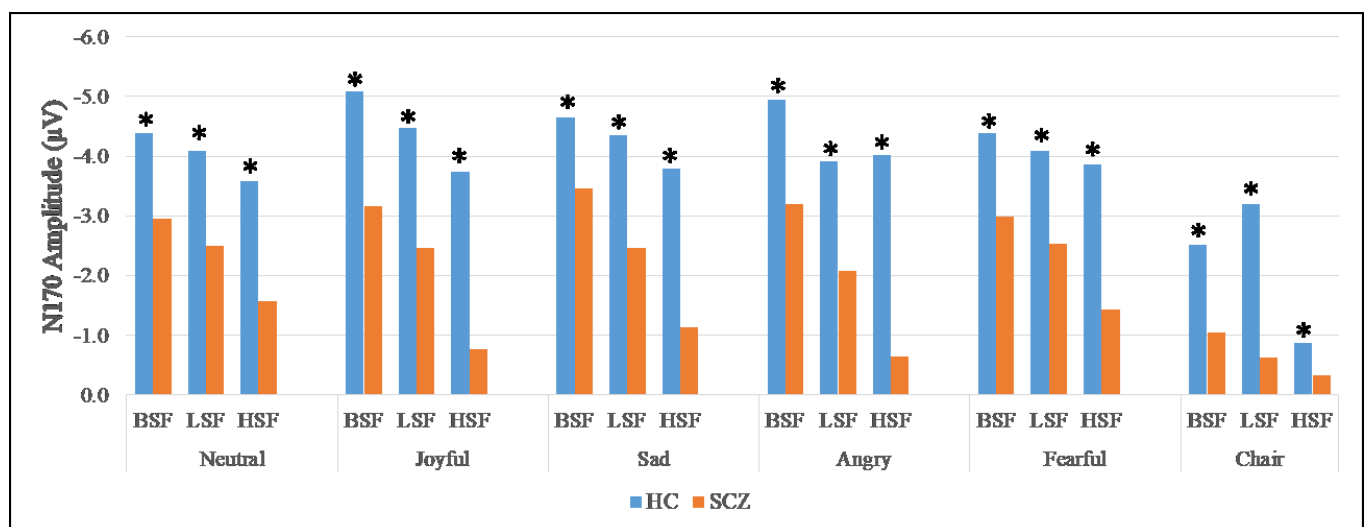


Figure 3.3 N170 amplitude comparison between groups across facial expression and chair stimuli. Asterisk signifies significant difference between groups.

P300 mean activity

Because of the number of conducted contrasts (N=18), a Bonferroni corrected $\alpha = .002$ was used to identify significant group differences. Planned contrast were conducted to test for P300 mean activity impairments in all stimulus category and spatial filtering conditions. These showed that, compared to the control group, the patient group had significantly ($p < .001$) smaller P300 mean activity to neutral and emotional expressions for all three SF conditions. Table 3 shows the F values and related information for group difference for all facial expression and SF conditions. The largest impairment was observed for LSF neutral and fearful faces, although all the effect sizes were in the high range. Planned contrasts for chair stimuli showed smaller P300 mean activity in patients relative to controls for all three SF conditions: BSF ($F [1, 40] = 61.77, p < 0.001, r = 0.78$), LSF ($F [1, 40] = 79.81, p < 0.001, r = 0.82$) and HSF ($F [1, 40] = 39.29, p < 0.002, r = 0.70$). The greatest impairment was observed for LSF chair stimuli.

Table 3.

Significant N170 amplitude and P300 mean activity group difference contrast analyses F values and effect sizes (r) for each facial expression and the three SF conditions.

Facial expression	Spatial Frequency	N170 Group Differences		P300 Group Differences	
		F value	Effect size (r)	F value	Effect size (r)
Neutral	BSF	33.65	0.68	62.63	0.78
	LSF	41.91	0.67	101.79	0.85
	HSF	33.71	0.68	25.75	0.63
Joyful	BSF	61.86	0.78	58.84	0.77
	LSF	66.68	0.79	49.06	0.74
	HSF	73.14	0.80	39.57	0.71
Sad	BSF	23.78	0.61	62.58	0.78
	LSF	59.37	0.77	86.86	0.83
	HSF	58.96	0.77	39.64	0.71
Angry	BSF	51.07	0.74	23.83	0.61
	LSF	56.02	0.76	62.27	0.78
	HSF	93.95	0.84	60.53	0.78
Fearful	BSF	32.13	0.67	51.72	0.75
	LSF	40.13	0.71	101.34	0.85
	HSF	49.50	0.74	33.45	0.67

Note: df were 1, 40 and $p < .001$ for all contrasts.

Summary: Hypothesis 1

In summary, patients showed, relative to controls, smaller N170 amplitudes in response to all facial expressions across all spatial filtering conditions. Contrary to previous work (Kim et al., 2015; Obayashi et al., 2009) and to our hypotheses, this impairment across the SF domains was also observed at later stages of processing, as reflected in the P300 mean activity. Note that similar patterns are seen in accuracy scores. Impairment in specific spatial frequency was only observed with P100 amplitudes to BSF filtered sad and angry faces, LSF filtered sad and fearful faces and HSF neutral faces. Thus, in line with our expectations, which were based on Kim et al.'s (2015) work, there was some evidence of greater impairment for LSF filtered threatening faces. Specifically, we can conclude that since P100 amplitudes of HSF and BSF filtered fearful faces was intact, there is evidence for greater impairment of LSF filtered fearful faces at that stage. However, this greater impairment is no longer observed at the N170 and P300 stages. That is, impairment in response to specific facial expressions was observed at the early visual stage, indexed by the P100, whereas an impairment in response to all facial expressions was observed at the structural encoding stage, indexed by the N170, as well as later stages, as indexed by the P300 and accuracy scores.

With respect to determining whether the impairments observed with patients are specific to faces, we compared results for neutral faces and chairs. Patients showed, relative to the controls, impaired processing of neutral faces starting at P100 stage, whereas impaired processing to chair stimuli was observed at the later N170 stage. Specifically, smaller P100 amplitude to HSF filtered neutral faces was observed whereas there was no difference in P100 amplitude to chair stimuli. Further, at the N170 and P300 stages, both neutral and chair stimuli showed reduced amplitudes and mean activity in patients with schizophrenia for all three SF

conditions. These results suggested that the facial impairment observed for N170 and later stages may not be specific to faces and may instead be more of a global impairment of visual processing.

3.4.2 Hypothesis 2: Patients Will Show Impaired Early Rapid Processing of Threat.

Based on previous work suggesting an impairment in the processing of threatening faces in schizophrenia (Bediou et al., 2005; Gur et al., 2007), and on previous work showing that early threat processing is carried out via rapid analysis of LSF information (Bar, 2003; Bar et al., 2006b; Holmes, et al., 2005; Tamietto & de Gelder, 2010; Vuilleumier et al., 2003), we hypothesized that patients would show smaller and longer P100 and N170 amplitudes and latencies to LSF angry and fearful faces than to BSF or HSF ones. Conversely, we anticipated that healthy controls would show larger and shorter P100 and N170 amplitudes and latencies to LSF threatening faces relative to BSF and HSF filtered ones. The P100 and N170 grand-average waveforms in response to threatening faces across SF conditions for the two groups are shown in Figure 3.4.

P100 amplitude and latency

Given the number of conducted contrasts ($N=15$), a Bonferroni corrected $\alpha = .004$ was used to identify significant group differences. In summary, we found no evidence of the hypothesized deficit in P100 amplitude or latency in response to LSF filtered threatening faces. Rather, for amplitude, the difference between groups was that patients showed larger amplitudes to LSF stimuli relative to BSF ones, whereas controls showed equivalent amplitudes across BSF and LSF conditions. If anything, this suggests that in relative terms there is a *higher* response in patients with schizophrenia to LSF filtered angry facial expressions. Specifically, both groups

showed larger P100 amplitudes to angry and fearful expressions over the parietal sites during BSF and LSF presentations compared with HSF ones. This pattern was also observed over the occipital sites in both groups in response to fearful expressions. A different pattern of responses across groups was only observed for angry expressions over the occipital sites. Specifically, the control group showed larger P100 amplitudes to BSF and LSF presentation compared with HSF ones and no difference between BSF and LSF presentations, whereas the patient group showed larger amplitudes to BSF and LSF presentation compared with HSF and larger amplitudes to LSF compared with BSF presentation. Regarding latency, there was again no consistent evidence of delayed P100 in patients with schizophrenia. The details of the P100 findings for both groups are presented in Appendix H.

N170 amplitude and latency

The N170 is typically more pronounced over the right hemisphere (Bentin et al. 1996; Fan et al. 2015; Dundas et al. 2015; Kovács et al. 2013; Luo et al. 2010; Rossion et al. 2003; Sagiv and Bentin 2001) and therefore the N170 analyses presented here focused on that location (P₈). As with the P100, there was no clear evidence of the hypothesized smaller amplitude or longer latency of the N170 elicited by LSF threatening faces in patients. There were some differences between controls and patients in the pattern of amplitudes across SF conditions; however, none of these showed a greater reduction in N170 amplitude for LSF threatening faces relative to BSF and HSF in patients than in controls. Rather, for amplitude, the difference between groups was that patients showed larger amplitude to LSF filtered angry and fearful expressions relative to HSF filtered ones, whereas controls showed equivalence between LSF and HSF. If anything, this suggests that in relative terms there is a higher response in patients to LSF filtered angry facial expressions. Similarly, latency patterns were not consistently in the

expected directions. The details of the N170 findings for both group are presented in Appendix H.

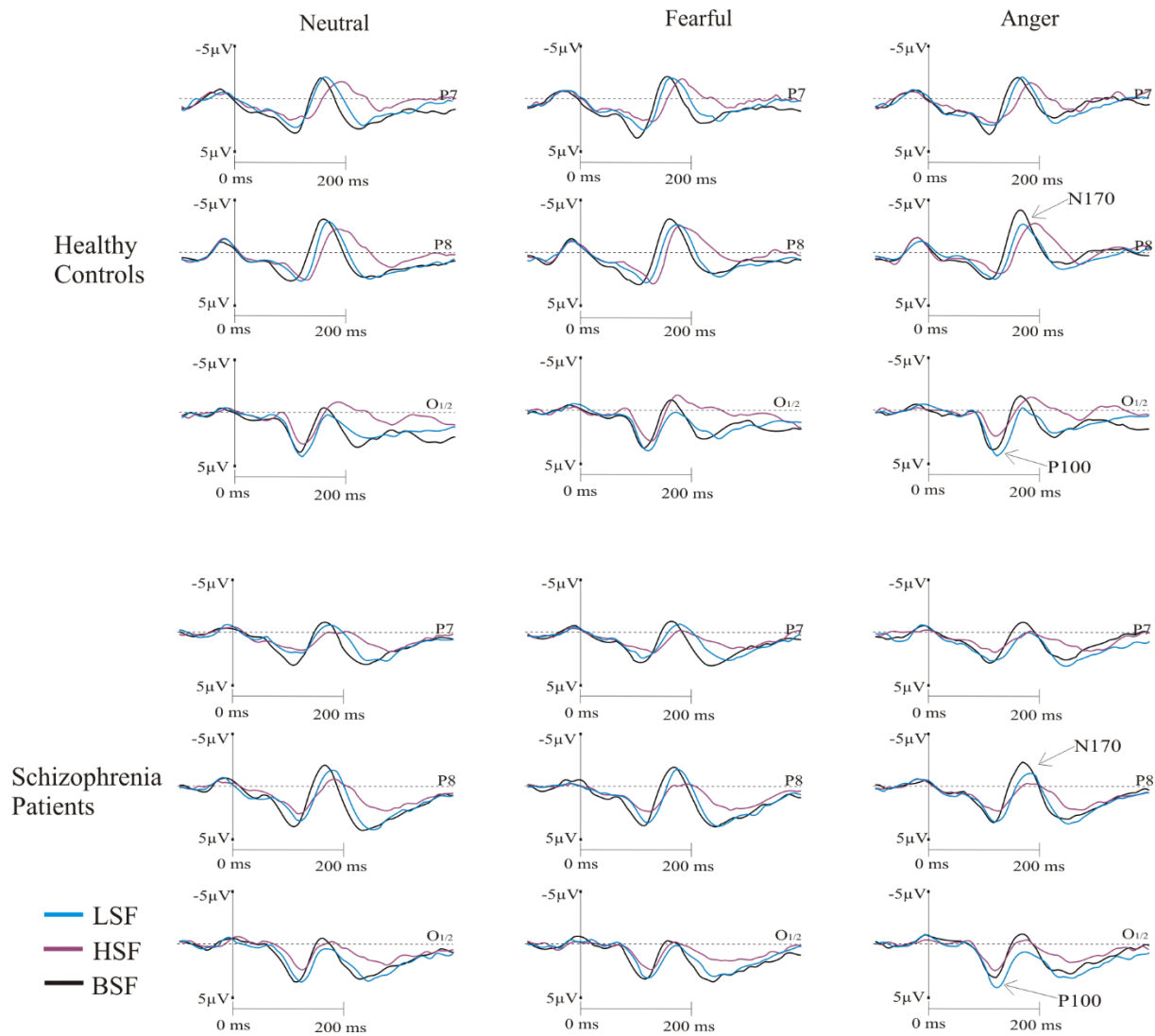


Figure 3.4 P100 and N170 grand averaged waveforms in response to neutral, fearful and angry facial expressions for all three SFs measured over occipital site (O_1 and O_2 pooled), as well as P_7 and P_8 sites.

Summary: Hypothesis 2

Our electrophysiological data provide no evidence to support the hypothesis that patients with schizophrenia show a deficit in the processing of threatening faces due to a disruption in processing of LSFs. This is compatible with evidence from our other N170 analyses, suggesting that the deficit is more general in scope, extending to all faces and perhaps other visual objects.

3.5 Discussion

The present study adds to the limited literature exploring ERP deficits in the visual pathways during processing both facial expressions and non-face stimuli. We examined whether patients with schizophrenia showed ERP (P100, N170 and P300) and accuracy impairments in response to LSF, HSF, and BSF pictures of faces during an emotional expression categorization task. We tested whether patients with schizophrenia, like healthy controls, are sensitive to SF manipulations of threatening faces. Finally, the present study examined whether impairments were specific to faces or were also observed with non-face stimuli (pictures of chairs).

Overall, patients showed smaller amplitude, mean activity, and accuracy scores in response to face stimuli—regardless of emotional expression or SF manipulation—beginning at the face-sensitive N170 stage. Thus, impairments of emotional expression recognition in patients with schizophrenia (e.g., Kohler et al., 2010; Savla et al., 2012) may not be accounted for solely by deficits in the M-pathway, as impairments were observed for BSF, LSF and HSF manipulated faces. Further, similar impairments were observed for chair stimuli, suggesting a more generalized cognitive and sensory problem (Addington & Addington, 1998; Sach et al., 2004) starting at the N170 stage. However, within-group patterns of responding to SF-manipulated

threatening facial expressions did differ across the two groups, suggesting relatively greater cortical activity in response to LSF information in threatening faces in the patient group.

Impairment in processing specific spatial frequency ranges was only observed with P100 amplitudes to BSF filtered sad and angry faces, LSF filtered sad and fearful faces, and HSF neutral faces. Thus, in line with our expectations, and based on Kim et al's (2015) work, there was some evidence of greater impairment for LSF filtered threatening faces. Specifically, we can conclude a greater impairment of LSF filtered fearful faces because we observed P100 amplitude group difference for LSF filtered fearful faces and did not observe P100 amplitude group difference in response to HSF and BSF filtered fearful faces. Impairment in response to specific facial expressions was observed starting at the early visual stage, as indexed by the P100, but this specificity was not evident at the structural encoding stage, as indexed by the N170, nor at later processing stages, as indexed by the P300 and accuracy scores.

Structural encoding of faces, indexed by the N170, has been repeatedly shown to be abnormal in patients with schizophrenia (Bediou et al., 2007; Caharel et al., 2007; Jung et al., 2012; Kirihaara et al., 2012; Lee et al., 2011; Lynn & Salisbury, 2008; Turetsky et al., 2007). In line with previous studies, the present study found smaller N170 in not only BSF, but also LSF and HSF filtered faces, including both threatening faces and neutral ones. Similar group differences between patients with schizophrenia and controls for N170 amplitude to BSF faces have been previously reported (Bediou et al., 2007; Caharel et al., 2007; Jung et al., 2012; Kirihaara et al., 2012; Lee et al., 2011; Lynn & Salisbury, 2008; Turetsky et al., 2007). However, ours is the first evidence of impaired N170 amplitude to LSF and HSF filtered stimuli in this patient group (Kim et al., 2015; Obayashi et al., 2009).

Group differences were observed for P300 mean activity to BSF, LSF and HSF filtered faces, regardless of emotional expression. This impairment across the SF domains was also observed behaviourally, with accuracy scores. These later stages of processing are thought to involve higher-order emotional classification and decision-making processes. These findings are compatible with the idea that the decreased structural encoding indexed by the N170 observed in the patients' impacted later stages, regardless of SF manipulation (Turetsky et al., 2008).

Regarding processing of threatening faces within each group, modulations of P100 and N170 amplitude by SF manipulations showed different patterns in the patient vs. the control group. Specifically, patients showed larger P100 amplitude to LSF filtered relative to BSF filtered angry faces ($LSF > BSF$). In contrast, the controls showed a different pattern ($LSF = BSF$). P100 amplitude patterns did not differ within each group for fearful expressions. In terms of P100 amplitude in response to HSF threatening faces, both groups showed similar patterns of responding – HSF filtered threatening faces resulted in the smallest amplitudes. Patients showed significantly larger N170 amplitudes for BSF and LSF fearful faces compared with HSF fearful faces ($BSF > HSF$; $LSF > HSF$), while controls showed larger N170 amplitudes between BSF and HSF fearful faces ($BSF > HSF$). Similarly, with angry facial expressions, the patient group showed larger amplitude to LSF compared with HSF, while the control group did not show this difference. Thus, the P100 and N170 amplitude within-groups data showed no evidence of the hypothesized early visual deficit to LSF filtered threatening faces. Rather, for amplitude, the difference between the groups was that the patients showed larger amplitude for LSF suggesting, in relative terms, a higher response to LSF angry expressions. These within group differences are contrary to Obayashi et al. (2009)'s findings of augmented P100 amplitude in response to LSF faces ($LSF > BSF > HSF$) in healthy controls.

Kim et al. (2015) found differences between SF conditions in fearful faces in the patient group (BSF>HSF; BSF>LSF) and in controls (LSF>HSF). The authors interpreted the early P100 response to fearful faces to be consistent with M-pathway deficiencies in patients (Kim et al., 2015). The results from the present study cannot corroborate these previous findings of M-pathways impairments. Indeed, the equivalence in P100 activity between BSF and LSF filtered fearful facial expressions and larger amplitude for LSF relative to BSF filtered angry facial expressions may suggest a bias or higher response to LSF information in patients, which is consistent with behavioural findings from Laprevate et al. (2010). The P100 amplitude within-subject findings, and the N170 amplitude findings show that the difference in responding between groups may be related to greater activation of LSF relative to HSF, possibility suggesting a higher response to LSF information to threatening facial expressions at a structural encoding stage.

If LSF information is over-persistent in patients with schizophrenia, they may be more likely to use coarse visual-spatial information to make decisions regarding faces and other visual inputs. This would contribute to their difficulties with facial processing, and in turn, their impairments in social functioning. Our hypothesis is in line with behavioural results from Laprevote et al. (2010), who conducted a study to investigate the processing of high and low spatial frequencies in the perception of facial expressions in patients with schizophrenia. They reported that, contrary to healthy controls, the patients focused preferentially on the LSF component of the image, regardless of the emotion shown, despite responding accurately in response to HSF information in non-hybrid faces. They hypothesized that the time course of concurrently perceiving LSF and HSF information may be impaired, such that patients with schizophrenia need a longer duration of time to process LSF information. They suggest two

reasons why this may occur: “the mechanism of integrating HSF and LSF is altered” or “LSF processing is over-persistent” (Laprevote et al., 2010, pg. 4168). Further work is needed to link our findings to this phenomenon. Future work could use ERP measurements in combination with hybrid face stimuli to replicate the present study and track the time course of impairments in both hybrid and control face images.

Finally, the present study found N170 and P300 impairments in response to SF-manipulated chair stimuli. Patients showed, relative to controls, impaired processing of neutral faces starting at P100 stage whereas impaired processing to chair stimuli was observed at the later N170 stage. Specifically, reduced P100 amplitudes to HSF filtered neutral faces was observed and no difference in P100 amplitude to chair stimuli were seen. Further, at the N170 and P300 stages, both neutral and chair stimuli showed reduced processing for all three SF conditions. These results suggested that the facial impairment observed for N170 and later processing may not be specific to faces and may instead be more of global impairment of visual processing. However, the behavioural data from the present study cannot corroborate these claims. This is because the relevant reaction time and accuracy measures were not obtainable for the chair stimuli. Future research should address the hypothesis that face, facial expression and non-face object processing deficits are specific to early visual processing by including a task involving relevant behavioural measures for all stimulus types.

The patients’ overall general face impairment across all SF conditions is not in line with the hypothesis of a subcortical magnocellular deficit in schizophrenia that leads to impaired processing of LSFs (Butler & Javitt, 2005). Given that LSFs are preferentially conveyed by the magnocellular pathways, this kind of deficit would imply a perception impairment of LSF information, which we do not observe in our study. Our results instead suggest a heightened

response to LSF threatening information, relative to BSF conditions, in the patient group. This implies that patients may not use spatial frequency information, specifically LSF for processing threatening information, in the same manner as controls.

3.5.1 Conclusion

Visual processing, specifically face and emotional expression processing, is important for understanding and engaging in one's surroundings. Understanding of this rich information requires a number of perceptual and cognitive processes, which appear to be impacted in patients with schizophrenia. A fuller understanding of the mechanisms at play in these difficulties is necessary in order to better comprehend and treat this disorder. Here we have demonstrated that patients with schizophrenia have a general impairment in processing faces, irrespective of emotional expression and SF-manipulations, beginning at the structural face encoding stage. We have also shown evidence that similar impairments are observed in processing chair stimuli. The earlier visual processing stage, as reflected by the P100, was found to be disrupted in patients with schizophrenia relative to controls with specific emotions and SF conditions. However, the patients showed heightened processing of LSF threatening information as reflected with P100 and N170 amplitudes. Our findings add to the limited extant ERP and SF-manipulation literature with this patient group, suggesting that patients' preference for coarse LSF threatening information in processing faces may be contributing to the observed difficulties with face and emotion processing.

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CHAPTER 4 : STUDY 3

Investigation of Emotional Expression Processing Following Cognitive Behavioural Therapy for

Patients with Schizophrenia: An Event-related Potentials Study

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4.1 Abstract

Objectives: Growing evidence supports the use of cognitive behavioural therapy (CBT) for psychosis, including CBT for voices (CBTv), which targets auditory verbal hallucinations (AVH). No researchers have investigated whether CBTv affects the electrophysiological markers of schizophrenia. The aim of the present study was to observe the effects of CBTv on electrophysiological measures of facial expression processing in patients with persistent and distressing positive symptoms—specifically AVH.

Methods: Twenty-five patients with schizophrenia who experienced AVH were randomly assigned to a treatment group (N =14) or a waitlist group (N =11). The treatment group received group CBTv for 5-6 months in addition to their usual treatment. The matched waitlist group received treatment as usual for the 5-6 months. Patients' neural processing during a facial expression categorization task, as well as their symptoms, were assessed at baseline and at the end of group CBTv treatment.

Results: The CBTv treatment (N =11), but not the treatment as usual group (N = 9), showed shorter P100 latency in response to facial expressions following treatment compared with baseline. Furthermore, some elements of patients' symptom scores, specifically relating to amount of negative content of voices and 'omnipotence' of voices, were modified following CBTv treatment but not treatment as usual.

Conclusions: This study demonstrates CBTv-induced changes to the early stages of facial expression processing. We thus provide evidence that CBTv decreases early visual information processing time, suggesting that this therapy may mediate improved functioning by increasing information processing speed.

Key words: Schizophrenia; cognitive-behavioural therapy; event-related potentials; auditory-verbal hallucinations; face processing

Investigation of Emotional Expression Processing Following Cognitive Behavioural Therapy for Patients with Schizophrenia: An Event-related Potentials Study

4.2 Introduction

Cognitive Behavioural Therapy (CBT) is a promising approach to reducing distress related to symptoms characteristic of schizophrenia (Zimmermann, Favrod, Trieu & Pomini, 2005). The present study used event related potential (ERP) measurements to assess changes in brain function following group CBT for voices (CBTv) in a sample of patients with schizophrenia while they performed a facial expression categorization task. Our sample was specifically composed of auditory hallucinators and the form of CBT they underwent was targeted at their hearing of voices. We hypothesized that ERP measures of brain function would be altered in the direction of shorter latencies and larger amplitudes following completion of group CBTv compared to baseline. That is, we expected electrophysiological indicators to move in the direction of levels observed in healthy controls. Similarly, we expected to observe a change in appraisal to hearing voices, evidenced by change in symptoms scores.

Auditory hallucinations are a common characteristic of schizophrenia, with prevalence estimates ranging between 40% and 80% (Sommer, Slotema, Daskalakis, Derks, Blom, & van der Gaag, 2012). Pharmacotherapies are not completely effective in treating and reducing distress in these patients. Many patients remain symptomatic despite adequate doses of antipsychotic drugs (Kane, 1996; Lieberman et al., 2005). These patients become chronic, causing an impaired quality of life and a diminished cognitive capacity, leading to poor functional outcomes. The negative impacts of experiencing auditory hallucinations have been found to affect not only the auditory modality, but also extend to impairments in visual processing (Bruder et al., 2011; van Lutterveld, Sommer & Ford, 2011), including face

processing (Kayser et al., 2012). Cognitive Behavioural Therapy (CBT) may be a promising approach for improving information processing difficulties in schizophrenia and, by so doing, facilitating social cognition and daily functioning (Pontillo et al., 2016). As such, CBT has been suggested as a complement to pharmacotherapies, specifically to target psychosis in treatment resistant cases (Pilling et al., 2002a,b; Tarrier & Wykes, 2004; Zimmermann et al., 2005).

Specialized Cognitive Behavioural Therapy for psychosis (CBTp) has been developed to decrease patient's distress associated with hallucinations and delusions (Haddock et al., 1998) and is recommended as an adjunctive treatment for individuals who experience persistent auditory hallucinations (NICE clinical guidelines; National Collaborating Centre for Mental Health, 2009). Multiple meta-analyses on the effectiveness of CBTp have evaluated treatment effects on the frequency and severity of positive symptoms (Lynch, Laws & McKenna, 2010; Lincoln et al., 2012; Pfammatter, Junghan, & Brenner, 2006; van der Gaag et al., 2014; Wykes, Steel, Everitt & Tarrier, 2008; Zimmermann et al., 2005). They have found that CBTp demonstrates modest but significant positive impact in controlled studies (average effect around 0.35 - 0.40; Sivec & Montesano, 2012). The meta-analyses found that CBTp reduces positive symptoms (Pfammatter et al., 2006; Zimmermann et al., 2005), negative symptoms (Rector & Beck, 2001), and general psychopathology (Wykes et al., 2008; Sarin, Wallin & Widerlov, 2011).

Several authors have advocated for administering tailored therapy based on symptoms specific to hallucinations and/or delusion (Morrison & Barratt, 2010, Steel et al., 2012), such as CBT for voices (van der Gaag et al., 2014). Although evidence of the effectiveness of CBT to specifically target auditory verbal hallucinations is growing, individual CBT for voices remains costly and demands typically exceed available resources. An alternative to individual therapy is

group therapy, as it is cost effective, provides a place for patients to relate to other's experiences, to feel less stigmatized and more accepted, and helps to improve social functioning (Goodliffe, Hayward, Brown, Turton, & Dannahy, 2010; Lecomte et al., 2008; McLeod, Morris, Birchwood, & Dovey, 2007a). Three randomized controlled trials (RCTs) of group CBT for voices (CBTv) have been conducted. An RCT comparing group CBTv to treatment as usual (TAU) with a sample size of 85 outpatients found significant improvements in social functioning for up to 6 months after the end of group CBTv, as well as some improvement in self-esteem and effective coping strategies (Wykes et al., 2005). Another RCT demonstrated significant reduction in voice frequency and in perceived voice power, as well as a trend towards distress reduction, and at a much lower cost than individual therapy (McLeod, Morris, Bichwood, & Dovey, 2007a,b). Finally, a third RCT compared group CBTv to a treatment consisting of supportive therapy and found significant improvements in general symptoms and positive symptoms (Penn et al., 2009).

Neuroimaging studies suggest that psychotherapy can lead to lasting structural changes in brain regions important for effective information processing (see Weingarten & Strauman, 2015 for review). Studies have documented neural changes following CBT for a number of psychological illnesses (depression: Fu et al., 2008; obsessive compulsive disorder: Schwartz, Stoessel, Baxter, Martin & Phelps, 1996; panic disorder: Prasko et al., 2004; social anxiety: Furmark et al., 2002; and specific anxiety: Schienle et al., 2009). Two studies have examined neural changes following CBT treatment of psychosis (Kumari et al., 2010; Kumari et al., 2011). Of the two studies, only one study explored changes in face processing following a course of CBTp (Kumari et al., 2011). The authors examined functional brain changes following CBT for psychosis in patients with persistent and distressing positive symptoms of schizophrenia. Participants completed an implicit affective processing task with stimuli depicting facial

emotions of fear, anger, happiness or neutrality. Following treatment, patients in the CBTp group showed a decrease in activation of a network of regions (e.g., inferior frontal lobe, insula, thalamus, occipital lobe) during processing of angry and fearful facial expressions (Kumari et al., 2011). The authors suggested that their study was the first to provide evidence that CBTp attenuates brain responses to threatening stimuli. They also suggested that the treatment may mediate symptom reduction by promoting the processing of threats in a less distressing way (Kumari et al., 2011).

Using electrophysiological measures, such as event-related potentials (ERPs), is an effective way to assess various levels of perceptual and cognitive processing. Several studies have shown smaller or delayed ERP activation in patients with schizophrenia to facial emotion recognition or face perception tasks (McCleery et al., 2014; Earls, Curran, & Mittal, 2015). The P100 (thought to index assessment of early-stage visual information; Earls et al., 2015), N170 (thought to reflect the earliest stage of facial structural encoding or identifying an image as a face; Hinojosa, Mercado & Carretie, 2015), and P300 (thought to involve cognitive processing related to facial affect; Turetsky et al., 2008; Shah et al., 2018) have all been reported to be impaired in patients with schizophrenia relative to controls (Earls et al., 2015; McCleery et al., 2015; Turetsky et al., 2008). Researchers have suggested that experiencing auditory hallucinations interferes with processing in both auditory and visual modalities (Bruder et al., 2011; van Lutterveld, Sommer & Ford, 2011). Kayser et al. (2012) examined whether patients' tendency to experience auditory hallucinations affects early visual processing. The authors found that patients who reported experiencing auditory hallucinations had substantially reduced N170 to faces compared to controls and non-hallucinators (Kayser et al., 2012), suggesting that the association between impaired auditory processing and hearing voices is not limited to the

auditory modality but also extends to impairment in visual processing as well, and face processing in particular (Kayser et al., 2012). Thus patients with auditory hallucinations show increased distress over hearing the voices as well as experience impairments secondary to the positive symptoms (i.e., impaired early visual processing).

4.2.1 The Present Study

Group CBT for schizophrenia has been shown to reduce overall symptoms, including distress associated with auditory hallucinations. Also, it has been shown to improve social functioning (Wykes et al., 2005; McLeod et al., 2007a,b; Penn et al., 2009). Although there is evidence of CBTv's effectiveness in schizophrenia patients, no researchers have investigated if CBTv affects the electrophysiological markers of schizophrenia. The aim of the present study was to observe, for the first time, what kind of neural changes, if any, might emerge following CBT for voices in patients with persistent and distressing positive symptoms—specifically auditory verbal hallucinations. This was done by testing whether ERPs elicited by facial expressions were altered in patients with schizophrenia following completion of CBTv. Measuring ERPs pre- and post-therapy allowed us to observe any underlying neurophysiological changes that arose as a result of CBTv intervention.

The participants underwent Cognitive Behavioural Therapy for Voices (CBTv) group therapy, which was designed to be especially effective in helping patients cope with auditory hallucinations. The CBTv administered integrated attentional training (Wells, 1990) and acceptance and commitment therapy (Bach & Hayes, 2002) with the goal of reducing the emotional salience and distress associated with voices. The resulting reduction in perceived threat of the voices with CBTv was expected to allow for greater focusing on external rather than internal stimuli (i.e., voices) and hence, positively impact cognitive and daily functioning. As

such, we expected to observe larger and shorter P100 and N170 amplitudes and latencies, and larger P300 mean activity, in response to viewing facial expressions following completion of CBTv. We also hypothesized that we would observe reduced clinical ratings of hallucinatory activity and an improvement in accuracy scores on the social cognition measure MiniPONS. Finally, we also predicted an improvement in accuracy scores and reaction times in categorizing facial expressions. We did not expect to observe any changes in these measures following the wait time period in the treatment-as-usual group. Our prior work comparing facial processing in this sample of patients and healthy controls revealed a general impairment in facial expression processing across 6 basic emotions (Shah et al., 2018). Based on our findings from prior work we did not hypothesize a change in processing of any one particular emotional expression or group of expressions, and as such, did not include an emotional expression factor in our analyses.

4.3 Methods

4.3.1 Participants

The study involved twenty-five (10 women, 15 men) individuals with schizophrenia (SCZ), who were diagnosed by trained psychiatrists using the Structural Clinical Interview (SCID) for DSM-IV-TR. All participants included in the study: (i) were between the ages of 18 and 60; (ii) reported a consistent history of auditory verbal hallucinations over the course of their illness; (iii) exhibited a score greater than 3 (reflecting mild or greater auditory/verbal hallucinatory experience) on the hallucination item of the PANSS Positive Symptom Scale and less than 65 on the total PANSS score; (iv) had no history of neurological conditions or head injury; (v) were clinically stable, as indicated by no significant change in symptoms or medication, for at least the 3 month period prior to testing; (vi) had included in their primary medication one of the atypical antipsychotics; and (vii) were willing to participate in 5-6 months

of CBT for voices group therapy in addition to their usual treatment. All participants were administered the Positive and Negative Symptoms Scale (PANSS; Kay, Fiszbein, & Opler, 1987) and the Global Assessment of Functioning (GAF; DSM-IV-TR, 2000).

Nineteen adult controls (8 women, 11 men) with no psychiatric history were also assessed. Healthy controls (HC) were matched to the patient group with regard to gender, age and education level. Control participants were interviewed by a trained investigator to ensure absence of: psychopathology, alcohol or drug abuse (assessed with an adaptation of the structured clinical interview, non-patient version [SCID-I/NP]; First, Spitzer, Gibbon, & Williams, 1996), history of seizures, history of significant brain trauma, or known anatomical brain lesion. HCs completed the Beck Depression Inventory-II (BDI-II; Beck et al., 1996) and the Beck Anxiety Inventory (BAI; Beck, Epstein, Brown, & Steer, 1988). Additionally, the presence of schizophrenia history in a first-degree relative constituted an exclusion criterion. A hearing test was also administered and those who exhibited a hearing loss of >30 dB SPL were excluded from study participation (none were excluded for this reason). Participants with refractive error were required to correct their vision with glasses while undergoing the study assessments.

4.3.2 Study Design

Of 25 patients recruited, 14 (8 males) patients received CBT for voices (CBTv) group therapy for 5-6 months in addition to their usual treatment (CBTv+TAU group) and 11 (7 males) continued their treatment as usual (TAU-only group). The patients in both groups were recruited from the Outpatient Schizophrenia Program of the Royal Ottawa Mental Health Centre and randomly assigned to one of two groups. The patients in the study followed a randomized parallel group design. The recruitment and creation of groups involved: (i) a patient referral

through hospital psychiatrist to the study team; (ii) the introduction of the study requirements and involvement by the study team and consent from participants; (iii) completion of screening session to ensure patients met the study requirements; (iv) recruitment into the CBTv+TAU group, based on clinical suitability; and (v) recruitment into the TAU-only group based on similar demographic and clinical characteristics. Groups were matched with respect to clinical history (duration of illness, number of episodes/hospitalizations), medication, PANSS score, Hallucinations Scale (PSYRATS; Haddock et al., 1999) ratings, age, education level and gender. Patients in the CBTv+TAU group received CBTv for 5-6 months, while patients in the TAU-only were followed for 5-6 months of the study followed by 5-6 months of CBTv treatment. Patient assessments were compared with healthy controls tested on the same experiments, but assessed only once. Refer to Figure 4.1 for study outline schematic.

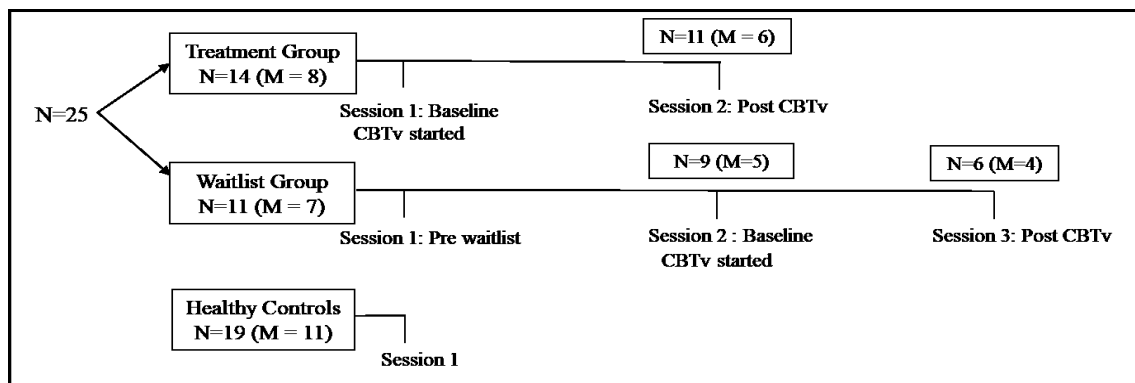


Figure 4.1 Study design with number of participants in each group at the beginning and after completing all study assessment.

Of the 14 patients recruited in the CBTv+TAU group, 11 patients (6 males) completed all assessments at baseline and follow-up and provided usable EEG data. Of the 11 patients recruited in TAU-only group, 9 (5 males) completed all assessments at baseline and follow-up and provided usable EEG data. The TAU-only group also received CBTv+TAU following completion of their TAU-only group period. Thus 5 patient participants dropped out or provided unusable data, giving an attrition rate of 20%. Of the 9 patients who completed the TAU-only

group, 6 completed all assessment at baseline, follow-up and post CBTv and provided usable EEG data. Throughout the study, patients continued with their regular medication and psychosocial interventions. Primary reasons for patient-drops or exclusions from the study were: (i) consent withdrawal; (ii) incomplete or unusable EEG data at both time points; (iv) medication change; and (v) onset of medical illness. Table 1 shows clinical and demographic characteristics of the final patient samples in both groups. Study sessions consisted of obtaining assessment of mood, psychotic symptoms, and social cognitive functioning. Also, most importantly for the current study, EEG activity during a facial expression categorization task was measured.

Table 1.

Demographics, clinical characteristics and task performance data of patients and HCs.

Demographics	CBTv+TAU group (N = 11; 6 males)		TAU-only group (N = 9; 5 males)		HC (N=19; 11 males)
	Mean $\pm$ SD Baseline	Mean $\pm$ SD Follow-up	Mean $\pm$ SD Baseline	Mean $\pm$ SD Follow-up	Mean $\pm$ SD
Age (years)	44.82 $\pm$ 13.82		48.78 $\pm$ 12.09		47.00 $\pm$ 7.97
Education (Years)	4.64 $\pm$ 1.43		5.50 $\pm$ 1.18		5.37 $\pm$ 1.38
Duration of illness (Years)	18.88 $\pm$ 11.39		21.78 $\pm$ 9.60		
BDI	10.46 $\pm$ 8.18	9.09 $\pm$ 7.80	16.60 $\pm$ 16.29	16.50 $\pm$ 14.38	4.97 $\pm$ 4.77
BAI	20.91 $\pm$ 13.03	16.82 $\pm$ 14.14	22.20 $\pm$ 14.74	19.00 $\pm$ 13.54	3.95 $\pm$ 4.28
MiniPONS %	60.14 $\pm$ 9.30	59.31 $\pm$ 11.10	65.63 $\pm$ 7.76	64.24 $\pm$ 6.02	76.55 $\pm$ 1.47
GAF ^a	46.00 $\pm$ 9.22	50.10 $\pm$ 7.65	44.60 $\pm$ 11.84	52.86 $\pm$ 17.17	
PSYRATS Total	25.09 $\pm$ 5.77	22.64 $\pm$ 6.80	27.50 $\pm$ 4.62	27.40 $\pm$ 5.99	
PANNS ^b					
Positive Scale	15.45 $\pm$ 4.83	15.80 $\pm$ 5.06	15.60 $\pm$ 3.74	16.71 $\pm$ 5.74	
Negative Scale	15.82 $\pm$ 4.83	15.20 $\pm$ 4.16	15.33 $\pm$ 4.39	14.43 $\pm$ 4.86	
General	33.54 $\pm$ 4.90	28.80 $\pm$ 4.51	31.33 $\pm$ 6.79	28.43 $\pm$ 9.27	
Psychopathology					
Performance					
Emotion clacification accuracy (%)					
Neutral	63.79 $\pm$ 32.36	69.46 $\pm$ 30.01	59.47 $\pm$ 34.65	62.60 $\pm$ 38.58	70.39 $\pm$ 26.98
Joyful	85.29 $\pm$ 9.32	84.03 $\pm$ 24.18	89.04 $\pm$ 14.73	74.98 $\pm$ 35.73	94.35 $\pm$ 18.17
Sad	69.77 $\pm$ 2.74	60.75 $\pm$ 23.85	58.99 $\pm$ 20.09	70.92 $\pm$ 19.34	73.21 $\pm$ 24.41
Angry	75.43 $\pm$ 4.66	74.55 $\pm$ 31.18	67.36 $\pm$ 19.82	65.42 $\pm$ 36.06	88.68 $\pm$ 14.42
Fearful	75.21 $\pm$ 8.98	74.30 $\pm$ 24.18	82.00 $\pm$ 14.76	77.75 $\pm$ 26.86	88.84 $\pm$ 18.33

PSYRATS: The Auditory Hallucinations subscale from the Psychotic Symptom Rating Scale; PANNS: Positive and Negative Syndrome Scale; MiniPONS:Short Multichannel Version of the Profile of Nonverbal Sensitivity.

a, b: follow-up for the GAF and PANNS measures included missing data (1 missing case for the CBT + TAU group and 3 missing cases for the TAU-only group).

4.3.3 Cognitive Behavioural Therapy for Voices (CBTv) Protocol

After baseline assessments, the CBT+TAU group received 5-6 months of a course of group CBT for voices treatment. Consistent with the NICE and PORT guidelines (NICE, 2010; Kreyenbuhl, Buchanan, Dickerson, & Dixon, 2010), group CBTv was delivered using a manualized approach. This was done in 18 planned sessions over 5 months, facilitated by highly trained group leaders. The CBTv intervention incorporated CBT strategies for positive symptoms and Attention Training (ATT) as well as Acceptance and Commitment Therapy (ACT) within a CBT framework. Each participant was given a copy of the participant manual, which included all homework/practice assignments. The 18 session CBTv group was administered on a weekly basis for five months (during the last two months, sessions were spread out to every two weeks). Each CBTv group had approximately 9 participants. Adherence to the CBTv protocol across the groups was assessed by adherence to the treatment manual and measured by the Cognitive Therapy Scale for Psychosis (CTS-Psy; Haddock et al., 2001).

4.3.4 Symptom Assessment

Patients were assessed independently at two test sessions: at baseline, and at the end of therapy (5 months after baseline). The TAU-only group was assessed at three test sessions: baseline, at the end of waitlist period (5 months after baseline) and at the end of therapy (10 months after baseline). The MiniPONS was administered during the test sessions to measure social cognition skills. The following primary CBTv outcome measures were implemented:

Positive and Negative Syndrome Scale. The Structured Clinical Interview for the PANSS (Kays et al., 1987) is a 30-item rating scale designed to measure the presence and severity of psychopathology in patients with schizophrenia, schizoaffective disorder, and other psychological disorders. The PANSS was completed by a trained clinician following a semi-

structured interview format and using available clinical information. The clinician was blind to the group assignments. Each item was rated by the clinician on a Likert scale ranging from 1 (not present) to 7 (extremely severe). Three subscales scores were derived: Positive Symptoms scores (possible range of scores: 9-49); Negative Symptoms Scores (possible range of scores: 7-49) and General Symptoms Scores (possible range of scores; 16-112).

The Psychotic Symptom Rating Scales (PSYRATS). The PSYRATS (Haddock, McCarron, Tarrier, & Faragher, 1999) includes two scales designed to measure the severity of a number of dimensions of auditory hallucinations and delusions. Only the Auditory Hallucinations subscale was administered to the patients, which includes an 11-item scale that assesses dimensions of auditory hallucinations. The items include frequency, duration, location, loudness, amount and intensity of distress, amount and intensity of negative content, disruption, controllability, and number of voices. Symptoms scores are rated on a 5-point ordinal scale (0-4).

Global Assessment of Functioning (GAF). The GAF (DSM-IV-TR, 2000) was be used to rate the patients' social, occupational, and psychological functioning. The GAF is an overall measure of how patients are doing and can be useful in tracking the clinical progress of individuals in global terms. The GAF scores range from 1 - 100, where lower scores indicate reduced functioning and higher scores indicate that the patient is not in need of therapy. The GAF was completed by a trained clinician, who was blind to the group assignments.

Beliefs About Voices Questionnaire-Revised (BAVQ-R): Chadwick, Lee & Birchwood, 2000; Appendix I). The BAVQ-R is a 35-item self-report questionnaire that measures perceptions about, and emotional and behavioural response to, auditory verbal hallucinations. The items are rated on a 4-point scale ranging from 0 (disagree) to 3 (strongly agree). The questionnaire consists of five subscales measuring different meanings given to the voices:

omnipotence with six items (e.g., "My voice is very powerful"), *malevolence* with six items (e.g., "My voice is persecuting me for no good reason"), *resistance* with nine items (four items for *emotion*: e.g., "My voice frightens me" and five items for *behaviour*: e.g., "When I hear my voice usually I tell it to leave me alone"), *benevolence* with six items (e.g., "My voice wants to help me") and *engagement* with eight items (four for *emotion*: e.g., "My voice makes me feel calm" and four for *behaviour*: e.g., "I seek the advice of my voice").

Social Cognition. The Short Multichannel Version of the Profile of Nonverbal Sensitivity (MiniPONS; Banziger, Scherer, Hall, & Rosenthal, 2011) was used to assess social cognition, that is, the ability to recognize the communication of feelings, attitudes, and intentions from nonverbal expression in face, voice, gestures, and body postures. The MiniPONS correlates highly with the full version and has shown construct validity through significant correlations with other tests of emotion recognition ability (Banziger, Scherer, Hall, & Rosenthal, 2011). The shorter version of the Pons was used to account for the limited time during test sessions. A series of 64 two-second video clips of a Caucasian female were used in the MiniPONS. Each scene contained, either singly or in combination, facial expressions, voice intonations, and bodily gestures. After watching each scene the participants were asked which of two labels (e.g., 'talking to a child' or 'saying a prayer') best described the scene. A practice session was administered with 3 scenes out of the other 64 scenes not shown to ensure participants understood the task. The percentage of correct responses was used as the dependent measure.

4.3.5 EEG Session Procedures

Prior to EEG testing, participants abstained for a minimum of 3 hours from caffeine and nicotine (if smokers), and beginning at midnight, from alcohol and drugs (other than regular prescribed medication). Consumption of breakfast or lunch was permitted. Upon arrival at the

laboratory, all participants were administered a MiniPONS. Only patient participants were administered the PSYRATS (Haddock, McCarron, Tarrier, & Faragher, 1999) to measure the severity of a number of dimensions of auditory hallucinations. Electrodes were applied to the participant's scalp and face, from which EEG activity was recorded while completing the facial expression categorization task. The study was approved by the Research Ethics Boards of the Royal Ottawa Mental Health Centre and the University of Ottawa. Informed consent was obtained from all participants prior to participation.

4.3.6 Facial Expression Categorization Task

Stimuli. Facial expression stimuli were derived from Gosselin, Kirouac, and Dore (1995). Within the image database from which the face stimuli were drawn, three intensities of each emotion were presented: 20%, 50%, and 100%. Expressions at 20% intensity from each emotion expressed were labeled as neutral. This is because expressions at 20% intensity cannot be reliably differentiated from one another (Orgeta & Phillip, 2008). The same four actors that depicted the 50% and 100% intensity emotional expressions also depicted the neutral faces. Each facial expression was displayed by 4 actors (2 female and 2 male). The validity of these expressions and their intensity has been previously established (Gosselin et al., 1995).

Twenty photographic faces displaying one of five facial expressions (4 joyful, 4 angry, 4 fearful and 4 sad; and 4 neutral) were selected for use from the database. Each facial expression image was presented 17 times, yielding a total of 340 trials with facial expression stimuli. In addition to face stimuli, 4 different chair photographs were used as control stimuli and each chair photograph was presented 17 times for a total of 68 trials with chair stimuli. Altogether, there were 408 trials (340 with faces and 68 with chairs).

All photographs were digitized and converted to grey-scale images and matched for luminance and contrast. Neck and background were cropped out and the face stimuli were trimmed into rectangles. The images were then scaled to have the same height (513 pixels) while maintaining the original aspect ratio.

Facial Expression Categorization Task Procedures. During the task, all participants were seated in a comfortable chair and viewed all stimuli presented on a 17-inch computer screen positioned approximately 1 m in front of the seated participant in a dark room. Each grey-scale picture of a neutral, joyful, fearful, angry, or sad facial expression, as well as each chair stimulus, was presented a total of 68 times. Trials were presented in random order. Three rest periods were given, one after each quarter of the trials had been completed. Each trial began with a fixation cross (200ms), followed by a face or chair stimulus (500ms). For 120 of the trials, the face or chair stimulus was followed by a response prompt asking the participant to identify the emotion being expressed via a key press. A blank screen appeared between trials (ITI = 800-1000 ms). An equal number of trials requiring a response appeared for each stimulus type (i.e., 20 for each facial expression and 20 for the chairs). Participants' responses and reaction times (RT) were recorded automatically. Responses were requested for chair stimuli as well as face stimuli, even though the chairs would not normally be said to express an emotion. This was done in order to keep the behavioural response for face and chair stimuli as consistent as possible. We were concerned that not having a response requested for chairs would create a kind of go/no-go task, which was not our aim. As such, we requested participants to respond to the chair stimuli behaviourally. However, these responses were not otherwise meaningful, and so responses and RT to chair stimuli were not analyzed.

4.3.7 Electrophysiological Recordings and Data Reduction

During the facial expression categorization task, continuous EEG activity was recorded with a cap embedded with Ag+/Ag+-Cl ring electrodes (EasyCap®, Herrsching-Breitbrunn, Germany) at 32 scalp sites positioned according to the 10-10 system of electrode placement. Additional electrodes were placed on the orbital ridges and external canthi of the eyes to monitor vertical and horizontal electrooculographic (EOG) activity and subsequently minimize contamination from eye movements and blinks. Linked electrodes positioned at the left and right mastoids served as the reference and a frontally positioned electrode served as the ground. Electrode impedances were kept below 5 K Ω and EEG activity was digitally sampled at 500 Hz (BrainVision Recorder®, Richardson, TX, USA). The electrical signals were amplified with a bandwidth filter set at 0.1-70 Hz and stored on hard disk for subsequent off-line processing and analysis (BrainVision Analyzer2).

Off-line EEG data analysis was carried out using BrainVision Analyzer 2 (BrainVision Analyzer®, Richardson, TX, USA). During off-line signal processing, analytical procedures were applied to the stored digitized recordings: (1) individual trials were filtered at 0.1-30.0 Hz; (2) an ocular correction software algorithm (Gratton, Coles, & Donchin, 1983) was employed to correct for the effects of eye movements and blinks based on the EOG recordings; (3) Data was segmented into 1600 ms epochs for each stimulus, with a timespan from 100 ms pre-stimulus onset to 1500 ms post stimulus onset. Epochs with responses were pooled with those without responses; (4) trial epochs with EEG voltages greater than $\pm 75\mu\text{V}$ were removed; (5) filtered epochs were baseline corrected by subtracting averaged electrical activity 100 ms prior to stimulus onset and (6) codes synchronized with stimulus delivery were used to average together

epochs associated with the different stimulus categories (i.e., angry, fearful, joyful, neutral, and sad faces, plus chairs).

4.3.8 ERP Analyses

ERPs were identified based on visual examination of grand-averaged waveforms and previous literature (Campanella, Montedoro, Streel Verbanck & Rosier, 2006; Jung, Kim, Kim, Im & Lee, 2012; Lee, Kim, Kim & Bae, 2010; Luo et al., 2010; Turetsky, Kohler, Indersmitten, Bhati, Charbonnier, & Gur, 2007; Wynn et al., 2008). The following components were identified for facial expressions and chair stimuli: P100 (measured at P_{7/8} and O_{1/2}; with maximum positive voltage within the time window of 80-130ms following face stimulus onset), N170 (measured at P_{7/8}; with maximum negative voltage within the time window of 140-230ms following stimulus onset), and P300 (measured at P_z with mean positive activity within the time window of 200-600 ms). All peak amplitudes and mean amplitudes were measured relative to mean pre-stimulus voltage levels. Peak latencies of the P100 and N170 (i.e., time to reach maximum voltage) were assessed relative to stimulus onset.

4.3.9 Statistical Analysis

CBTv+TAU compared with TAU-only groups: baseline comparisons.

Independent samples t-tests were used to compare the final CBTv+TAU and TAU-only groups at baseline on age, gender, education, MiniPONS scores, and clinical symptoms scores (PANSS, PSYRATS, GAF, BDI and BAI). Independent samples t-tests were also used to compare behavioural performance indices (accuracy and median RT) across groups. These were calculated regarding the identification of all facial expressions (i.e., accuracy for joyful, angry,

sad, fearful and neutral face stimuli collapsed together). An alpha level of 0.05 for testing significance was maintained.

Effects of CBTv: Symptom, accuracy and ERP changes in CBTv+TAU compared TAU groups.

CBTv treatment changes in clinical symptom (PANSS, GAF, PSYRATS and PSYRATS items) and social cognition (MiniPONS) scores were analyzed using paired-samples t-tests for both the CBT+TAU and TAU-only groups. Behavioural performance (accuracy and median RT) data was analyzed with mixed repeated measures ANOVA using group (CBTv+TAU and TAU-only) as a between-subjects factor and time (baseline and follow-up) as within-subjects factor.

P100 amplitude and latency data were analyzed with mixed repeated measures ANOVA using group (CBTv+TAU and TAU-only) as a between-subjects factor and site (occipital, parietal), hemisphere (right, left) and time (baseline, follow-up) as within-subjects factors. N170 amplitude and latency data were analyzed with mixed repeated measures ANOVA using group (CBTv+TAU and TAU-only) as a between-subjects factor and hemisphere (right, left) and time (baseline, follow-up) as within-subjects factors. P300 mean activity data was analyzed with mixed repeated measures ANOVA using group (CBTv+TAU and TAU-only) as a between-subjects factor and time (baseline, follow-up) as within-subjects factors. Significant main effects or interactions involving the group factor were followed up by within-subjects ANOVAs for each group. An alpha level of $p < .05$ for testing significance was maintained.

Patient group compared with healthy participants.

We tested for differences between the patient group (at baseline) and the healthy control group in age, education, clinical symptom scores (BDI and BAI) and MiniPONS accuracy scores using independent samples t-tests. Similar comparisons regarding performance were tested for

using an ANOVA with Group (SCZ, HC) as the between-subjects variable and facial expression (fearful, joyful, sad, angry and neutral) as the within-subjects variable. Group differences in ERP responses to facial expressions between patients (at baseline) and healthy controls were also tested for with repeated-measures ANOVAs. These had group (SCZ, HC) as the between-subject variable and facial expression (fearful, joyful, sad, angry and neutral), hemisphere (right, left: for P100 and N170) and site (parietal, occipital: only for P100) as within-subjects variables. The error terms from the ANOVA were used to conduct planned contrasts (Rosenthal & Rosnow, 1985) to test study hypotheses (Shah et al., 2018)⁴.

4.4 Results

4.4.1 CBTv+TAU compared with TAU-only groups: baseline comparisons

Demographic, clinical and behavioural measures

The final CBTv+TAU and TAU-only groups were similar in age, gender, years of education, duration of illness, and all clinical symptom scores (BDI, BAI, PANSS positive items, PANSS negative items, PANNS total score, and PSYRATS total score). Accuracy scores and reaction times to respond to facial expressions were also similar between the CBTv+TAU and TAU groups. Table 1 provides means and standard deviations for both groups.

⁴ The detailed results of these ANOVAs can be found in Shah et al. (2018), but in summary, patients with schizophrenia were slower at identifying all facial expressions, including neutral ones. They also showed smaller P100 amplitude to sad, angry and fearful facial expressions relative to healthy controls. N170 amplitude was smaller in patients in response to neutral, joyful, angry, and fearful facial expression. Patients showed smaller P300 mean amplitudes to all facial expressions, including neutral ones.

4.4.2 Effects of CBTv: task performance and symptom scores

The ANOVA revealed no changes in accuracy scores or reaction time in facial expression categorization at follow-up (post-treatment) compared to baseline (pre-treatment) in either the CBTv+TAU or TAU-only groups ($F < 1$ for Group, and Group x Time). Paired-sample t-tests were conducted to test for changes in symptoms scores and MiniPONS accuracy scores between baseline (pre-treatment) and follow-up (post-treatment) in both the CBTv+TAU and the TAU-only groups. There were no significant differences in symptom scores from baseline to follow-up for GAF, PANSS-positive, and PSYRATS-total scores.

CBTv+TAU group

PSYRATS items. The paired sample t-test for the CBT+TAU revealed a significant difference across testing sessions in the score for one of the PSYRATS items: ‘amount of negative content’, where the treatment group reported a reduced amount of negative content in their voices following group CBTv treatment ($M = 2.18$, $SD = 1.17$) relative to baseline ($M = 3.00$, $SD = .89$); $t(10) = 2.76$, $p = .02$. The treatment group also showed a trend towards reduction in the ‘loudness of auditory hallucinations’ following group CBTv treatment ($M = 1.73$, $SD = .65$) relative to baseline ($M = 2.18$, $SD = .75$); $t(10) = 1.84$, $p = .09$.

BAVQ-R. A significantly improved BAVQ-R subscale ‘omnipotence’ score was observed in the CBTv+TAU group following group CBTv treatment ($M = 4.64$, $SD = 5.66$) relative to baseline ($M = 7.00$, $SD = 5.16$); $t(10) = 2.34$, $p = .04$). A trend towards improvement in ‘resistance-behaviour’ subscale following group CBTv treatment ($M = 10.64$, $SD = 4.46$) relative to baseline ($M = 8.73$, $SD = 4.96$); $t(10) = -1.92$, $p = .08$ was also observed.

MiniPONS. A trend toward improvement in MiniPONS accuracy scores following group CBTv treatment ($M = 64.69\%$, $SD = 11.27$) relative to baseline ($M = 59.31\%$, $SD = 11.10$); $t(9) = -1.96$, $p = .08$ was observed.

TAU-only group

The significant differences reported above in the CBTv+TAU group following treatment were not observed in the TAU-only group. However, the TAU-only group did reveal a trend towards reduction of PANSS negative scores ($t(5) = 2.45$, $p = .06$) and a trend towards improvement of BAVQ-R subscale ‘benevolence’ ($t(8) = -2.18$, $p = .06$) at follow-up (PANSS negative: $M = 14.00$, $SD = 5.17$; BAVQ-R ‘benevolence’: $M = 5.44$, $SD = 4.80$) relative to baseline (PANSS negative: $M = 16.00$, $SD = 3.69$; BAVQ-R ‘benevolence’: $M = 2.56$, $SD = 3.47$).

4.4.3 Effects of CBTv: ERP changes following CBTv

P100 Amplitude and Latency

The P100 amplitude mixed repeated measures ANOVA revealed significant site by group ($F[1, 18] = 5.07$, $p = .04$, $\eta_p^2 = .22$), and time by hemisphere by group ($F[1, 18] = 6.19$, $p = .02$, $\eta_p^2 = .26$) interactions. A follow-up ANOVA within the CBTv+TAU group showed significant time by hemisphere ($F[1, 10] = 5.97$, $p = .04$, $\eta_p^2 = .37$) and site by hemisphere interactions ($F[1, 10] = 10.03$, $p = .01$, $\eta_p^2 = .50$). Follow-up pairwise comparisons of the time by hemisphere interaction revealed larger ($p = .02$) P100 amplitude over the right ($M = 5.05\mu V$, $SD = 2.61$) compared with the left ($M = 3.75\mu V$, $SD = 1.34$) hemisphere at follow-up.

A follow-up ANOVA within the TAU-only group showed a significant ($F[1, 8] = 10.52$, $p = .01$, $\eta_p^2 = .57$) interaction of time by site. Follow-up pairwise comparison of the time by site

interaction revealed larger ($p = .009$) P100 amplitude over the occipital ($M = 5.53 \mu V$, $SD = 3.17$) relative to the parietal ($M = 4.03 \mu V$, $SD = 2.31$) site at follow-up. Neither the CBTv+TAU nor the TAU-only group showed a P100 amplitude treatment effect.

The P100 latency mixed repeated measures ANOVA revealed significant time by group ($F [1, 18] = 14.51, p = .001, \eta_p^2 = .45$) interaction. A follow-up ANOVA within the CBTv+TAU group showed significantly ($F [1, 10] = 19.68, p = .001, \eta_p^2 = .66$) shorter P100 latency following completion of group CBTv ($M = 109.48$ ms, $SD = 7.11$) compared with baseline ($M = 114.44$ ms, $SD = 7.54$; Figure 4.2). A similar follow-up ANOVA within the TAU-only group did not show any significant main or interaction effects.

N170 Amplitude and Latency

The N170 amplitude mixed repeated measures ANOVA revealed significantly larger amplitude ($F [1, 18] = 10.12, p = .005, \eta_p^2 = .67$) in the CBTv+TAU group ($M = -3.34 \mu V$, $SD = .75$) compared with the TAU-only group ($M = -0.40 \mu V$, $SD = .17$). The N170 latency mixed repeated measures ANOVA revealed significant time by hemisphere by group ($F [1, 18] = 7.04, p = .02, \eta_p^2 = .28$) interaction. Follow-up N170 amplitude and latency ANOVAs within the CBTv+TAU and TAU-only groups did not show any main or interaction treatment effects.

P300 Mean Amplitude

The P300 mean amplitude mixed repeated measures ANOVA did not reveal any main or interaction effects.

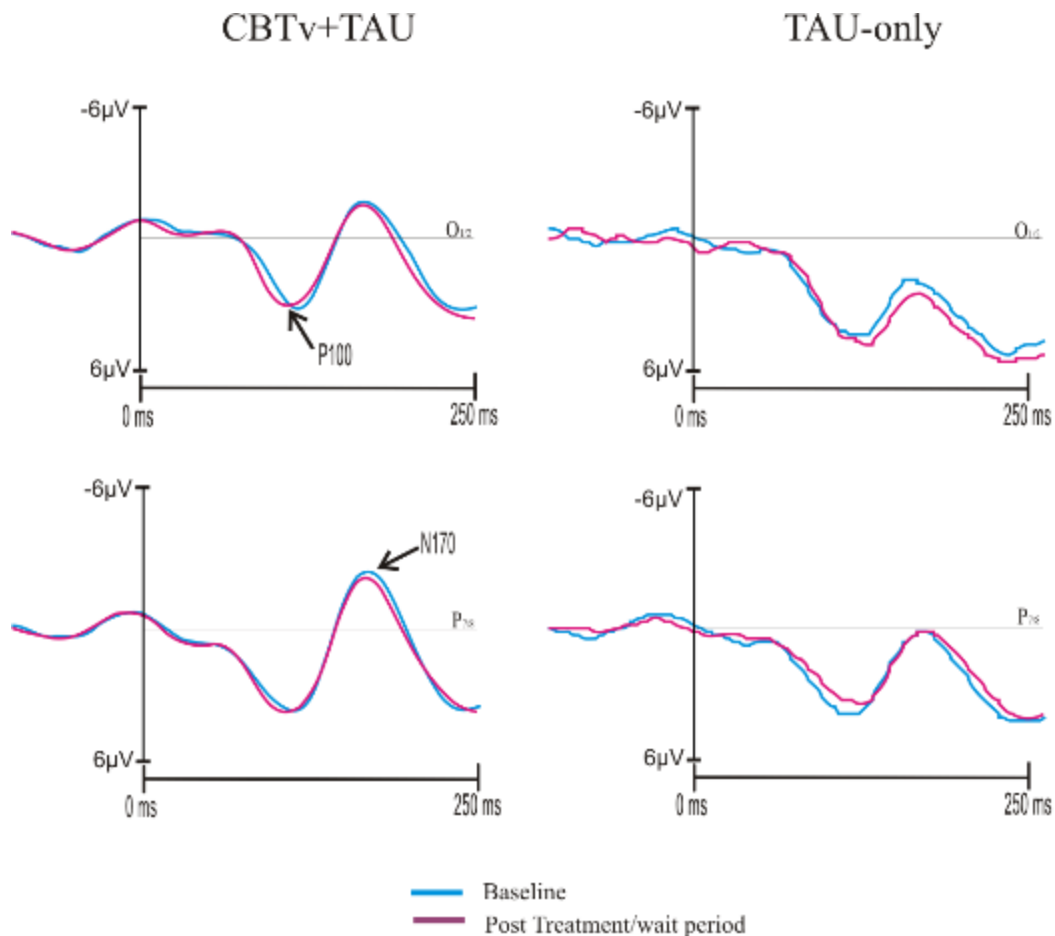


Figure 4.2 P100 and N170 grand averaged waveforms in response to facial expressions measured at baseline and following CBTv treatment or wait period. P100 is measured over occipital site (O_1 and O_2 pooled), N170 is measured over parietal sites (P_7 and P_8 pooled).

4.5 Discussion

This study was the first to investigate neural changes following 5-6 months of CBT for voices (CBTv) in patients with schizophrenia using event-related potentials and a facial expression categorization task. We expected that CBTv would significantly reduce clinical ratings of hallucinatory activity found in patients with schizophrenia and improve behavioural performance and ERP amplitudes and latencies during the facial expression categorization task.

4.5.1 Clinical symptom findings

Based on previous findings of both randomized and non-randomized controlled trials of CBTv (Wykes et al., 2008; McLoed et al., 2007a,b; Gottlieb et al., 2013), reductions from baseline to post-treatment measures of hearing voices and related distress were predicted in the present study. These predictions were borne out. Specifically, the CBTv+TAU group reported a significantly reduced amount of negative content of voices, and improved outcomes on the *omnipotence: power of voice* item of the BAVQ-R. Further, the treatment group showed a trend towards reduction in loudness of voices and improved MiniPONS accuracy score following treatment.

Contrary to our expectations, based on the findings of randomized controlled trials of CBTp and CBTv (Birchwood et al., 2014; McLoed et al., 2007a,b; Penn et al., 2009; Shawyer et al., 2012; Wykes et al., 2005), the CBTv+TAU group did not show significantly reduced PANSS symptom severity, PSYRATS total scores or GAF scores at follow-up. One possible explanation for the discrepancy between our findings and those from previous studies is related to the theoretical approach taken for treatment and the measurements used to test efficacy of treatment. That is, within the general framework of CBT, different theoretical approaches may have been used in our study versus previous ones (Pontillo et al., 2016). The effects of CBT for voices have mostly been investigated by examining the efficacy of CBTp on the overall severity of positive symptoms (hallucinations and delusions combined: Thomas et al. 2014). Previous study designs involved participants experiencing a broad range of psychotic experiences (hallucinations, delusions, negative symptoms), resulting in sample heterogeneity, delivery of therapy based on a broad range of behavioural and cognitive principles, and examination outcomes using broad indices of psychological states, such as overall positive symptoms

(Thomas et al., 2014). In contrast, our sample included individuals who experienced auditory verbal hallucinations and the treatment was focused specifically on beliefs about the voices' omnipotence and the patients' relationships with the voices.

The focus of CBTv is not on reducing experience of voices or frequency and severity of symptoms, but rather on reducing the perceived power of voices and in turn the related distress experienced by patients (Birchwood & Trower, 2006). Our findings showing reduced omnipotence and negative content of voices are in line with goals of the reduced perceived threat with CBTv as well as Birchwood and Trower's (2006) explanation of the focus of CBT treatment for voices.

Our TAU-only group showed a trend towards reduced PANSS-negative symptoms and of improvement on BAVQ-R subscale 'benevolence' from baseline to follow-up. The reason for this is unclear. The TAU-only group showed no change in other symptoms from baseline to follow-up in any of the following: PSYRAT total, PSYRATS items, GAF, PANNS positive, PANNS general, and MiniPONS scores. This was expected given that the inclusion criteria required all patients to be clinically stable, to be on same medication for 3 months prior to study entry, and to have no change in medication during the course of the study.

4.5.2 Behavioural and ERP findings

Although we found slower response time to categorizing all facial expressions (Shah et al., 2018) between patients with schizophrenia and healthy controls, we did not find improvement in response time following group CBTv treatment. Additionally, the CBTv+TAU group did not improve in accuracy of categorizing facial expressions from baseline to follow-up. The CBTv+TAU and TAU-only groups displayed similar performance on the task during both

sessions. These null findings are in line with Kumari et al. (2011), who found neural changes in a number of brain structures following CBTp that did not extend to behavioural performance improvements in the treatment group.

In line with our hypothesis, the CBTv+TAU group at follow-up showed earlier perceptual response to facial expressions, as indexed by the P100, than they did at baseline. The P100 is believed to reflect early-stage visual information processing (Luck et al., 1994; Santesso et al., 2008) and early preconscious direction of attention (Lee, Gosselin, Wynn & Green, 2011; Pizzagalli et al., 2002; Turetsky et al., 2007; Turetsky et al., 2008; Utama, Takemoto, Koike & Nakamura, 2009). P100 amplitude deficits in patients with schizophrenia have been frequently reported in response to non-face and face stimuli (Earls et al., 2015; Onitsuka et al., 2013; Shah et al., 2018). However, only a limited number of studies have found longer P100 latencies in patients with schizophrenia during tasks involving faces (Lee et al., 2010; Wynn et al., 2008). The longer P100 latency may be reflective of patients' general inefficiency in earlier stages of visual information processing (Lee et al., 2010; Wynn et al., 2008) and attending. Our study is the first to show a change in P100 latency following a course of group CBTv treatment in patients with schizophrenia. Our findings are compatible with those of Kumari et al. (2011), who found reduced fMRI activation after CBTp in visual (occipital) areas, which are thought to primarily subserve early perceptual processing (Adolphs, 2002) and to receive feedback from areas processing visual emotion (Catani, Jones, Donato, & Ffytche, 2003).

Our CBTv protocol included attention training as well as acceptance and commitment therapy (ACT) interventions. Attention training was included to target auditory verbal hallucinations experienced in this population. Auditory verbal hallucinations are thought to be related to attentional processing. Levels of self-focused attention predict whether or not

individuals experience auditory verbal hallucinations, and thus self-focused attention is implicated in the mediation of auditory verbal hallucinations (Ensum & Morrison, 2003; Morrison & Haddock, 1997). Acceptance and mindfulness (a key component of ACT) have been found to alter ERP following treatment in patients with bipolar disorder and healthy individuals (Howells, Lauri, Ives-Deliperi, Horn, & Stein, 2014; Lin, Fisher, Roberst, & Moser, 2016). Attention training and ACT were integrated into group CBTv with the goal of reducing emotional salience and distress associated with hearing voices. In turn, the reduction of the perceived threat of voices with CBTv was expected to allow for a greater focusing on external rather than internal stimuli (voices) and hence, impact cognitive and social functioning. Our findings of shorter P100 latency to facial expressions provide some evidence, at a neural level, of change in attention to external stimuli.

Contrary to our hypothesis, we did not observe significant changes in P100 amplitude, N170 amplitude and latency, or P300 mean activity following a course of CBTv. The reason for this is unclear. It is plausible that earlier perceptual improvements observed in the present study following CBTv did not transfer to later more conscious processing stages. Delayed P100 latencies in patients with schizophrenia have been reported, but amplitudes of P100 and the latency and amplitude of subsequent N170 have been found to be intact in patients (Wynn et al., 2008). Researchers have suggested that the pathways for the early processing of facial expression content, reflected in the P100, and the later structural encoding of facial features, reflected in the N170, are dissociable (Pourtois, Dan, Grandjean, Sander, & Vuilleumier, 2005; Pourtois, Grandjean, Sanders, & Vuilleumier, 2004; Vuilleumier & Pourtois, 2007). This could be a reason why the present study found increased efficiency in early processing and attending to visual

information, but did not observe any effects at later structural encoding and affect processing stages.

It is important to note the observed N170 amplitude difference between the CBTv+TAU and TAU-only group. One explanation for difference in N170 amplitudes between groups could be that the randomization process was flawed in some way. However, this explanation does not explain the insignificant differences in clinical ratings, and performance scores between groups at baseline. Another explanation could be related to the effects of antipsychotic medication. Antipsychotic medication has shown effects on neural activation (Anderer, Semlitsch & Pascual-Marqui, 2002; Pompela, Bueno, Lucchesi, Manzano, Galduroz & Tufik, 2000). Longer P100 latency during visual discrimination task has been shown following an acute dose of bromazepam (Puga et al., 2007). However, researchers have found little to no evidence to suggest that the N170 deficits reported in patients with schizophrenia stem from or are correlated with antipsychotic medication (Batty, Francis, Innes-Brown, Joshua, & Rossel, 2014; Maher, Mashboon, Ekstrom, Lukas & Chen, 2016). It is unclear as to the result of the N170 amplitude difference between our patient groups, especially given no difference emerged for P100 amplitude, behavioural performance indices and clinical rating scores at baseline. Even with the smaller N170 in the TAU-only group, relative to the CBTv+TAU group, our P100 latency effects cannot be discounted. P100 is observed prior to N170 and over both the occipital and parietal sites. As such any uncertainty in the N170 data should not influence the P100 data.

4.5.3 Study Limitations

The study was not designed primarily to test the efficacy of CBTv. Rather, the study aimed to observe changes in ERPs over the course of CBTv. As such, the task did not specifically target mechanisms involved in improved attention, mindfulness practice, or

cognitive restructuring related to auditory verbal hallucinations. Further, we only tested changes in processing in the visual modality. Another limitation is that we have not yet done a long-term follow-up to determine if the benefits observed in this study are sustained following completion of group CBTv. Finally, our sample size would be considered small. Future research could investigate the effects of CBTv on clinical rating of AVH, as well as the neural responsiveness as measured with a larger sample size and range of tasks (e.g., acoustic change detection, working memory, emotional expression identification).

4.5.4 Conclusion

Researchers have demonstrated that experiencing auditory hallucinations interferes with auditory and visual processing, and face processing in particular (Bruder et al., 2011; Kayser et al., 2012; van Lutterveld, Sommer & Ford, 2011). This study provides the first evidence that a course of group CBT for voices alters early perceptual processing of faces in patients with auditory verbal hallucinations. Demonstrating CBTv-induced changes to socially relevant information – faces – is important because there is a lack of knowledge about the neural mechanisms that underlie the benefits of psychotherapy (Birchwood et al., 2014; McLoed et al., 2007a,b; Penn et al., 2009; Shawyer et al., 2012; Wykes et al., 2005) observed with CBT for patients with schizophrenia. The present study provides a starting point for exploring neural changes following psychotherapy in this population. Further studies are required to examine electrophysiological changes that accompany CBT, in particular those that reflect information processing related to specific symptoms of schizophrenia, and their effects on face and emotion processing and social cognition.

4.6 References

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CHAPTER 5 : GENERAL DISCUSSION

5.1 Summary

The work presented in this thesis assessed electrophysiological indices of face and emotional expressions processing in patients with schizophrenia experiencing auditory hallucinations. It probed the role of low-level visual information using spatial frequency ranges in face and emotional expression processing, with the aim of clarifying the relationship between visual pathway deficits and altered emotion recognition in patients with schizophrenia. Further, it aimed to assess electrophysiological changes following group cognitive behavioural therapy for voices treatment in the patient group. With respect to the first goal, earlier and later stage electrophysiological indices were found to be smaller in individuals with schizophrenia than in healthy control participants. These impairments were also observed with spatial frequency manipulated images of emotional expressions. However, impaired amplitudes in response to emotional expressions were not altered following CBTv, only early perceptual latency effects were improved.

5.2 Impairments of Emotional Facial Processing in Schizophrenia Patients: Evidence from P100, N170 and P300 ERP Components in a Sample of Auditory Hallucinators: Summary

Patients with schizophrenia were slower at responding to classification of all emotional expressions and were less accurate at identifying angry facial expressions. Although only identification of angry expressions revealed a statistically significant difference, visual examination of the data suggests that patients have poorer correct response in identifying all facial expressions. These behavioural performance findings are in line with the well documented (Barkhof et al., 2015; Kohler et al., 2010) impairment in emotion recognition in this population.

Deficits in earlier visual information processing, as indexed by P100 amplitude, was observed in response to negative facial expressions (sad, angry and fearful). This emotion-specific deficit observed in our patient sample generalized to all facial expressions during the structural encoding and higher order information processing stages, as indexed by the N170 and P300. These findings replicated previous reports of impaired P100, N170 and P300 in response to facial expressions (Barkhof et al., 2015; Earls et al., 2015; Kohler et al., 2010; McCleery et al., 2015; Turetsky et al., 2008). Our findings, along with previous reports, provide support for the suggestion that patients with schizophrenia show earlier perceptual deficits to specific emotional expressions or sets of expressions, which then contribute to the later structural encoding and higher order cognitive impairments of face processing that are observed in this population (Campanella et al., 2006; Caharel et al., 2007; Turetsky et al., 2007; Lynn & Salisbury, 2008; Ibáñez et al., 2012).

We included non-face stimuli to investigate whether the deficit with facial expressions results from an impairment in visual processing of facial information, or from a basic visual processing impairment. Early P100, N170 and later P300 impairments to chair stimuli in patients with schizophrenia relative to control were observed. Impairment to neutral faces was observed for N170 and P300, whereas processing of chair stimuli was found to be disturbed in patients beginning at the earlier P100 stage extending to P300. Our finding in response to chair stimuli suggest that the N170 and P300 impairments observed to facial expressions may not be specific to faces and that they may reflect a general impairment of visual information processing (Baudouin et al., 2002). A limitation of our study is that we do not have reliable behavioural performance data for the non-face chair stimuli to corroborate claims of general impairment in processing visual information. Nevertheless, our electrophysiological findings in response to

chair stimuli, which follow a similar pattern to the ERP responses to facial expressions, should not be discounted.

With regards to within-group data, patients exhibited a different pattern of ERP modulation across facial expressions than controls for P100 and N170, but not for P300. Patients showed smaller P100 amplitudes to sad faces relative to neutral, joyful, angry and fearful facial expressions. Controls showed larger P100 amplitudes to joyful, sad and angry faces relative to neutral ones. Patients showed no N170 amplitude differences in the patient group across any facial expressions. The control group showed N170 amplitude modulation across facial expressions. Both groups showed similar P300 modulation across facial expressions. Considering the P100, N170, and P300 group differences and the P100 amplitude effects of emotional expressions observed within controls (neutral faces < joyful, sad and angry) and not in the patients, we suggest that processing of faces and their affective content may begin during this early stage of visual information processing and that this is disturbed in the patient population (Luck et al., 1994; Earls et al., 2015). The results of the present study also suggest that the N170 deficit in the patient group could be attributed to a decrease in earlier visual processing as indexed by a smaller P100.

The central aim of this study was to replicate previous reports of impaired ERPs in response to facial expressions in a homogenous sample of patients with schizophrenia. Unlike previous studies, our study sample included those whose primary difficulties were the experience of distressing and chronic auditory verbal hallucinations. By including individuals who experience auditory hallucinations in the study, we were able to speak to the relationship between cross modality impairments observed in this population. Specifically, experiencing auditory hallucinations impacts processing of visual information, resulting in behavioural

impairments (Kayser et al., 2012). Findings of smaller N170 and P300 amplitudes to stimuli in the present study are in line with Kayser et al. (2012)'s suggestion that visual impairments may be symptom-specific or that they may be more profound in patients who experience auditory hallucinations relative to those who do not. Although we replicated previous reports with our narrowly defined sample, we did not find correlations between PANSS symptom scores and ERP data. Our sample of patients does not allow for investigating the relationship between specific symptoms and ERP impairments to visual information. In future work, it will be important to attempt to replicate findings from the present study and compare the relationship between different forms or symptoms of schizophrenia and responses to visual stimuli. In doing so, we may determine if electrophysiological findings vary across symptoms of schizophrenia, and if patients without hallucinations show similar impairments to those observed in the present study.

The present study replicated previous findings with a more homogenous sample of patients than previous studies used. Specifically, we examined only those who experience auditory hallucinations. In doing so, we supported previous studies that showed: (1) deficits in behavioural performance measures in patients with schizophrenia in both emotional and non-emotional faces (Barkhof et al., 2015; Kohler et al., 2010), (2) smaller early P100 amplitudes in patients, providing support for the suggestion that patients show P100 deficits to specific emotional expression or set of expression (Earls et al., 2015); (3) N170 deficits in patients with schizophrenia during processing of neutral and emotional facial expressions (McCleery et al., 2015); (4) smaller P300 to all facial expressions (Turetsky et al., 2008); and (5) impaired P100 and N170 amplitudes to non-face stimuli (Butler et al., 2007). Our findings add to the existing ERP literature suggesting that face-processing deficits in schizophrenia arise from early-stage deficits in visual processing, and that these may extend to non-face stimuli.

5.3 ERP Evidence of Impaired Visual Processing in Schizophrenia During Processing of Spatial Frequency-Filtered Emotional Facial Expressions- Summary

The impaired emotional expression recognition observed in schizophrenia has been suggested to be due to abnormalities in bottom-up processing at early stages of visual perception. Studies show that patients with schizophrenia have behavioural impairments in using low spatial frequency information in objects, faces and simple stimuli (Butler et al., 2005; Calderone et al., 2013; Martinez et al., 2008; O'Donnell et al., 2002; Martinez et al., 2012; Silverstein et al., 2010), suggesting general problems with the M-pathway. The goal of the second study presented in this thesis was to examine the relationship between visual pathway deficits and altered processing of facial expressions, including threatening ones, in patients with schizophrenia. This was done using both behavioural and ERP measures.

Group differences in response to spatial frequency (SF) filtered facial expressions emerged for N170 amplitudes and P300 mean activity– regardless of emotional expression and SF manipulation. Impairments to specific facial expressions and SF filters only emerged during the early P100 visual perceptual stage. As reported in Shah et al. (2018), these findings support suggestions of dysfunction beginning at earlier visual perception stage (Campanella et al., 2006; Foxe, Murray & Javitt, 2005), which then influences later face structural encoding – indexed by the N170- and to higher-order disturbance – as indexed by P300. Our findings suggest that impairments of emotional expression recognition in patients with schizophrenia (e.g., Kohler et al., 2010; Savla et al., 2012) may not be accounted for solely by deficits in the magnocellular-pathway (Butler & Javitt, 2005), as impairments were observed for BSF, LSF and HSF manipulated faces.

With respect the question of whether impairment was specific to faces or was also observed with non-face stimuli, we found smaller N170 amplitude and P300 mean activity in response to chair stimuli in patients with schizophrenia. This was true regardless of SF manipulation. Unlike for neutral faces, the P100 to chair stimulus was intact in the patient group for all three SFs. We interpreted these findings to suggest that smaller N170 amplitude and P300 mean activity observed for all facial expressions and SFs may be related to a more global impairment of visual processing, rather than a structural encoding deficit.

With respect to the question of whether impairments in P100 and N170 are more profound for LSF filtered threatening faces, evidence emerged during the early perceptual P100 stage. Smaller P100 amplitudes were observed in the patient group, relative to the controls, in response to unfiltered broad spatial frequency (BSF) sad and angry faces, low spatial frequency (LSF) filtered sad and fearful faces and high spatial frequency (HSF) neutral faces. In line with Kim et al. (2010)'s work, the present study found some evidence of greater impairment for LSF filtered threatening faces. Given P100 amplitude to HSF and BSF filtered fearful faces was intact in patients and that disturbance in P100 was observed for LSF filtered fearful faces, we concluded that there is evidence of more profound deficit in LSF filtered threatening information. This impairment in the M-pathway during processing of threatening information is not observed during the structural encoding – N170 and later higher-order decoding - P300 stages. The group differences that emerged for P100 differ from those that emerged for N170 and P300. This could be related to the suggestion that the pathways for the early processing of emotional content, reflected in the P100, and the later structural encoding of facial features, reflected in the N170, are dissociable (Pourtois et al., 2004; 2005; Vuilleumier et al., 2007).

We found different patterns of ERP responses in patients than in healthy controls to threatening facial expressions in LSF, HSF and BSF filtered condition. Patients showed larger P100 amplitudes to LSF filtered relative to BSF filtered angry faces, while the controls showed no difference in P100 amplitudes to LSF filtered relative to BSF filtered angry faces. No differences in P100 amplitude patterns within each group emerged for fearful expressions. Also, both groups showed HSF filtered threatening faces to produce smaller P100 amplitudes relative to LSF and BSF filtered ones. Patients showed larger N170 amplitudes for BSF and LSF fearful faces compared with HSF fearful faces, while controls showed larger N170 amplitudes between BSF and HSF fearful faces and no difference between LSF and HSF ones. Similarly, with angry facial expressions, the patient group showed larger N170 amplitude to LSF compared with HSF, while the control group did not show this difference. Although the between group data showed evidence of impaired visual deficits to LSF filtered threatening facial expressions, the within-group data suggests something different. The present study, contrary to findings from Obayashi et al (2009), found equivalence in P100 activity between BSF and LSF filtered fearful facial expressions and larger amplitude to LSF relative to BSF filtered angry facial expressions within the patient group. These findings suggest a bias for higher response to LSF information in patients (Laprevote et al., 2010).

The heightened response to LSF threatening information, relative to BSF information, in the patient group implies that our sample may use SF information in a different manner than controls, which could account for the deficits observed in later high-order facial recognition. We propose that patients may be using coarse visual-spatial information to make decisions regarding faces, rather than fine details. This in turn contributes to their difficulties with facial processing. Our suggestion is in line with behavioural results from Laprevote et al (2010), who found that

patients, relative to controls, focused preferentially on the LSF components of the image. The authors found accurate responses to HSF information. They suggested that patients may need a longer duration of time to process LSF information, which prevents them from concurrently perceiving LSF and HSF information (Laprevote et al., 2010).

Our findings add to the limited extant literature on ERP and SF-manipulation with this patient group. The present study demonstrated a general impairment in processing faces and chair images, regardless of emotional expression and SF-manipulation, beginning at the structural face encoding stage. Disruption in specific emotional expressions and SF-manipulation was observed during the earlier visual processing stage. During the same earlier visual processing stage and for the structural face encoding stages, patients showed heightened response to LSF threatening information, whereas controls did not. Our results imply that patients may not use spatial frequency information, specifically LSFs, for processing threatening information in the same manner as controls, which in turn could be contributing to the observed difficulties in face and emotional processing, and in turn impairment in social functioning. Further work is required to determine the mechanisms involved in integrating LSF and HSF information in this patient population.

5.4 Investigation of Emotional Expression Processing Following Cognitive Behavioural Therapy for Patients with Schizophrenia: An Event-related Potentials Study- Summary

Our previous work (Shah et al., 2018) showed impaired ERP responses to facial expressions in schizophrenia patients who experience auditory verbal hallucinations. We showed that the impacts of experiencing auditory hallucinations also affects visual processing (Bruder et al., 2011; van Lutterveld et al., 2011), including face processing. The aim of the last study presented in this thesis was to explore, for the first time, any neural changes following cognitive

behavioural therapy for voices (CBTv) in patients with persistent and distressing auditory verbal hallucinations. This was done by testing whether ERPs elicited by facial expressions were altered in patients following completion of CBTv.

Following CBTv, shorter P100 latency was observed in response to facial expressions than at baseline. The control patient group (the treatment as usual only group) did not show change in P100 latency following the same pre – post period. No changes in N170 or P300 following CBTv were observed.

Auditory verbal hallucinations are thought to be related to attentional processing and excessive focus on internal stimuli. The CBTv protocol used in the study included attention training as well as acceptance and commitment therapy interventions to target the attention and attribution to auditory verbal hallucinations experienced by the patient group. These intervention were integrated with CBT intervention to reduce emotional salience and distress associated with hearing voices. In turn, reduced focus on internal stimuli (voices) and increased focus on external stimuli (Ensum & Morrison, 2003; Morrison & Haddock, 1997) were expected to positively impact cognitive and social functioning.

The P100 is believed to reflect early-stage visual information processing (Luck et al., 1994; Santesso et al., 2008) and early preconscious direction of attention (Lee et al., 2011; Pizzagalli et al., 2002; Turetsky et al., 2007; Turetsky et al., 2008; Utama et al., 2009). Our study is the first to show a change in P100 latency following a course of group CBTv treatment in patients with schizophrenia, suggesting an improvement in efficiency in earlier stages of visual information processing speed. Given the lack of knowledge about the neural mechanism that underlie benefits of CBT (Birchwood et al., 2014) for patients with schizophrenia, assessing

ERPs changes following treatment may prove to be useful in understanding the varying clinical responses and future work should continue to assess this.

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APPENDICES:

APPENDIX A: Global Assessment of Functioning (GAF)

Global Assessment of Functioning (GAF) Scale

(From DSM-IV-TR, p. 34.)

Consider psychological, social, and occupational functioning on a hypothetical continuum of mental health-illness. Do not include impairment in functioning due to physical (or environmental) limitations.

Code	(Note: Use intermediate codes when appropriate, e.g., 45, 68, 72.)
100 91	Superior functioning in a wide range of activities, life's problems never seem to get out of hand, is sought out by others because of his or her many positive qualities. No symptoms.
90 81	Absent or minimal symptoms (e.g., mild anxiety before an exam), good functioning in all areas, interested and involved in a wide range of activities, socially effective, generally satisfied with life, no more than everyday problems or concerns (e.g. an occasional argument with family members).
80 71	If symptoms are present, they are transient and expectable reactions to psychosocial stressors (e.g., difficulty concentrating after family argument); no more than slight impairment in social, occupational or school functioning (e.g., temporarily failing behind in schoolwork).
70 61	Some mild symptoms (e.g. depressed mood and mild insomnia) OR some difficulty in social, occupational, or school functioning (e.g., occasional truancy, or theft within the household), but generally functioning pretty well, has some meaningful interpersonal relationships.
60 51	Moderate symptoms (e.g., flat affect and circumstantial speech, occasional panic attacks) OR moderate difficulty in social, occupational, or school functioning (e.g., few friends, conflicts with peers or co-workers).
50 41	Serious symptoms (e.g., suicidal ideation, severe obsessional rituals, frequent shoplifting) OR any serious impairment in social, occupational, or school functioning (e.g., no friends, unable to keep a job).
40 31	Some impairment in reality testing or communication (e.g., speech is at times illogical, obscure, or irrelevant) OR major impairment in several areas, such as work or school, family relations, judgment, thinking, or mood (e.g., depressed man avoids friends, neglects family, and is unable to work; child frequently beats up younger children, is defiant at home, and is failing at school).
30 21	Behavior is considerably influenced by delusions or hallucinations OR serious impairment in communication or judgment (e.g., sometimes incoherent, acts grossly inappropriately, suicidal preoccupation) OR inability to function in almost all areas (e.g., stays in bed all day; no job, home, or friends).
20 11	Some danger of hurting self or others (e.g., suicide attempts without clear expectation of death; frequently violent; manic excitement) OR occasionally fails to maintain minimal personal hygiene (e.g., smears feces) OR gross impairment in communication (e.g., largely incoherent or mute).
10 1 0	Persistent danger of severely hurting self or others (e.g., recurrent violence) OR persistent inability to maintain minimal personal hygiene OR serious suicidal act with clear expectation of death. Inadequate information.

APPENDIX B: Positive and Negative Syndrome Scale

Date Rated: _____ Time Rated: _____ Rater's Initials: ____/____/____
 (m/d/y) (24 hr clock)

POSITIVE AND NEGATIVE SYNDROME SCALE (PANSS)

Directions: Check (✓) the term for each symptom which best describes the patient's condition over the past 72 hours and not relative to any other time.

POSITIVE SCALE

Symptom		Description						
		Absent	Very Mild	Mild	Moderate	Mod. Severe	Severe	Extreme
1	Delusions	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
2	Conceptual Disorganization	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
3	Hallucinatory Behaviour	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
4	Excitement	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
5	Grandiosity	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
6	Suspiciousness/Persecution	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
7	Hostility	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐

NEGATIVE SCALE

Symptom		Description						
		Absent	Very Mild	Mild	Moderate	Mod. Severe	Severe	Extreme
1	Blunted Affect	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
2	Emotional Withdrawal	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
3	Poor Rapport	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
4	Passive/ apathetic social withdrawal	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
5	Difficulty in abstract thinking	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
6	Lack of spontaneity and flow of conversation	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐

7	Stereotyped Thinking	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
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POSITIVE AND NEGATIVE SYNDROME SCALE (PANSS) – Continued*
GENERAL PSYCHOPATHOLOGY SCALE

Symptom		Description						
		Absent	Very Mild	Mild	Moderate	Mod. Severe	Severe	Extreme
1	Somatic Concern	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
2	Anxiety	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
3	Guilt Feelings	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
4	Tension	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
5	Mannerisms and Posturing	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
6	Depression	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
7	Motor Retardation	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
8	Uncooperativeness	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
9	Unusual Thought Content	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
10	Disorientation	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
11	Poor Attention	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
12	Lack of Judgement and Insight	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
13	Disturbance of Volition	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
14	Poor Impulse Control	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
15	Preoccupation	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
16	Active Social Avoidance	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐

*Refer to symptom definitions in the Rating Scales Procedures Manual.

APPENDIX C: SCID Adapted Screening Questionnaire

CBTv Study

Date: _____

ID: _____

Session: _____

SCID-Adapted Screening Questions

- Have you ever sought treatment or been treated for emotional or psychiatric problems?

NO YES: _____

If YES: What for? Did you obtain any treatment?

-
- Have you ever sought treatment or been treated for drug or alcohol abuse?

NO YES: _____

What is your daily (or weekly) alcohol consumption?

-
- Do you use street drugs? (e.g. marijuana, cocaine)

NO YES: _____

If YES: What kind(s)? How Often?

MOOD EPISODES

Depressive

- Has there been a period of time when you were feeling depressed or down most of the day nearly, every day?

NO YES: _____

- ...what about losing interest or pleasure in things you usually enjoy?

NO YES: _____

(Skip the following if NO)

If YES: How long did this period last? _____

If YES: Just before this began were you: Physically ill? Drinking alcohol or using street drugs? Did this begin soon after someone close to you died?

NO YES: _____

Manic

- Has there been a period of time when you were feeling so good, excited, or hyper that other people thought you were not your normal self or you were so hyper that you got into trouble?
NO YES: _____
-

(Skip the following if NO)

If YES: How long did this period last? _____

If YES: Just before this began were you: Physically ill? Drinking alcohol or using street drugs?

NO YES: _____

ANXIETY DISORDERS

Panic

- Have you ever had a panic attack, when you suddenly felt frightened or suddenly developed a lot of physical symptoms?
NO YES: _____
-

(Skip the following if NO)

If YES: Have these attacks ever come on completely out of the blue – in situations where you don't expect to be nervous or uncomfortable?

NO YES: _____

If YES: Just before you began having panic attacks, were you: Taking any drugs, caffeine, diet pills, or any other medications? Physically ill?

NO YES: _____

Agoraphobia

- Were you ever afraid of going out of the house alone, being in crowds, standing in a line or traveling on buses or trains?
NO YES: _____
-

(Skip the following if NO)

If YES: What were you afraid would happen?

Does participant mention anxiety about being in place/situation from escape may be difficult or embarrassing or in which help may not be available in the event of panic-like symptoms?

NO YES: _____

If YES: Just before you began having these fears, were you: Taking any drugs, caffeine, diet pills, or any other medications? Physically ill?

NO YES: _____

Social Phobia

- Is there anything that you have been afraid to do or felt uncomfortable doing in front of other people, like speaking, eating or writing?

NO YES: _____

(Skip the following if NO)

If YES to “Public Speaking”: Do you think that you are more uncomfortable than most people who are in a similar situation?

NO YES: _____

If YES: What were you afraid would happen?

Does participant mention that exposure to the feared social situation almost invariably provokes anxiety, which may take the form of a situationally bound or situationally predisposed panic-attack?

NO YES: _____

If YES: Just before you began having these fears, were you: Taking any drugs, caffeine, diet pills, or any other medications? Physically ill?

NO YES: _____

GAD

- In the last six months, have you been particularly nervous or anxious?

NO YES: _____

=

(Skip the following if NO)

If YES: What do you worry about?

- During the past six months, would you say that you are worrying more often than not?

NO YES: _____

- When you are worrying, do you find it difficult to stop?

NO YES: _____

- When you're feeling anxious or nervous, do you feel:

___ Restless ___ Frequently tired ___ Trouble concentrating/Mind goes blank ___ Irritable

___ Tense muscles ___ Sleep disturbance

(3 of the above must be present)

PSYCHOTIC SYMPTOMS

Delusions

- Has it ever seemed like people were talking about you or taking special notice of you?

NO YES: _____

(Skip the following if NO)

If YES: Were you convinced they were talking about you or did you think it might have been your imagination?

NO YES: _____

- What about receiving special messages from the TV, radio, or newspaper, or from the way things were arranged around you?

NO YES: _____

- What about anyone going out of their way to give you a hard time, or trying to hurt you?

NO YES: _____

- Did you ever feel that you were especially important in some way, or that you had special powers to do things that other people couldn't do?

NO YES: _____

- Did you ever feel that someone or something outside yourself was controlling your thoughts or actions against you will?

NO YES: _____

Auditory Hallucinations

- Did you ever hear things that other people couldn't hear, such as noises, or the voices of people whispering or talking? (Were you awake at the time?)

NO YES: _____

(Skip the following if NO)

If YES: What did you hear? How often did you hear it?

If VOICES: Did they comment on what you were doing or thinking? _____

How many voices did you hear? Were they talking to each other? _____

Visual Hallucinations

- Did you ever have visions or see things that other people couldn't see? (Were you awake at the time?)

NO YES: _____

Other Symptoms

(The following items are rated based on observations)

Catatonic behaviour, Grossly disorganized behaviour, Grossly inappropriate affect or Disorganized speech

NO YES: _____

Affective flattening

NO YES: _____

ALCOHOL AND DRUG USE

Alcohol use

- Has there been any time in your life when you had five or more drinks (beer, wine, or liquor) on one occasion?

NO YES: _____

(Skip the following if NO)

If YES:

- What are your drinking habits like? (How much do you drink?)

- When in your life were you drinking the most? (How long did that period last?)
Record date of heaviest use and describe pattern : _____

During that time...

- How often were you drinking? _____
- What were you drinking? How much? _____
- Did your drinking cause problems for you? _____
- Did anyone object to your drinking? _____

If alcohol dependence seems likely, then participant CAN NOT participate in this study

Drug and medicine use

- Have you ever used street drugs?
NO YES: _____
- Have you ever gotten “hooked” on a prescribed medicine or taken a lot more of it than you were supposed to?
NO YES: _____

(Skip the following if NO)

If YES:

Guidelines for rating level of drug and medicine use:

Street Drug:

- When were you using (DRUG) the most? _____
- Has there been a time when you used it at least ten times in a one-month period of time?

(1) has ever taken street drug more than 10 times in a one-month period

Prescribed Medicine:

(2) reports becoming dependent on a prescribed drug OR using much more of it than was prescribed

- If drug group never used or used only once, or if prescribed drug used as directed → circle “1”

- If drug used at least twice, but less than level indicated on (1) → circle “2”
- If drug used at level indicated in item (1) or if possibly dependent on prescribed drug (item (2) is true) → circle “3”

Drug list:

Circle the name of each drug ever used (or write in name if other)	Period of heaviest use (age or date, and duration) and describe pattern of use	Level of use
Sedatives - hypnotics – anxiolytics: Quaalude, Seconal, Valium, Xanax, Librium, barbiturates, Miltown, Ativan, Dalmane, Halcion, Restoril, or other :	_____ _____ _____	1 2 3
Cannabis: marijuana, hashish , THC, or other: _____	_____ _____ _____	1 2 3
Stimulants: amphetamine, “speed”, crystal meth, dexadrine, Ritalin, “ice”, or other: _____	_____ _____ _____	1 2 3
Opioids: heroin, morphine, opium, Methadone, Darvon, codein, Percodan, Demerol, Dilaudid, unspecified or other:	_____ _____ _____	1 2 3
Cocaine: intranasal, IV, freebase, crack, “speedball”, unspecified or other:	_____ _____ _____	1 2 3
Hallucinogens/PCP: LSD, mescaline, peyote, psilocybin, STP, mushrooms, PCP (“angel dust”), Extasy, MDMA, or other: _____	_____ _____ _____	1 2 3
Other: steroids, “glue”, paint, inhalants, nitrous oxide (“laughing gas”), amyl or butyl nitrate (“popers”), nonprescription sleep or diet pills, unknown, or other:	_____ _____ _____	1 2 3

APPENDIX D : Beck Depression Inventory (II) questionnaire

1. Sadness:

- 0 I do not feel sad.
- 1 I feel sad much of the time.
- 2 I feel sad all the time.
- 3 I am so sad or unhappy that I can't stand it.

2. Pessimism:

- 0 I am not discouraged about my future.
- 1 I feel more discouraged about my future than I used to be.
- 2 I do not expect things to work out for me.
- 3 I feel my future is hopeless and will only get worse.

3. Past Failure:

- 0 I do not feel like a failure.
- 1 I have failed more than I should have.
- 2 As I look back, I see a lot of failures.
- 3 I feel I am a total failure as a person.

4. Loss of Pleasure:

- 0 I get as much pleasure as I ever did from the things I enjoy.
- 1 I don't enjoy things as much as I used to.
- 2 I get very little pleasure from the things I used to enjoy.
- 3 I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings:

- 0 I don't feel particularly guilty.
- 1 I feel guilty over many things I have done or should have done.
- 2 I feel guilty most of the time.
- 3 I feel guilty all the time.

6. Punishment Feelings:

- 0 I don't feel I am being punished.
- 1 I feel I may be punished.
- 2 I expect to be punished.
- 3 I feel I am being punished.

7. Self-Dislike:

- 0 I feel the same about myself as ever.
- 1 I have lost confidence in myself.
- 2 I am disappointed in myself.
- 3 I dislike myself.

8. Self-Criticalness:

- 0 I don't criticize or blame myself more than usual.
- 1 I am more critical of myself than I used to be.
- 2 I criticize myself for all of my faults.
- 3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes:

- 0 I don't have any thoughts of killing myself.
- 1 I have thoughts of killing myself, but I would not carry them out.
- 2 I would like to kill myself.
- 3 I would kill myself if I had the chance.

10. Crying:

- 0 I don't cry anymore than I used to.
- 1 I cry more than I used to.
- 2 I cry over every little thing.
- 3 I feel like crying, but I can't.

11. Agitation:

- 0 I am no more restless or wound up than usual.
- 1 I feel more restless or wound up than usual.
- 2 I am so restless or agitated that it's hard to stay still.
- 3 I am so restless or agitated that I have to keep moving or doing something.

13. Indecisiveness:

- 0 I make decisions about as well as ever.
- 1 I find it more difficult to make decisions than usual.
- 2 I have much greater difficulty in making decisions than I used to.
- 3 I have trouble making any decisions.

14. Worthlessness:

- 0 I do not feel I am worthless.
- 1 I don't consider myself as worthwhile and useful as I used to.
- 2 I feel more worthless as compared to other people.
- 3 I feel utterly worthless.

15. Loss of Energy:

- 0 I have as much energy as ever.
- 1 I have less energy than I used to have.
- 2 I don't have enough energy to do very much.
- 3 I don't have enough energy to do anything.

16. Changes in Sleeping Pattern:

0 I have not experienced any change in my sleeping pattern.

1a I sleep somewhat more than usual.

1b I sleep somewhat less than usual.

2a I sleep a lot more than usual.

2b I sleep a lot less than usual.

3a I sleep most of the day.

3b I wake up 1-2 hours early and can't get back to sleep.

17. Irritability:

0 I am no more irritable than usual.

1 I am more irritable than usual.

2 I am much more irritable than usual.

3 I am irritable all the time.

18. Changes in Appetite:

0 I have not experienced any changes in my appetite.

1a My appetite is somewhat less than usual.

1b My appetite is somewhat greater than usual.

2a My appetite is much less than before.

2b My appetite is much greater than usual.

3a I have no appetite at all.

3b I crave food all the time.

19. Concentration Difficulty:

0 I can concentrate as well as ever.

1 I can't concentrate as well as usual.

2 It's hard to keep my mind on anything for very long.

3 I find I can't concentrate on anything.

20. Tiredness or Fatigue:

0 I am no more tired or fatigued than usual.

1 I get more tired or fatigued more easily than usual.

2 I am too tired or fatigued to do a lot of the things I used to do.

3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex:

0 I have not noticed any recent change in my interest in sex.

1 I am less interested in sex than I used to be.

2 I am much less interested in sex now.

3 I have lost interest in sex completely.

Total____(sum)

APPENDIX E: Beck Anxiety Inventory questionnaire

Below is a list of common symptoms of anxiety. Please carefully read each item in the list. Indicate how much you have been bothered by that symptom during the past month, including today, by circling the number in the corresponding space in the column next to each symptom. **Please leave column sums and scoring blank.**

	Not At All	Mildly but it didn't bother me much.	Moderately - it wasn't pleasant at times	Severely – it bothered me a lot
Numbness or tingling	0	1	2	3
Feeling hot	0	1	2	3
Wobbliness in legs	0	1	2	3
Unable to relax	0	1	2	3
Fear of worst happening	0	1	2	3
Dizzy or lightheaded	0	1	2	3
Heart pounding/racing	0	1	2	3
Unsteady	0	1	2	3
Terrified or afraid	0	1	2	3
Nervous	0	1	2	3
Feeling of choking	0	1	2	3
Hands trembling	0	1	2	3
Shaky / unsteady	0	1	2	3
Fear of losing control	0	1	2	3
Difficulty in breathing	0	1	2	3
Fear of dying	0	1	2	3
Scared	0	1	2	3
Indigestion	0	1	2	3
Faint / lightheaded	0	1	2	3
Face flushed	0	1	2	3
Hot/cold sweats	0	1	2	3
Column Sum				

Scoring - Sum each column. Then sum the column totals to achieve a grand score. Write that score here _____.

APPENDIX F: Psychotic Symptom Rating Scales –Auditory Hallucinations Scale

PSYRATS

Please rate the degree of your hallucinations.

ID: _____

Date: _____

A. Auditory Hallucinations

1. Frequency

- | | |
|---|---|
| Voices not present or present less than once a week | 0 |
| Voices occur at least once a week | 1 |
| Voices occur at least once a day | 2 |
| Voices occur at least once an hour | 3 |
| Voices occur continuously or almost continuously | 4 |

2. Duration

- | | |
|--|---|
| Voices not present | 0 |
| Voices last for a few seconds, fleeting voices | 1 |
| Voices last for several minutes | 2 |
| Voices last for at least one hour | 3 |
| Voices last for hours at a time | 4 |

3. Location

- | | |
|--|---|
| No voices present | 0 |
| Voices sound like they are inside head only | 1 |
| Voices outside the head, but close to ears or head | 2 |
| Voices inside head may also be present | |
| Voices sound like they are inside or close to ears and outside head away from ears | 3 |
| Voices sound like they are outside the head only | 4 |

4. Loudness

- | | |
|--------------------------------------|---|
| Voices not present | 0 |
| Quieter than own voice, whispers | 1 |
| About the same loudness as own voice | 2 |
| Louder than own voice | 3 |
| Extremely loud, shouting | 4 |

5. Beliefs re: origin of voices

Voices not present	0
Believes voices to be solely internally generated and related to self	1
Holds <50% conviction that voices originate from external causes	2
Holds >50% (but <100%) conviction that voices originate from external causes	3
Believes voices are solely due to external causes	4

6. Amount of negative content of voices

No unpleasant content	0
Occasional unpleasant content (<10%)	1
Minority of voice content is unpleasant or Negative (<50%)	2
Majority of voice content is unpleasant or Negative (>50%)	3
All of the voice content is unpleasant or negative	4

7. Degree of negative control

Not unpleasant or negative	0
Some degree or negative content, but not personal comments relating to self or family	1
Personal verbal abuse, comments on behaviour	2
Personal verbal abuse relating to self-concept	3
Personal threats to self (threats to harm self or family, extreme instructions, commands to harm self or others)	4

8. Amount of distress

Voices not distressing at all	0
Voices occasionally distressing, majority not distressing (<10%)	1
Minority of voices distressing (<50%)	2
Majority of voices distressing, minority not distressing (>50%)	3
Voices always distressing	4

9. Intensity of distress

Voices not distressing at all	0
Voices slightly distressing	1
Voices are distressing to a moderate degree	2
Voices are very distressing, although subject could feel worse	3
Voices are extremely distressing, feel the worst he/she could possibly feel	4

10. Disruption to life caused by voices

No disruption to life, able to maintain social/family relationships (if present)	0
Voices cause minimal amount of disruption to life	1
Voices cause moderate amount of disruption to life causing some disturbance to daytime activity and/or family and social activities.	2
Voices cause severe disruption to life so that hospitalization is usually necessary.	3
Voices cause complete disruption of daily life requiring hospitalization.	4

11. Controllability of voices

Subject believes they can have control over the voices and can always bring on or dismiss the voices at will.	0
Subject believes they can have some control over the voices on the majority of occasions	1
Subject believes they can have some control over the voices approximately half the time	2
Subject believes they can have some control over the voices, but only occasionally. The majority of the time the subject experiences voices that are uncontrollable.	3
Subject has no control over when the voices occur and cannot dismiss or bring them on at all.	4

APPENDIX G: Supplementary Information for Study 1: ANOVA tables for all analyses

ANOVA tables for all analyses

The ANOVA tables include the original degrees of freedom (*df*), epsilon (ϵ), *F* value, effect size and epsilon-corrected *p* values to compensate for violations of sphericity.

Table 1. Analysis of variance (ANOVA) of accuracy scores with group (schizophrenia patients and control group) as the between subjects factor and emotion category (neutral faces, fearful, joyful, sad, angry).

Source	<i>df</i>	ϵ	<i>F</i>	<i>np</i> ²	<i>p</i>
Group	1	-	4.085	0.093	0.050
Error (Group)	40	-			
Condition (Con)	4	0.587	14.30	0.263	0.000
Group x condition	4	0.587	0.409	0.010	0.698
Error (Con)	160	0.587			

Table 2. Analysis of variance (ANOVA) of response time scores with group (schizophrenia patients and control group) as the between subjects factor and emotion category (neutral faces, fearful, joyful, sad, angry).

Source	<i>df</i>	<i>ε</i>	<i>F</i>	<i>np²</i>	<i>p</i>
Group	1	-	17.291	.302	.000
Error (Group)	40	-			
Condition (Con)	4	0.774	2.810	.066	.041
Group x Condition	4	0.774	1.102	.027	.352
Error (Con)	160	0.774			

Table 3. Analysis of variance (ANOVA) of P100 amplitude with group (schizophrenia patients and control group) as the between subjects factor and emotion category (fearful, joyful, sad, angry and neutral faces), site (parietal, occipital) and hemisphere (left, right) as within-subjects factors.

Source	<i>df</i>	ε	<i>F</i>	<i>np</i> ²	<i>p</i>
Group	1	-	.312	.008	.579
Error (Group)	40	-			
Site (Site)	1	-	.190	.005	.665
Site x Group	1	-	.577	.014	.452
Error (Site)	40	-			
Hemisphere (Hem)	1	-	.574	.014	.453
Hemisphere x Group	1	-	.280	.007	.600
Error (Hem)	40	-			
Condition (Con)	4	-	.674	.017	.586
Group x Condition	4	-	3.568	.082	.012
Error (Con)	160	-			
Site x Hemisphere	1	-	5.571	.122	.023
Hemisphere x Site x Group	1	-	.072	.002	.789
Error (Hem x Site)	40	-			
Site x Condition	4	0.770	4.337	.098	.006
Site x Condition x Group	4	0.770	1.770	.042	.155
Error (Site x Con)	160	0.770			
Hemisphere x Condition	4	-	1.220	.030	.305
Hemisphere x Condition x Group	4	-	.552	.014	.698
Error (Hem x Con)	160	-			
Hemisphere x Site x Condition	4	-	1.057	.026	.380
Hemisphere x Site x Condition x Group	4	-	1.120	.027	.347
Error (Hem x Site x Con)	160	-			

Table 4. Analysis of variance (ANOVA) of P100 amplitude with group (schizophrenia patients and control group) as the between subjects factor and stimulus type (chair, faces [emotional expression pooled]), site (parietal, occipital) and hemisphere (left, right) as within-subjects factors.

Source	<i>df</i>	ϵ	<i>F</i>	<i>np</i> ²	<i>p</i>
Group	1	-	.161	.004	.690
Error (Group)	40	-			
Site (Site)	1	-	.881	.022	.353
Site x Group	1	-	.134	.003	.716
Error (Site)	40	-			
Hemisphere (Hem)	1	-	.121	.003	.729
Hemisphere x Group	1	-	.043	.001	.836
Error (Hem)	40	-			
Condition (Con)	1	-	10.760	.212	.002
Group x Condition	1	-	1.245	.030	.271
Error (Con)	40	-			
Site x Hemisphere	1	-	4.552	.102	.039
Hemisphere x Site x Group	1	-	.731	.018	.398
Error (Hem x Site)	40	-			
Site x Condition	1	-	14.383	.264	.000
Site x Condition x Group	1	-	10.097	.202	.003
Error (Site x Con)	40	-			
Hemisphere x Condition	1	-	.657	.016	.423
Hemisphere x Condition x Group	1	-	.408	.010	.527
Error (Hem x Con)	40	-			
Hemisphere x Site x Condition	1	-	.147	.004	.704
Hemisphere x Site x Condition x Group	1	-	5.830	.127	.020
Error (Hem x Site x Con)	40	-			

Table 5. Analysis of variance (ANOVA) of N170 amplitude effect with group (schizophrenia patients and control group) as the between subjects factor and condition (neutral faces and chairs) and hemisphere (left, right) as within-subjects factors.

Source	<i>df</i>	ϵ	<i>F</i>	<i>np</i> ²	<i>p</i>
Group	1	-	3.074	.071	.087
Error (Group)	40	-			
Hemisphere (Hem)	1	-	8.034	.167	.007
Hemisphere x Group	1	-	.603	.015	.442
Error (Hem)	40	-			
Condition (Con)	1	-	35.604	.471	.000
Group x Condition	2	-	.184	.005	.670
Error (Con)	40	-			
Hemisphere x Condition	1	-	.619	.015	.436
Hemisphere x Condition x Group	1	-	.102	.003	.751
Error (Hem x Con)	40	-			

Table 6. Analysis of variance (ANOVA) of N170 amplitude with group (schizophrenia patients and control group) as the between subjects factor and emotion category (fearful, joyful, sad, angry and neutral faces), and hemisphere (left, right) as within-subjects factors.

Source	<i>df</i>	<i>ε</i>	<i>F</i>	<i>np</i> ²	<i>p</i>
Group	1	-	2.472	.058	.124
Error (Group)	40	-			
Hemisphere (Hem)	1	-	6.094	.132	.018
Hemisphere x Group	1	-	.408	.010	.526
Error (Hem)	40	-			
Condition (Con)	4	0.803	2.253	.053	.081
Group x Condition	4	0.803	1.413	.034	.240
Error (Con)	160	0.803			
Hemisphere x Condition	4	-	.784	.019	.522
Hemisphere x Condition x Group	4	-	.117	.003	.965
Error (Hem x Con)	160	-			

Table 7. Analysis of variance (ANOVA) of N170 amplitude with group (schizophrenia patients and control group) as the between subjects factor and stimulus type (chair, faces [emotional expression pooled]), and hemisphere (left, right) as within-subjects factors.

Source	<i>df</i>	<i>ε</i>	<i>F</i>	<i>np</i> ²	<i>p</i>
Group	1	-	3.582	.082	.066
Error (Group)	40	-			
Hemisphere (Hem)	1	-	8.309	.172	.006
Hemisphere x Group	1	-	.525	.013	.473
Error (Hem)	40	-			
Condition (Con)	1	-	49.873	.555	.000
Group x Condition	1	-	.030	.001	.863
Error (Con)	40	-			
Hemisphere x Condition	1	-	.892	.022	.351
Hemisphere x Condition x Group	1	-	.075	.002	.785
Error (Hem x Con)	40	-			

Table 8. Analysis of variance (ANOVA) of P100-N170 amplitude difference with group (schizophrenia patients and control group) as the between subjects factor and emotion category (fearful, joyful, sad, angry, neutral) and hemisphere (left, right) as within-subjects factor.

Source	<i>df</i>	ϵ	<i>F</i>	<i>np</i> ²	<i>p</i>
Group	1	-	1.785	.043	.189
Error (Group)	40	-			
Hemisphere (Hem)	1	-	8.492	.175	.006
Hemisphere x Group	1	-	.168	.004	.684
Error (Hem)	40	-			
Condition (Con)	4	-	2.030	.048	.093
Group x Condition	4	-	.993	.024	.413
Error (Con)	160	-			
Hemisphere x Condition	4	0.699	.816	.020	.516
Hemisphere x Condition x Group	4	0.699	.344	.009	.779
Error (Hem x Con)	160	0.699			

Table 9. Analysis of variance (ANOVA) of P1-N170 amplitude difference with group (schizophrenia patients and control group) as the between subjects factor and stimulus type (chair, faces [emotional expression pooled]), and hemisphere (left, right) as within-subjects factors.

Source	<i>df</i>	ϵ	<i>F</i>	<i>np</i> ²	<i>p</i>
Group	1	-	3.226	.075	.080
Error (Group)	40	-			
Hemisphere (Hem)	1	-	10.285	.205	.003
Hemisphere x Group	1	-	.649	.016	.425
Error (Hem)	40	-			
Condition (Con)	1	-	45.645	.533	.000
Group x Condition	1	-	.367	.009	.548
Error (Con)	40	-			
Hemisphere x Condition	1	-	1.520	.037	.225
Hemisphere x Condition x Group	1	-	.183	.005	.671
Error (Hem x Con)	40	-			

Table 10. Analysis of variance (ANOVA) of P300 mean activity with group (schizophrenia patients and control group) as the between subjects factor and emotion category (fearful, joyful, sad, angry, neutral) as within-subjects factor.

Source	<i>df</i>	ε	<i>F</i>	<i>np</i> ²	<i>p</i>
Group	1	-	6.216	.134	.017
Error (Group)	40	-			
Condition (Con)	4	-	6.532	.140	.000
Group x Condition	4	-	.173	.004	.952
Error (Con)	160	-			

Table 11. Analysis of variance (ANOVA) of P300 mean amplitude with group (schizophrenia patients and control group) as the between subjects factor and stimulus type (chair, faces [emotional expressions pooled]) as within-subjects factor.

Source	<i>df</i>	<i>ε</i>	<i>F</i>	<i>np²</i>	<i>p</i>
Group	1	-	6.356	.137	.016
Error (Group)	40	-			
Condition (Con)	1	-	49.517	.553	.000
Group x Condition	1	-	.020	.001	.887
Error (Con)	40	-			

Table 12. Analysis of variance (ANOVA) of P100 amplitude within the patient group with emotion category (fearful, joyful, sad, angry and neutral), site (parietal, occipital) and hemisphere (left, right) as within-subjects factors.

Source	<i>df</i>	<i>ε</i>	<i>F</i>	<i>np²</i>	<i>p</i>
Site (Site)	1	-	.057	.003	.813
Error (Site)	22	-			
Hemisphere (Hem)	1	-	.737	.032	.400
Error (Hem)	22	-			
Condition (Con)	4	-	1.287	.055	.281
Error (Con)	88	-			
Hemisphere x Site	1	-	3.384	.133	.079
Error (Hem x Site)	22	-			
Site x Condition	4	-	1.203	.052	.315
Error (Site x Con)	88	-			
Hemisphere x Condition	4	-	.391	.017	.814
Error (Hem x Con)	88	-			
Hemisphere x Site x Condition	4	-	.381	.017	.821
Error (Hem x Site x Con)	88	-			

Table 13. Analysis of variance (ANOVA) of P100 amplitude within the control group with emotion category (fearful, joyful, sad, angry and neutral), site (parietal, occipital) and hemisphere (left, right) as within-subjects factors.

Source	<i>df</i>	<i>ε</i>	<i>F</i>	<i>np²</i>	<i>p</i>
Site (Site)	1	-	.666	.036	.425
Error (Site)	18	-			
Hemisphere (Hem)	1	-	.034	.002	.856
Error (Hem)	18	-			
Condition (Con)	4	0.655	3.264	.154	.035
Error (Con)	72	0.655			
Hemisphere x Site	1	-	2.339	.115	.144
Error (Hem x Site)	18	-			
Site x Condition	4	0.618	4.806	.211	.009
Error (Site x Con)	72	0.618			
Hemisphere x Condition	4	-	1.381	.071	.249
Error (Hem x Con)	72	-			
Hemisphere x Site x Condition	4	-	2.442	.199	.054
Error (Hem x Site x Con)	72	-			

Table 14. Analysis of variance (ANOVA) of N170 amplitude within the patient group with emotion category (fearful, joyful, sad, angry and neutral), and hemisphere (left, right) as within-subjects factors.

Source	<i>df</i>	ε	<i>F</i>	<i>np</i> ²	<i>p</i>
Hemisphere (Hem)	1	-	3.578	.140	.072
Error (Hem)	22	-			
Condition (Con)	4	0.660	.645	.029	.570
Error (Con)	88	0.800			
Hemisphere x Condition	4	-	.291	.013	.883
Error (Hem x Con)	88	-			

Table 15. Analysis of variance (ANOVA) of N170 amplitude within the control group with emotion category (fearful, joyful, sad, angry and neutral), and hemisphere (left, right) as within-subjects factors.

Source	<i>df</i>	<i>ε</i>	<i>F</i>	<i>np²</i>	<i>p</i>
Hemisphere (Hem)	1	-	2.772	.133	.113
Error (Hem)	18	-			
Condition (Con)	4	-	4.667	.206	.002
Error (Con)	72	-			
Hemisphere x Condition	4	-	.600	.032	.664
Error (Hem x Con)	72	-			

Table 16. Analysis of variance (ANOVA) of P100-N170 amplitude difference within the patient group with emotion category n (fearful, joyful, sad, angry and neutral), and hemisphere (left, right) as within-subjects factors.

Source	<i>df</i>	<i>ε</i>	<i>F</i>	<i>np²</i>	<i>p</i>
Hemisphere (Hem)	1	-	6.350	.224	.019
Error (Hem)	22	-			
Condition (Con)	4	-	.608	.027	.658
Error (Con)	88	-			
Hemisphere x Condition	4	0.745	.460	.020	.710
Error (Hem x Con)	88	0.745			

Table 17. Analysis of variance (ANOVA) of P100-N170 amplitude difference within the control group with emotion category (fearful, joyful, sad, angry and neutral), and hemisphere (left, right) as within-subjects factors.

Source	<i>df</i>	<i>ε</i>	<i>F</i>	<i>np²</i>	<i>p</i>
Hemisphere (Hem)	1	-	3.244	.153	.08
Error (Hem)	18	-			
Condition (Con)	4	-	3.114	.147	.032
Error (Con)	72	-			
Hemisphere x Condition	4	0.439	.670	.036	.500
Error (Hem x Con)	72	0.439			

Table 18. Analysis of variance (ANOVA) of P300 mean activity within the patient group with emotion category (fearful, joyful, sad, angry and neutral).

Source	<i>df</i>	<i>ε</i>	<i>F</i>	<i>np²</i>	<i>p</i>
Condition (Con)	4	-	4.073	.156	.004
Error (Con)	88	-			

Table 19. Analysis of variance (ANOVA) of P300 mean activity within the control group with emotion category (fearful, joyful, sad, angry and neutral).

Source	<i>df</i>	ϵ	<i>MS</i>	<i>F</i>	<i>np</i> ²	<i>p</i>
Condition (Con)	4	-	3.083	2.757	.133	.034
Error (Con)	72	-	1.118			

APPENDIX H: Supplementary Information for Study 2: Detailed Hypothesis 2 Findings

P100 Amplitude and Latency

Within both groups, for angry facial expressions, the planned contrasts revealed significantly larger P100 amplitudes over the parietal sites during BSF (HC: $F [1, 18] = 43.99, p < 0.001, r = 0.84$; SCZ: $F [1, 22] = 32.95, p < 0.001, r = 0.77$) and LSF (HC: $F [1, 18] = 12.54, p < 0.004, r = 0.64$; SCZ: $F [1, 22] = 20.66, p < 0.001, r = 0.70$) presentations compared with HSF conditions. For fearful facial expressions larger P100 amplitude was observed for BSF presentation compared with HSF condition (HC: $F [1, 18] = 34.09, p < 0.001, r = 0.81$; SCZ: $F [1, 22] = 20.33, p < 0.001, r = 0.69$).

Within the control group and over the occipital sites, for both angry and fearful facial expressions, significantly larger P100 amplitudes during BSF (fearful: $F [1, 18] = 15.74, p < 0.001, r = 0.68$; angry: $F [1, 18] = 64.34, p < 0.001, r = 0.88$) and LSF (fearful: $F [1, 18] = 26.62, p < 0.001, r = 0.77$; angry: $F [1, 18] = 60.99, p < 0.001, r = 0.88$) presentation compared with HSF condition were observed (i.e., for both fearful and angry expressions: $BSF > HSF$; $LSF > HSF$).

Within the patient group and over the occipital sites, for angry facial expressions, significantly larger P100 amplitudes during LSF presentation compared with BSF ($F [1, 22] = 11.78, p < 0.004, r = 0.59$) and HSF ($F [1, 22] = 48.19, p < 0.001, r = 0.83$) condition were observed. Further, larger P100 amplitude to angry facial expressions during BSF presentation compared with HSF ($F [1, 22] = 12.31, p < 0.002, r = 0.60$) condition was observed. (i.e., angry expressions: $LSF > BSF > HSF$). For fearful facial expressions larger P100 amplitudes were observed for BSF ($F [1, 22] = 16.60, p < 0.001, r = 0.66$) and LSF ($F [1, 22] = 13.19, p < 0.002, r = 0.61$) presentation compared with HSF condition (i.e., fearful expression: $[BSF=LSF] > HSF$).

P100 latency differences were only observed in the control group: shorter P100 latency only over the parietal sites was observed for fearful expressions in the BSF compared with LSF ($F [1, 18] = 1.70, p < 0.004, r = 0.61$) and HSF ($F [1, 18] = 17.04, p < 0.001, r = 0.70$) conditions (i.e., fearful: $BSF < (LSF = HSF)$). No differences between spatial frequency filtered angry faces was observed for the P100 latency over the occipital sites in the control group (i.e., angry: $BSF=LSF=HSF$). No differences between spatial frequency filtered threatening facial expressions was observed for the P100 latency in the patient group.

N170 Amplitude and latency

Within both groups, significantly larger N170 amplitude was observed for BSF compared with both the LSF (HC: $F [1, 18] = 19.35, p < 0.05, r = 0.72$; SCZ: $F [1, 22] = 17.78, p < 0.05, r = 0.67$) and HSF (HC: $F [1, 18] = 15.69, p < 0.05, r = 0.68$; SCZ: $F [1, 22] = 91.82, p < 0.001, r = 0.90$) filtered angry facial expressions and for BSF compared with HSF (HC: $F [1, 18] = 4.82, p < 0.05, r = 0.46$; SCZ: $F [1, 22] = 34.93, p < 0.05, r = 0.78$) filtered fearful facial expressions. Only within the patient group, the contrast analyses found significantly larger N170 amplitude to

LSF compared with HSF filtered angry ($F [1, 22] = 28.78, p < 0.001, r = 0.75$) and fearful ($F [1, 22] = 17.65, p < 0.05, r = 0.67$) facial expressions.

Within both groups, significantly shorter N170 latency was observed for fearful expressions in BSF compared with both LSF (HC: $F [1, 22] = 12.41, p < 0.001, r = 0.64$; SCZ: $F [1, 22] = 10.92, p < 0.05, r = 0.58$) and HSF (HC: $F [1, 22] = 50.61, p < 0.001, r = 0.86$; SCZ: $F [1, 22] = 31.08, p < 0.001, r = 0.77$) and shorter latency for LSF compared with HSF (HC: $F [1, 22] = 12.89, p < 0.001, r = 0.65$; SCZ: $F [1, 22] = 5.15, p < 0.05, r = 0.44$) filtered faces (i.e., for fearful facial expressions latency: $BSF < LSF < HSF$). Whereas for the angry expressions, different patterns were observed within each group. In the control group N170 latency difference was observed in the BSF compared with HSF ($F [1, 22] = 61.78, p < 0.001, r = 0.89$) and LSF compared with HSF ($F [1, 22] = 37.60, p < 0.001, r = 0.82$) conditions (i.e., for angry facial expressions latency: $[BSF=LSF] < HSF$). Whereas in the patient group, shorter N170 latency was observed for angry facial expressions filtered with BSF compared with LSF ($F [1, 22] = 7.64, p < 0.05, r = 0.51$) and HSF ($F [1, 22] = 13.59, p < 0.05, r = 0.62$) conditions. No difference in N170 latency of angry facial expression was observed in the LSF compared with HSF condition (i.e., for angry facial expressions: $BSF < [LSF=HSF]$).

APPENDIX I: The revised Beliefs About Voices Questionnaire (BAVQ-R)

BAVQ - R

CHADWICK, PAUL, LEES, SUSAN, BIRCHWOOD, MAX
The revised Beliefs About Voices Questionnaire (BAVQ-R)

(from The British Journal of Psychiatry 2000 177: 229-232)

There are many people who hear voices. It would help us to find out how you are feeling about your voices by completing this questionnaire. Please read each statement and tick the box which best describes the way you have been feeling in the *past week*.

If you hear more than one voice, please complete the form for the voice which is dominant.

Thank you for your help.

Name:

Age:

		Disagree	Unsure	Slightly Agree	Strongly Agree
1	My voice is punishing me for something I have done				
2	My voice wants to help me				
3	My voice is very powerful				
4	My voice is persecuting me for no good reason				
5	My voice wants to protect me				
6	My voice seems to know everything about me				
7	My voice is evil				
8	My voice is helping to keep me sane				
9	My voice makes me do things I really don't want to do				
10	My voice wants to harm me				
11	My voice is helping me to develop my special powers or abilities				
12	I cannot control my voices				
13	My voice wants me to do bad things				
14	My voice is helping me to achieve my goal in life				

15	My voice will harm or kill me if I disobey or resist it				
		Disagree	Unsure	Slightly Agree	Strongly Agree
16	My voice is trying to corrupt or destroy me				
17	I am grateful for my voice				
18	My voice rules my life				
19	My voice reassures me				
20	My voice frightens me				
21	My voice makes me happy				
22	My voice makes me feel down				
23	My voice makes me feel angry				
24	My voice makes me feel calm				
25	My voice makes me feel anxious				
26	My voice makes me feel confident				

When I hear my voice, usually ...

		Disagree	Unsure	Slightly Agree	Strongly Agree
27	I tell it to leave me alone				
28	I try and take my mind off it				
29	I try and stop it				
30	I do things to prevent it talking				
31	I am reluctant to obey it				
32	I listen to it because I want to				
33	I willingly follow what my voice tells me to do				
34	I have done things to start to get in contact with my voice				
35	I seek the advice of my voice				