PSYCHOPHYSICAL AND ELECTROPHYSIOLOGICAL ASSESMENT OF EARLY VISUAL PROCESSING AND EMOTION RECOGNITION DEFICITS IN SCHIZOPHRENIA

By

ILANA ABELES

A dissertation submitted to the Graduate Faculty in Psychology, in partial fulfillment of
the requirements for the degree of Doctor of Philosophy,
The City University of New York

2011

This manuscript has been read and accepted for the Graduate Faculty in Psychology in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy

Date_ ___________ Dr. Pamela Butler, PhD_______________

____

Chair of Examining Committee

Date______________ Dr. Maureen O'Connor, PhD____________

____

Executive Officer

Dr. Daniel Javitt______________________

Dr. Antonio Convit____________________

Dr. Peter Lakatos_____________________

Dr. Tracy Dennis______________________

Supervisory Committee

THE CITY UNIVERSITY OF NEW YORK

Abstract

PSYCHOPHYSICAL AND ELECTROPHYSIOLOGICAL ASSESMENT OF EARLY VISUAL PROCESSING AND EMOTION RECOGNITION DEFICITS IN SCHIZOPHRENIA

By

Ilana Abeles

Advisor: Dr. Pamela Butler

Previous data suggest that patients with schizophrenia have preferential magnocellular (M) versus parvocellular (P) visual dysfunction. The goal of Experiment 1 was to characterize M-stream impairment in the patient population using a novel approach. Contrast thresholds at varying luminance levels were investigated. M- and P-biased responses were examined by using scotopic and photopic luminance conditions, respectively. Patients exhibited contrast threshold deficits during scotopic conditions, indicative of M-stream dysfunction. Further, the pattern of contrast threshold responses at photopic levels indicated relatively preserved patient P-pathway functionality.

Experiment 2 used separate behavioral and electrophysiological paradigms to investigate contributions of low-level visual pathway dysfunction in patients to emotion perceptual processing deficits. Contrast response curves for the dorsal (P1) and ventral (N170) pathways were elicited in response to contrast-manipulated emotional faces. Results showed that the dorsal P1's pattern of response was impaired in patients while their N170 contrast response curves remained intact. Contributions of visual pathway dysfunction to impaired emotion recognition and affect-related processing, as indexed by the P250 amplitude, were then assessed. P250 activity in patients was reduced at all contrasts. Overall, across groups, the P1 component predicted both P250 amplitude and emotion recognition ability. Taken together, these data support the hypothesis that emotion recognition deficits in patients result from M/dorsal stream dysfunction.

Experiment 3 examined the spatial-temporal oscillatory dynamics of schizophrenia patients during processing of complex visual stimuli. FFT-spectrum activity and underlying generators of the delta, theta and alpha oscillatory frequencies were first assessed. Activity in the pre and post-stimulus intervals, and the ratio between them (event-related de/synchronization: ERD/ERS) were also evaluated. FFT-data revealed controls had significantly greater alpha band activation in posterior electrodes as compared to patients. Conversely, patients exhibited greater theta-band activation over anterior electrodes versus controls. Topographical analysis suggested patients had abnormal underlying neural generators that gave rise to impaired theta and alpha-band activity. Further, instantaneous delta-band activity was significantly greater in patients during pre- and post-stimulus intervals, possibly reflecting an overall generalized deficit. Finally, the data revealed that patients had a substantially reduced alpha-ERD, highlighting their impairment in low-level visual cortical gating mechanisms during processing of visual sensory inputs.

Dedication

This dissertation is dedicated to the members of my wonderfully loving family, especially Mom and Dad, who have been there for me every step of the way. I am truly thankful for your unconditional love and encouragement.

Acknowledgements

This thesis is a result of the outstanding collaboration between the City College of New York, and the Nathan Kline Institute for Psychiatric Research. I would first like to wholeheartedly thank Dr. Pamela Butler for her mentorship and support throughout my graduate school years. Thank you so much for your insight, guidance and friendship over the years, and I truly wish you the best in the future. I'd also like to thank Dr. Pejman Sehatpour for his technical direction and assistance and for our discerning discussions regarding our data. I am eternally grateful to Dr. Manuel Gomez-Ramirez for countless insightful conversations and for invaluable assistance with projects included in this dissertation. My heartfelt appreciation goes to my undergraduate biology advisor, Dr. Jeff Doyle, who encouraged me to leave ecology and follow my heart, and continued to lend guidance and support throughout my undergraduate years.

I would also like to express my sincere appreciation to my friends and colleagues at NKI who I have had the privilege of working with, learning from and knowing: Dr. Daniel Javitt, Dr. Elisa Dias, Dr. Vance Zemon, Dr. John Smiley, Dr. John Foxe, Dr. Sophie Molholm, Dr. Antigona Martinez, Dr. Simon Kelly, Dr. Ed Lalor, Dr. Stephan Bickel, Nicole Weiskopf, Megan Perrin, Marina Ross and Jonathan Lehrfeld.

I thank my friends in New York for making this part of my life such a pleasurable experience filled with unforgettable memories, laughter, and unconditional support. A special thanks to Andrea Maurella for being a steadfast friend and always being there whenever needed.

I would like to say thank you to the two other musketeers, Josh Lucan and Ian Fiebelkorn, who began this journey at CCNY with me. Your friendship since the days of Bravest have been most appreciated and enjoyed. Finally, I would not have had such an amazing past 4.5 years without the incredible love and support of mi amor, Manuel Gomez-Ramirez. Thank you so much for seeing me through this journey and I sincerely look forward to our many journeys to come.

TABLE OF CONTENTS

LIST of TABLES

CHAPTER 2

CHAPTER 3

CHAPTER 4

LIST of ILLUSTRATIONS

CHAPTER 2

CHAPTER 3

CHAPTER 4

APPENDIX

CHAPTER 1

1.1 Introduction- Overview

Lower-level sensory processing deficits are a central element of schizophrenia psychopathology (Javitt, 2009; Kraepelin, 1904). A growing literature has focused on visual processing impairment in schizophrenia (Butler, Silverstein, & Dakin, 2008) and its contribution to functional outcome (Brenner, Lysaker, Wilt, & O'Donnell, 2002; Butler, Zemon et al., 2005; Gold, Goldberg, McNary, Dixon, & Lehman, 2002; Keri, Kiss, Kelemen, Benedek, & Janka, 2005; Laycock, Crewther, & Crewther, 2007; Sergi & Green, 2003; Sergi, Rassovsky, Nuechterlein, & Green, 2006). Further, a number of these low-level visual deficits are found in tasks that were biased toward the magnocellular/dorsal visual pathway (Butler et al., 2001; Gold et al., 2002; Kim, Wylie, Pasternak, Butler, & Javitt, 2006; Saccuzzo & Braff, 1981). This suggests that the magnocellular (M) system may be more impaired than the parvocellular (P) system in these patients.

The question of where and how visual processing is impaired in schizophrenia is still a matter of debate, but recent studies indicate that there are already deficits at initial levels of sensory processing within the M-pathway (Butler et al., 2007; Butler et al., 2001; Butler, Zemon et al., 2005; Slaghuis & Bishop, 2001). Experiment 1 of this dissertation utilized a psychophysical contrast threshold paradigm, implemented at different luminance levels, to investigate low-level M- and P- pathway integrity in patients with schizophrenia in a novel way.

Experiment 2 examined the contribution of visual processing deficits to emotion processing dysfunction in schizophrenia. While disorders of affect are well-known in schizophrenia (Kraepelin, 1904), the neuronal etiology of these deficits remains unclear.

In healthy subjects, face and emotion recognition have been shown to rely on M/dorsal stream processes in healthy controls (Calder et al., 2000; Leder, Candrian, Huber, & Bruce, 2001; Schyns & Oliva, 1999), but there is little information available on this topic for schizophrenia patients. There is evidence that these impairments are a secondary problem stemming from low-level visual processing dysfunction (Butler et al., 2009; Johnston, Stojanov, Devir, & Schall, 2005; Norton, McBain, Holt, Ongur, & Chen, 2009; Turetsky et al., 2007). Supporting this, recent behavioral studies have shown an association between M-stream dysfunction and emotion identification impairment in schizophrenia (Butler et al., 2009; Norton et al., 2009). Experiment 2 was conducted to investigate contributions of low-level visual pathway dysfunction to emotion processing deficits in schizophrenia using behavioral and electrophysiological methods.

In addition, researchers have recently begun to use time-frequency analyses to evaluate potential impairments in event-related oscillatory activity of patients that may contribute to their overall visual perception abnormalities. Most studies investigating visual perception have focused on gamma-band synchrony, but few have evaluated differences in lower-frequency bands during an event-related paradigm, even though recent data from animal physiology and healthy population studies have found that lower-frequency oscillations are critical for perception (e.g. Lakatos, Karmos, Mehta, Ulbert, & Schroeder, 2008). Experiment 3 evaluated lower-frequency oscillatory activity during a visual perceptual task.

In the following sections, a definition and brief history of schizophrenia research is provided, along with an explanation of potential neurochemical models that underlie schizophrenia pathology. Early visual pathways and later emotion perception networks are discussed as they relate to normal function in healthy controls and pathology in schizophrenia. A discussion about oscillatory techniques and findings within schizophrenia follows. Finally, the objectives of the dissertation are provided.

1.2 Definition of schizophrenia

Schizophrenia is a debilitating pathology that affects about 1% of the global population. Criteria for diagnosis necessitate the presence of two or more positive and/or negative symptoms and social/occupational dysfunction. Positive symptoms reflect the presence of atypical behavior that the unaffected population does not express. These include delusions, hallucinations (these are usually auditory), and incoherent thought and speech. These symptoms are usually improved by antipsychotic medications. Negative symptoms on the other hand reflect the absence of social and personal behavior that is present in the unaffected population. These manifest as flat affect, poverty of speech, lack of motivation, and social isolation. In addition to positive and negative symptomatology, patients with schizophrenia exhibit significant cognitive decline. This is now considered to be a core feature of schizophrenia, and is seen to persist even when other symptoms subside (Javitt, 2009). Further, neurocognitive dysfunction has been closely associated with patients' functional impairment, emphasizing its clinical importance.

1.3 Brief history of schizophrenia and its research

In 1904 Kraeplin described both perceptual and cognitive symptomatology within the schizophrenia population and termed the pathology “dementia praecox” (Kraepelin, 1904). However, later Bleuler dismissed the sensory and perceptual disturbances of patients, and attributed their impairments to higher-order dysfunction in thought processes (Bleuler, 1950). A focus on higher-level cognitive deficits permeated the literature for the next decade. It was not until McGhie and Chapman emphasized self-reported perceptual experiences in the schizophrenia population that investigators began to study possible sensory-level pathology (McGhie, 1964; McGhie & Chapman, 1961).

Currently, abnormal visual perception is thought to be a core characteristic of schizophrenia pathology (Butler, Silverstein et al., 2008; Javitt, 2009). Indeed, perception has been included as one of the domains in the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) project, which aims to develop standardized testing for use in assessing the efficacy of remediation strategies and drug therapies for patients with schizophrenia.

1.3.1 Top-down and dopaminergic models of schizophrenia

The “top-down” model describes schizophrenia psychopathology as resulting from dysfunction of higher-cortical areas, including prefrontal cortex and the medial-temporal lobes (Minzenberg, Laird, Thelen, Carter, & Glahn, 2009; Reichenberg & Harvey, 2007). In this model, perceptual, emotional and cognitive dysfunction is attributed to impairment of higher-level regions of the brain rather than sensory-level areas. Further, this model has frequently been associated with dopaminergic theories of schizophrenia.

The original hypothesis of excessive release of dopamine at synaptic sites in schizophrenia was based on the ability of dopamine agonists to mimic the positive symptoms of schizophrenia (Davis, Kahn, Ko, & Davidson, 1991). In addition, chlorpromazine, a D_2 dopamine antagonist, was found to calm agitated patients diagnosed with schizophrenia and bipolar disorder (Delay, Deniker, & Ropert, 1956a, 1956b). Later on, chlorpromazine and related drugs (antipsychotics) were found to specifically mitigate positive symptoms in patients and reverse psychoses induced by dopamine agonists, by blocking D_2 receptor sites (Krystal et al., 2005). In non-human primates, extensive dopaminergic innervation has been found throughout the brain, especially in higher-order areas, such as prefrontal cortex, with fewer projections to primary sensory cortices (Lewis, Campbell, Foote, Goldstein, & Morrison, 1987). This finding supported the top-down model which had a focus on pre-frontal cortical impairment and its effects on cognitive function in schizophrenia and de-emphasized sensory/perceptual level pathology.

The current antipsychotic medications (D_2 receptor antagonists) are effective in the reduction of positive symptomatology. However, these drugs have not shown efficacy in alleviating cognitive deficits, and some have been shown to exacerbate cognitive dysfunction in animal models (Castner, Williams, & Goldman-Rakic, 2000; Dorph-Petersen et al., 2005). It is well established that there are a variety of disturbances of cognition in schizophrenia, and there is evidence of higher-level cortical involvement that may involve dopaminergic abnormalities (Minzenberg et al., 2009; Reichenberg & Harvey, 2007). However, treatments to improve cognitive functioning that have been solely based on the dopaminergic model of schizophrenia have not been effective (Goff, Hill, & Barch, 2010). Thus, the dopamine hypothesis is unable to fully explain the cognitive pathology in schizophrenia (Javitt, 2007).

1.3.2 Glutamatergic theory of schizophrenia- the beginnings of bottom-up research

During the past two decades, the glutamatergic/GABAergic dysregulation model of schizophrenia has gained attention because of its potential to explain schizophrenia symptomatology more completely (Goff & Coyle, 2001; Javitt, 2004). Glutamate neurotransmitter hypofunction was first proposed as a neurochemical basis of schizophrenia due to the observed effects in healthy controls of N-methyl D-aspartate (NMDA)-glutamate channel antagonists, such as ketamine and phencyclidine (PCP). These drugs not only provoked psychosis, but induced negative symptomatology and cognitive decline as well. NMDA receptors are found both in frontal cortical areas and also throughout primary sensory cortices (Lewis et al., 1987). These findings suggested that NMDA hypofunction may play a large role in both higher-level cognitive deficits as well as in perceptual dysfunction, and that this receptor may provide a neurochemical substrate for ameliorating the wide range of symptoms of schizophrenia pathology.

Once researchers acknowledged that basic sensory input areas were vulnerable to dysregulation in schizophrenia, several questions arose: Is the dysfunction occurring at the earliest, input stages of sensory processing resulting in perceptual impairment in patients? And if so, are there secondary, higher-order consequences that manifest themselves later? The past two decades have seen a surge in studies dedicated to the evaluation of schizophrenia pathology from a bottom-up versus top-down perspective. Even though deficits are not localized to one area of the brain, and are seen across sensory modalities, the visual system has been heavily investigated (Javitt, Liederman, Cienfuegos, & Shelley, 1999), due to the abundance of information on the functioning of this system.

1.3.3 Visual backward masking paradigm: where it all started

The visual backward masking paradigm was initially used to investigate the speed of visual information processing in the healthy population and in patients with schizophrenia (Braff & Saccuzzo, 1985). In this paradigm, a target is presented and a masking stimulus follows at various interstimulus intervals (ISIs). At shorter ISIs, the mask can interrupt target stimulus processing and the participant cannot detect the target.

Visual information processing deficits in schizophrenia were initially evaluated in terms of the ‘transient’ and ‘sustained’ visual pathways. The channels were psychophysically defined, and found to process different perceptual attributes of visual stimuli. The <u>transient</u> visual pathway was thought to be rapidly responding, and be selective in processing briefly presented stimuli (like the onset of a target or mask), and location of stimuli. The <u>sustained</u> visual pathway was thought to respond more slowly and tonically as compared to the transient channel, and was thought to be selective in processing the fine-detail of stimuli (see Cadenhead, Serper, & Braff, 1998). In the visual backward masking paradigm, the sustained visual channel is thought to mediate the continuous processing of the target stimulus, and the transient channel is thought to process the brief presentation of the mask onset that causes disruption of sustained target processing needed for object identification. The interruption of sustained processing of the target is thought to result from inhibitory influences of the transient channel on the sustained channel (Breitmeyer & Ganz, 1976).

In this paradigm, patients needed longer ISIs to detect visual targets and appeared more susceptible to the disruptive effects of the masking stimulus than controls (Braff, 1981; Braff & Saccuzzo, 1985; Cadenhead et al., 1998; Green, Nuechterlein, & Mintz, 1994; Saccuzzo & Schubert, 1981). Researchers hypothesized that an overactive sub-cortical transient pathway caused greater inhibition of the sustained channel as compared to controls. As a result, patients needed longer ISIs in order to ensure the proper processing of the target stimulus. However, at that time, actual neuronal mechanisms underlying patients' deficit were not proposed. Regardless, this particular hypothesis prompted extensive research investigating <u>channel-specific</u> deficits in schizophrenia. The question now arises: Are there really preferential channel deficits in schizophrenia, and why? The following sections will address this question.

1.4 Visual pathway basics

The visual system has been extremely well-characterized in healthy human controls and exquisitely studied in animals as well. The current model of the human visual system involves separate magnocellular (M), parvocellular (P) and koniocellular (K) visual pathways. This dissertation will focus on the M- and P- pathways. Initially, psychophysical studies identified separate 'transient' and 'sustained' visual channels whose response properties were later shown to correspond to the anatomically-defined M- and P- pathways of primates, respectively (Bassi & Lehmkuhle, 1990; Breitmeyer & Williams, 1990; Livingstone & Hubel, 1987). The M- and P- visual streams project separately from the retina to layers 1-2 and 3-6 of the lateral geniculate nucleus (LGN) of the thalamus, respectively. From there, M-projections reach sublamina 4Cα of primary visual cortex (V1) and P-neurons terminate most noticeably in sublamina 4Cβ. From V1, the M-system projects to the thick stripes of V2, and on to dorsal parietal visual areas including middle temporal area, medial superior temporal area, and intraparietal area. There are also direct projections from the M-stream to the amygdala via the sub-cortical tecto-pulvinar pathway. The P-stream projects from layer 4Cβ of V1 to the thin stripes of V2 and then on to the ventral visual stream which includes area V4 and infero-temporal cortex (Liddell et al., 2005; Lund, 1973; Merigan & Maunsell, 1993; Schiller, Malpeli, &

Schein, 1979; Schroeder, Mehta, & Givre, 1998) (see Figure 1). However, substantial cross-over occurs, beginning after layer 4C of striate cortex.

These pathways can also be differentiated functionally. M-neurons are large, rapidly conducting, and convey global information of a visual scene via sensitivity to low-spatial frequency (LSFs) (Figure 2: left panel; and Figure 3: right panel). They are sensitive to high temporal frequencies, and are thought to play a major role in guiding eye-movements. Further, the M-pathway is insensitive to chromatic information. The M/dorsal stream is also known as the ‘where’ pathway because it helps in processing motion, location, and spatial relationships among stimuli. Parvocellular neurons are smaller, more slowly conducting, and convey fine-detailed information of the visual stimulus via high-spatial frequencies (HSFs) (Figure 2: right panel). They are more sensitive to stimuli of longer durations and slower temporal frequencies. Further, the P-pathway is sensitive to isoluminant chromatic signals (Derrington & Lennie, 1984; Kaplan, 1991; Tootell, Silverman, Hamilton, Switkes, & De Valois, 1988). The P/ventral stream is also known as the ‘what’ pathway because of its ability to transmit fine-detailed information (Figure 3: left panel).

Other properties that differentiate M and P pathways are contrast and overall luminance. These characteristics will be utilized to help differentiate M- from P-pathway processing in two of the studies within this dissertation. The M pathway plays a central role in scotopic (very low luminance: $\leq 1 cd/m^2$) vision. Further, scotopic vision is predominantly mediated by rod-photoreceptors that are proportionally more numerous in the periphery of the retina and have been shown to project heavily through to the M-ganglion cells of the retina in primates (Hassler, 1966). Further, gene-knockout studies conducted in mice have determined that at scotopic luminance, the rod-specific bipolar cells (precursors of the ganglion cells in the retina) dominate processing (Abd-El-Barr et al., 2009). In contrast, photopic vision (>30 cd/ m^2) is dependent primarily on cone photoreceptors (as the response of rod-photoreceptors saturates in high luminance) which send information to P-ganglion neurons of the retina. P-ganglion neurons have lower sensitivity to light, thus needing more luminance to respond, and begin to respond when luminance increases to levels >1cd/m^2 (Kaplan, 1991; Purpura, Kaplan, & Shapley, 1988; Purpura, Tranchina, Kaplan, & Shapley, 1990). Differences in luminance properties of M- and P-pathways will be exploited to examine the integrity of patient visual pathways in Experiment 1 of this dissertation.

M- and P- pathways are also differentiated in regards to processing stimulus contrast. In animal physiological studies, researchers have manipulated stimulus contrast to bias neural processing to the M- and P- pathways, and have measured their distinct responses. The underlying neurophysiological mechanism of ‘gain control’ offers an explanation of why unique contrast response curves are obtained for M- and P- pathways (Figure 4A). ‘Gain control’ is a mechanism that allows visual pathways to adapt and optimize their responses in different situations, and was first described in cat retinal ganglion cells (Shapley & Victor, 1978, 1981) and later extended to primates (Kaplan & Shapley, 1986). The M-pathway provides a prototypical example of gain control, functioning as a non-linear amplifier of response. M-pathway neurons respond robustly to low-contrast stimuli (<10% contrast) resulting in steep initial gain (or slope) of the contrast response curve. Once luminance contrast reaches about 16%, the inhibitory contrast gain control mechanisms result in saturated responses. This leads to a curve with a steep slope at low contrasts and shallow slope at high contrasts (Figure 4A) (Kaplan, 1991, 2003; Kaplan & Shapley, 1986; Kaplan & Shapley, 1982). NMDA receptors appear to mediate excitatory amplification of responses at low contrast within the M-neuron (Daw, Stein, & Fox, 1993). Recently, more attention has also been placed on the effects of NMDA receptors on inhibitory GABAergic neurons, as these GABAergic neurons are thought to play a role in the saturation of response at high-contrasts (Lisman et al., 2008) via coordination of pyramidal cell output (see Uhlhaas & Singer, 2010). Conversely, the P-pathway only begins to respond ~10% contrast and has been shown to produce a shallow, nearly linear contrast response curve over moderate to high ranges of contrast suggesting its response is mediated by separate neuronal mechanisms (Figure 4A).

Further, a human steady-state visual evoked potential (ssVEP) study (Zemon & Gordon, 2006) manipulated stimuli to bias processing towards the M- versus P- pathway to investigate human visual pathway responses. The ssVEP paradigm was utilized to specifically investigate sub-cortical pathway function in humans. During this paradigm, stimuli are presented at high frequencies and this is hypothesized to elicit a habituation of response at the cortical level, thereby sensitizing sub-cortical visual responses for subsequent evaluation. To preferentially activate the M-stream, low-contrast stimuli appeared and disappeared in a rapid sequence. In order to accentuate responses from the P-stream, stimuli with contrast values around a high-contrast pedestal were presented so that their contrast never went below 16% (Zemon & Gordon, 2006). The latter manipulation kept contrast above the level where the M-pathway saturates, so that all changes observed could be ascribed to the P-pathway.

In the M-biased condition, there was a steep amplification of response at low to mid contrasts and saturation of response at higher contrasts which is similar to the M-biased responses found in the retina and LGN of monkeys (Derrington & Lennie, 1984; Kaplan & Shapley, 1986; Zemon & Gordon, 2006). The P-biased condition produced linear curves in response to increasing contrast, mirroring previously recorded P-neuronal responses recorded in animals (e.g. of ssVEP responses: Figure 4C-D) (Kaplan, Purpura, & Shapley, 1987; Kaplan & Shapley, 1986; Zemon & Gordon, 2006). These findings support the use of contrast as an appropriate perceptual characteristic to manipulate in order to bias processing towards the M- and P- streams.

Another method commonly used to evaluate visual system functionality is to determine the contrast threshold for the reliable detection of different spatial frequency gratings (Figure 2). This measure is commonly referred to as a person's contrast threshold, or, if measured as the inverse of threshold, contrast sensitivity (CS). By plotting CS or threshold as a function of SF under specific conditions, human M and P pathway properties can be examined (e.g. Figure 5) (Slaghuis, 1998). SF gratings are commonly used to elicit CS curves because their perceptual traits, including average luminance, contrast, spatial frequency, phase, and temporal frequency can be easily manipulated to bias processing towards M and P pathways.

Contrast perception and processing has been evaluated using these techniques in a number of behavioral and electrophysiological paradigms in order to investigate preferential visual pathway dysfunction in patients with schizophrenia. These are described in detail below.

1.5 Early visual processing in patients with schizophrenia: evidence for a

preferential M/dorsal stream deficit

Patients with schizophrenia exhibit a number of basic visual processing impairments that are suggestive of preferential M/dorsal stream dysfunction. These deficits have been found in a number of psychophysical and electrophysiological paradigms.

Several studies have used contrast manipulations to evaluate whether behavioral deficits are pathway specific as first suggested by Braff and Sacuzzo (1985), or whether the deficits are general in nature. Experimental results support preferential M-pathway involvement in patient pathology. For instance, psychophysical studies have shown that patients exhibit preferential visual backward masking deficits to M-biased but not P-biased masks (Butler et al., 2002; Butler, Harkavy-Friedman, Amador, & Gorman, 1996; Saccuzzo & Braff, 1986; Schechter, Butler, Silipo, Zemon, & Javitt, 2003; Slaghuis, 2004; Slaghuis & Bakker, 1995**.** In addition, vernier acuity of both medicated and unmedicated patients was significantly reduced, as compared to controls, in a vernier task which involved low-contrast and LSF stimuli as opposed to the high-contrast, isoluminant color stimuli (Keri, Kelemen, Benedek, & Janka, 2004; Keri, Kelemen, Janka, & Benedek, 2005).

In addition, CS paradigms, where stimuli have been spatially and temporally manipulated to bias processing, have been conducted to evaluate visual pathway dysfunction in schizophrenia with mixed results. In general, patients have shown reduced contrast sensitivity in response to LSFs (Butler et al., 2009; Butler, Zemon et al., 2005; Keri, Antal, Szekeres, Benedek, & Janka, 2002; Slaghuis, 1998, 2004; Slaghuis & Thompson, 2003). However, some studies have shown comparable or larger deficits at mid- to higher SFs (Keri et al., 2002; Slaghuis, 1998, 2004; Slaghuis & Thompson, 2003) while others still have shown no difference between groups at high SFs (Figure 5) (Butler, Zemon et al., 2005). While it might appear from some of these CS studies that patients have both M- and P-pathway impairment, this may not necessarily be true. Confounding factors may have led to the discrepancy regarding mid to HSFs. At contrast threshold, HSFs are able to be detected at low-contrasts (<10%) which necessarily engages the M-pathway. Further, some animal physiological studies have shown that the M-pathway can be more sensitive than the P-pathway over a range of mid- to HSFs (Hicks, Lee, & Vidyasagar, 1983). Accordingly, contrast threshold deficits in patients with schizophrenia may be found in response to HSFs because of the engagement of the M-pathway.

Further, each of these previous contrast threshold studies presented stimuli at mid to high luminance levels which may not have optimally isolated the M- from the P-stream during LSF contrast threshold detection. To more effectively bias processing and clarify visual deficits in schizophrenia, luminance manipulation may be exploited to emphasize M-pathway function. As mentioned, previous anatomical data have indicated that rod-photoreceptors, which feed into M-ganglion cells, drive processing during scotopic vision with minimal input coming from cones (Abd-El-Barr et al., 2009; Lee, Smith, Pokorny, & Kremers, 1997). Accordingly, it has been shown that LSF stimuli at scotopic luminance, stimulate M-ganglion cells in monkey retina exclusively (Purpura et al., 1988). In addition, psychophysical data suggest that at scotopic luminances, LSFs are most efficiently resolved as opposed to HSFs (Savage & Banks, 1992). Further, contrast response curves generated at scotopic luminances in humans, were found to exhibit characteristics similar to curves from M-cells in the retina, LGN, and in V1 of animals (Benedek, Benedek, Keri, & Janaky, 2003; Hawken & Parker, 1984; Hicks et al., 1983; Purpura et al., 1988). These data suggest that the M-system can potentially be isolated in humans using scotopic luminance. In this way, any deficit in contrast threshold during scotopic vision would necessarily be due to impaired magnocellular neuronal activity.

Only two previous studies involving patients with schizophrenia have utilized luminance manipulation in a contrast threshold paradigm. Slaghuis and Bishop (2001) used flickering stimuli at varying temporal frequencies rather than SF gratings, and presented them at 3 cd/m^2, 33 cd/m^2, and 66 cd/m^2. Patients showed deficits at high temporal frequencies at the lowest luminance. While these particular conditions drove processing towards the M-pathway, they may not have isolated it. The only other study conducted using scotopic luminance manipulation implemented a detection paradigm using a circular test stimulus in the scotopic range (Gutherie, McDowell, & Hammond, 2006). In addition, these researchers measured participants' optical density. Because no significant between-group differences in threshold or optical density were found, the researchers concluded that M-system pathology occurs subsequent to rod-photoreceptor processing. Experiment 1 (Chapter 2) used a well-validated contrast threshold paradigm that was adapted to further investigate low-level M-system functionality in a novel way in the schizophrenia population. This paradigm used a combination of spatial frequency and luminance level (scotopic to photopic) manipulation in order to evaluate both M-pathway and P-pathway integrity in patients with schizophrenia. To our knowledge, this approach to help bias processing towards the M- versus P-pathway has not yet been used within the schizophrenia population.

Evidence for M-stream impairment in schizophrenia has been seen in a number of neurophysiological studies as well. ssVEPs have been used to evaluate potential low-level visual impairment in patients with schizophrenia (Butler, Zemon et al., 2005; Kim, Zemon, Saperstein, Butler, & Javitt, 2005). Butler et al. (2005) conducted a study in which stimuli were M- and P- biased using different levels of luminance contrast. Contrast response curves were subsequently evaluated for patients and controls. Patients' contrast response curves showed decreased gain at low-contrast, and a decreased plateau in response during the M-biased condition (Butler et al., 2001; Butler, Zemon et al., 2005) (Figure 4C). This indicates reduced signal amplification at low-contrast, and a saturation of response at high-contrasts that was lower than that observed in controls (Figure 4C). These data suggested that there is low-level visual processing dysfunction within the patient population. This is further supported by the finding that patients have reduced sub-cortical white matter integrity in the optic radiations that conduct information from LGN to striate cortex (Butler, Zemon et al., 2005). Further still, the ssVEP data mirror results seen following microinfusion of NMDA antagonists into cat LGN and visual cortex (Fox, Sato, & Daw, 1990; Kwon, Nelson, Toth, & Sur, 1992) (Figure 4B), consistent with glutamatergic theories of schizophrenia (Javitt & Zukin, 1991; Olney & Farber, 1995; Tsai & Coyle, 2002). In contrast, during the P-biased conditions, patients' responses were similar to controls and both groups exhibited linearly rising responses as contrast was increased (Figure 4D) (Butler, Zemon et al., 2005). This suggests relatively preserved early-stage activity within the parvocellular channel.

The visual deficit of patients is not isolated to sub-cortical visual pathways. Event-related potential (ERP) studies have used visual perceptual paradigms to investigate distinct cortical visual pathway processing abnormalities in patients with schizophrenia. These visual perceptual studies involving patients and healthy controls have focused on the early visual potentials P1, C1, and N1. The visual “P1” component (~100 ms post-stimulus onset) has been found to have a dorsal-stream generator that is principally driven by M-stream input (Martinez, Di Russo, Anllo-Vento, & Hillyard, 2001). Conversely, the “C1” (~90 ms post-stimulus onset) is reflective of primary visual cortex activation and has been shown to be particularly sensitive to P- information. Lastly, the “N1” component (~150 ms post-stimulus onset) is thought to reflect mainly ventral stream activity that is thought to receive bulk inputs from the P-stream (Allison, Puce, Spencer, & McCarthy, 1999; Bentin, Mouchetant-Rostaing, Giard, Echallier, & Pernier, 1999; Doniger et al., 2000).

Previous ERP studies have repeatedly found reduced P1 amplitudes, supporting the idea that patients exhibit impaired dorsal visual stream activity (Butler et al., 2004; Caharel et al., 2007; Campanella, Montedoro, Streel, Verbanck, & Rosier, 2006; Doniger, Foxe, Murrary, Higgins, & Javitt, 2002; Foxe, Doniger, & Javitt, 2001; Foxe, Murray, & Javitt, 2005; Haenschel et al., 2004; Schechter et al., 2005; Spencer et al., 2003; Yeap et al., 2006), but see (Bruder et al., 1998; Turetsky et al., 2007; van der Stelt, Frye, Lieberman, & Belger, 2004). Further, ventral stream activity, as indexed by N1 amplitude, has been shown to remain relatively intact (Doniger et al., 2002; Sehatpour et al., 2010). In particular, an ERP study conducted by Butler et al. (2007) investigated whether dorsal cortical dysfunction in schizophrenia was partially a consequence of impaired M-input to the dorsal cortical stream. Butler et al. (2007) utilized LSF and HSF stimuli to bias processing towards the M- and P-pathway respectively. Patients exhibited a reduction in the P1, C1 and N1 components in response to LSF stimuli but intact components in response to HSF stimuli (Figure 6) (Butler et al., 2007). This indicated that the cortical response, at the striate and extrastriate level, was impaired by deficient M-stream input. Alternatively, patients were able to generate comparable activations as controls during the P-biased condition, suggesting input from this pathway remained relatively intact. These data also suggested that previously documented dorsal stream response deficits were not due to intrinsic cortical dysfunction only. Along these lines, patients have also demonstrated low detection accuracy and reduced fMRI activation within occipital lobes for LSF sinusoidal gratings (Martinez et al., 2008; O'Donnell et al., 2002).

1.6 Contributions of low-level visual processing to higher-level visual processing

1.6.1 The M-Pathway and object processing

The M-pathway is not only important in early processing, but is also important for later ventral stream processes, such as object and emotion recognition. It is vital to understand how higher-order processing relies on lower-level visual processing integrity to appreciate how emotion processing may be disrupted in the schizophrenia patient population. The following sections expand on M-pathway contributions to both object and emotion processing.

Both M and P pathways play a role in the “frame and fill” model of visual object recognition, in which low resolution information is rapidly projected first to frontal brain areas via the dorsal (M) stream, and then back to the ventral visual areas, to join slower projections of high resolution information, arriving via the ventral (P) stream (Bar, Kassam et al., 2006; Kveraga, Boshyan, & Bar, 2007; Laycock et al., 2007; Schroeder et al., 1998; Vidyasagar, 1999). Thus, according to this model, the initial perception, a ‘gestalt’ global scene, is quickly extracted by the M-pathway, and facilitates or ‘primes’ later ventral stream areas associated with object recognition (Kveraga et al., 2007). A similar process may be involved in emotion recognition. Bar and colleagues (Bar, Kassam et al., 2006; Kveraga et al., 2007) recently found that during a visual recognition paradigm, M-biased stimuli significantly activated pathways from striate/extrastriate cortices to orbito-frontal cortices (OFC), an area associated with object and emotion perception, and from OFC to fusiform gyrus (FG), a ventral object recognition area highly associated with face processing (Kanwisher & Yovel, 2006). Conversely, P-biased stimuli significantly activated a pathway from occipital visual cortex to FG. These data provide evidence that fast M-projections link early dorsal, frontal, and later ventral areas and may play a vital role in connecting networks for emotion perception (Bar, Kassam et al., 2006; Kveraga et al., 2007).

Results from perceptual closure paradigms have also supported the “frame and fill” model. In the perceptual closure paradigm, pictures of objects are presented first with a substantial part of the image occluded, and images that are progressively more complete are presented until subjects can correctly identify the object, that is, when the brain is able to reconstruct, or ‘close’, the whole from its disconnected parts. Activity related to the actual closing of the object has been localized within the lateral occipital complex (LOC) of the ventral visual stream, and named the closure negativity component in ERP paradigms (Doniger et al., 2000; Sehatpour, Molholm, Javitt, & Foxe, 2006). ERP, fMRI and intracranial studies have revealed a widespread network of areas activated during the closure process (from perception to closure). From these studies, researchers proposed that M-information initially projects to the dorsal visual stream and then carries information to inferior frontal cortex and hippocampal regions. From there, back-projections send information to ‘prime’ the LOC, as slower P-information begins to arrive at the same ventral location (Sehatpour et al., 2006; Sehatpour et al., 2008). Accordingly, the confluence of M- and P-biased inputs to the LOC has been shown to result in the ‘closure’ process.

1.6.2 The M-pathway and emotion recognition: behavioral investigations

Behavioral studies have implied that the M/dorsal stream is important for facial affect recognition. Faces themselves are known to be processed holistically, and this type of processing has been shown to be facilitated by LSFs rather than HSFs (Goffaux & Rossion, 2006; Hancock, Bruce, & Burton, 2000; Sergent, 1984; Young, Hellawell, & Hay, 1987). Accordingly, studies have shown that facial configural information contributes to affect recognition (Calder et al., 2000). Facial configuration, perceived as a whole through the integration of independent facial features, is thought to be mediated by the M-pathway/dorsal stream.

To investigate the role of configural information in emotion recognition, Calder et al. (2000) used a paradigm in which the top half of one expression was aligned with the bottom half of a different expression. The participants, asked to identify the emotion of only one half, were slower to identify the expression in either half of the face when the two halves were aligned as opposed to when the two halves were misaligned. Global processing of the aligned face made it more difficult for subjects to respond, and this effect disappeared when the perceptual whole was abolished by misalignment (Calder et al., 2000; Leder et al., 2001). This result suggests that like facial identification, the emotion of a face is processed as a perceptual whole.

Further, Schyns and Oliva (1999) asked subjects to identify the gender or expression on a hybrid face consisting of one LSF face superimposed on one HSF face of different genders and emotions. The data revealed that emotion identification repeatedly depended upon LSF information and gender identification relied on HSF information. This finding has been replicated with the "Bubbles" technique and other methodologies as well (see Adolphs, 2002; Gosselin & Schyns, 2001; Schyns, Bonnar, & Gosselin, 2002). Further, Bar et al. (2006) found that participant judgments regarding emotional content of a face was more dependent on LSFs versus HSFs (Bar, Neta, & Linz, 2006).

The global processing of facial emotion and use of LSFs rather than HSFs to identify emotion suggest that the M-stream plays an important role within emotion processing and recognition. What about neurophysiological evidence as it pertains to emotion perception?

1.6.3 The M-pathway and emotion recognition: neurophysiological investigations

Researchers have utilized event-related potentials (ERPs) to examine M- and P-pathway contributions to facial affect processing.

Currently, there is no consensus in the literature as to when emotion exerts its effects. A number of studies have found that the P1 potential varies by emotion (Keil et al., 2001; Pizzagalli, Regard, & Lehmann, 1999; Pizzagalli et al., 2002; Turetsky et al., 2007), while others do not (Caharel et al., 2007; Obayashi et al., 2009). Pourtouis et al. (2005) conducted a study using SF manipulated emotion stimuli in order to investigate visual pathway contribution to emotion perception. Firstly, they showed that the P1 amplitude was enhanced to LSF emotional stimuli versus non-manipulated stimuli in general. They also demonstrated that the P1 was enhanced to fear versus neutral in both the non-manipulated and LSF conditions. Recent evidence from Vlamings and Goffaux (2009) corroborated this finding, showing that LSF, but not HSF, emotional stimuli elicited a larger P1 amplitude versus neutral stimuli. In a study using non-face emotional and neutral stimuli, the P1 was also enlarged to LSF negative emotional stimuli as compared to LSF neutral stimuli, and non-manipulated stimuli (Alorda, Serrano-Pedraza, Campos-Bueno, Sierra-Vazquez, & Montoya, 2007). These findings suggest that coarse-emotional cues in general (face or non-face), are preferentially extracted by the M-stream and subsequently transmitted to dorsal extrastriate regions as early as ~100 ms.

The N170 component (~170ms post-stimulus onset) has an occipito-temporal distribution and is thought to have a generator in fusiform gyrus (FG), an area hypothesized to be responsible for processing faces (Kanwisher & Yovel, 2006). Its amplitude is enhanced to faces versus other objects and it is also thought to reflect the structural encoding of facial features because of its sensitivity to their spacing and perceptual arrangement (Bentin & Deouell, 2000; Goffaux, Gauthier, & Rossion, 2003; Rossion et al., 1999; Streit, Wolwer, Brinkmeyer, Ihl, & Gaebel, 2001). While some studies have shown the N170 to be insensitive to emotion (Eimer & Holmes, 2002; Herrmann et al., 2002), a number of other studies have shown the N170 varies with emotion (Batty & Taylor, 2003; Eger, Jedynak, Iwaki, & Skrandies, 2003; Pizzagalli et al., 2002), and that larger amplitudes are found in response to emotional versus neutral stimuli (Ashley, Vuilleumier, & Swick, 2004; Blau, Maurer, Tottenham, & McCandliss, 2007; Caharel et al., 2007; Caharel, Courtay, Bernard, Lalonde, & Rebai, 2005; Turetsky et al., 2007; Williams, Palmer, Liddell, Song, & Gordon, 2006). This supports evidence from fMRI studies that have shown robust FG differentiation upon viewing of emotional stimuli (Sabatinelli, Lang, Bradley, Costa, & Keil, 2009; Vuilleumier, Armony, Driver, & Dolan, 2003; Whalen et al., 2004; Winston, Vuilleumier, & Dolan, 2003). Further, the N170 has been shown to be sensitive to SF manipulation as well, with some studies showing larger N170s to HSFs (Nakashima et al., 2008; Obayashi et al., 2009), or LSFs (Vlamings, Goffaux, & Kemner, 2009), but see (Eimer & Holmes, 2002; Holmes, Winston, & Eimer, 2005). Discrepancies in these findings may be based on the range of SFs used, how each study controlled for contrast and luminance differences within stimuli, and cognitive load differences among paradigms. Further, Vlamings et al. (2009) found that the N170 was specifically enhanced to fear versus neutral faces only during the LSF condition, suggesting that LSFs influence early ventral stream processing of emotional faces.

The posterior P250 and the frontal N250 components peak around ~250 ms, and show maximum activity over parieto-occipital and frontal cortices respectively. These components are less well-understood but are thought to be associated with affective-related processes. Indeed, previous studies have shown the components to be differentially sensitive to emotional information (Balconi & Pozzoli, 2003; Carretie, Martin-Loeches, Hinojosa, & Mercado, 2001; Carretie, Mercado, Tapia, & Hinojosa, 2001; Horley et al., 2001; Schutter, de Haan, & van Honk, 2004; Streit et al., 1999; Streit et al., 2001; Wynn, Lee, Horan, & Green, 2008). However, neural mechanisms underlying these components have not been thoroughly addressed within the emotion-perception literature.

In addition to electrophysiology, fMRI studies have provided evidence that the M-pathway plays an important role in driving emotion processing. Studies with healthy controls have revealed that differential responses to emotion in the amygdala and subsequently, fusiform cortex, were driven by LSFs (Vuilleumier et al., 2003; Whalen et al., 2004; Winston et al., 2003). In addition, Vuilleumier et al. (2003) found activation of the pulvinar region of the thalamus and the superior colliculus during the presentation of LSF <u>emotional</u> stimuli only. Further, the amygdala has shown to be differentially activated in response to emotional stimuli even during "blind-sight" studies where faces were presented at an unattended location (Anderson, Christoff, Panitz, De Rosa, & Gabrieli, 2003), masked (Morris, Ohman, & Dolan, 1998), or presented in the blind field of patients with occipital lesions (Hamm et al., 2003). Taken together, these data indicate that emotional information may be, in part, transmitted rapidly and directly from the M-pathway to limbic areas involved in emotion processing, via a sub-cortical route involving the phylogenetically older tecto-pulvinar (superior colliculus and pulvinar) pathway (Liddell et al., 2005; Morris, DeGelder, Weiskrantz, & Dolan, 2001; Vuilleumier et al., 2003). Further, the sensitivity of these areas specifically to LSFs implies the importance of the M-stream during emotion perception.

The neurophysiological data support behavioral evidence that the M/dorsal pathway is indeed important in object and emotion processing. What does this imply for schizophrenia patients?

1.6.4 Object processing deficits in patients with schizophrenia: evidence of M/dorsal stream dysfunction?

ERP perceptual closure studies conducted within the schizophrenia population have provided evidence that the “frame and fill” model breaks down during object recognition processing in patients due to M/dorsal stream dysfunction. Patients demonstrated an impaired P1 component followed later by a reduced ventral closure negativity component, reflective of LOC activation and perceptual closure ability (Doniger et al., 2002; Sehatpour et al., 2010). Conversely, the ventral N1 component was unimpaired, suggesting that later abnormal ventral stream activity (in LOC) was due to dorsal rather than ventral stream dysfunction. Along these lines, recent fMRI data demonstrated reduced activity within dorsal-occipital regions that resulted in widespread abnormal activations of neural regions implicated in the frame and fill model, including ventral visual stream regions (Sehatpour et al., 2010). This network dysfunction may also generalize to, and result in emotion recognition impairment.

1.6.5 Emotion recognition deficits in patients with schizophrenia: evidence of M/dorsal stream dysfunction?

Deficits in facial emotion recognition are among the most well documented impairments in schizophrenia, although the neuronal etiology remains unclear (Kerr & Neale, 1993; Kohler, Walker, Martin, Healey, & Moberg, 2009). There are two competing theories addressing this issue. One theory posits that patients’ deficit is an inherent emotional processing problem stemming from dysfunctional limbic structures (Edwards, Jackson, & Pattison, 2002; Gur et al., 2002; Holt et al., 2006; Kohler et al., 2003; Li, Chan, McAlonan, & Gong, 2009; Schneider et al., 2006). This is supported by older literature showing flat or inappropriate affect in evocative tasks (Aghevli, Blanchard, & Horan, 2003; Berenbaum & Oltmanns, 1992; Kring, Kerr, Smith, & Neale, 1993; Kring & Neale, 1996), deficits in recognition and discrimination of facial emotions (Heimberg, Gur, Erwin, Shtasel, & Gur, 1992; Kohler et al., 2003) and neuroimaging findings that have correlated abnormal activations only in the amygdala with emotional processing impairment (Gur et al., 2007).

The second theory suggests that the deficit reflects a more generalized, visually based dysfunction (Butler et al., 2009; Johnston et al., 2005; Norton et al., 2009; Turetsky et al., 2007)**.** A number of behavioral studies support this latter theory. For instance, studies find similar levels of impairment in non-emotional face processing tasks such as age and gender identification as in emotion recognition (Addington & Addington, 1998; Edwards et al., 2002; Feinberg, Rifkin, Schaffer, & Walker, 1986; Kerr & Neale, 1993; Kohler, Bilker, Hagendoorn, Gur, & Gur, 2000; Salem, Kring, & Kerr, 1996). Patients have also been shown to be able to experience normal levels of emotion in evocative tasks, suggesting relatively undamaged limbic functionality (Berlin, Givry-Steiner, Lecrubier, & Puech, 1998; Burbridge & Barch, 2007; Herbener, Rosen, Khine, & Sweeney, 2007; Herbener, Song, Khine, & Sweeney, 2008; Horan, Green, Kring, & Nuechterlein, 2006; Takahashi et al., 2004). Furthermore, recent studies have shown an association between M-stream dysfunction and emotion identification in schizophrenia, suggesting sensory-level contributions to impaired emotional processing (Butler et al., 2009; Norton et al., 2009).

The association between M-stream dysfunction and emotion recognition impairment is in-line with the finding that in general, patients show deficits in perceiving global form, preferring local features of a visual scene. This has been associated with facial perception dysfunction in schizophrenia (Chen, Nakayama, Levy, Matthysse, & Holzman, 2003; Ferman, Primeau, Delis, & Jampala, 1999; Frith, Stevens, Johnstone, Owens, & Crow, 1983; Goodarzi, Wykes, & Hemsley, 2000). Specifically, patients have exhibited problems processing the face itself as a configural whole and instead, rely mainly on featural-based processing. This has been shown to subsequently interfere with their emotion perception (Joshua & Rossell, 2009; Shin et al., 2008). In turn, configural evaluation has been associated with LSFs while feature-based assessment has been shown to be primarily mediated via HSF information (Calder et al., 2000; Goffaux, Hault, Michel, Vuong, & Rossion, 2005; Goffaux & Rossion, 2006; Joshua & Rossell, 2009; Shin et al., 2008), indicating M/dorsal stream dysfunction in patients impairs their ability to perceive the emotional face correctly (but see Laprevote, Oliva, Delerue, Thomas, & Boucart, 2010).

Several recent psychophysical studies have shown relationships between visual perceptual deficits and impaired emotion recognition in schizophrenia (Butler et al., 2009; Lee, Gosselin, Wynn, & Green, 2010; Norton et al., 2009). In a psychophysical study, we manipulated the contrast of face emotion stimuli and found contrast response functions in controls similar to those found in magnocellular neurons (Butler et al., 2009). Patients with schizophrenia had decreased initial slope and decreased plateau, indicative of involvement of magnocellular impairment in emotion processing deficits.

ERP paradigms have also been implemented to evaluate where and when emotion processing breaks down for patients with schizophrenia. As previously noted, studies have shown that healthy controls exhibit modulations as early as their P1 in response to emotional stimuli, implicating potential M/dorsal stream importance in emotion perception. While some studies have shown that patients have intact P1 amplitudes to non-manipulated emotional stimuli (Herrmann, Ellgring, & Fallgatter, 2004; Johnston et al., 2005; Obayashi et al., 2009; Turetsky et al., 2007; Wynn et al., 2008), others have shown their P1 to be reduced (Campanella et al. 2006; Caharel et al. 2007). Further, Obayashi et al. (2009) found that unlike controls, P1 of patients was insensitive to LSF information implicating patients had input problems from the M-stream (Obayashi et al., 2009). To our knowledge, no other ERP studies investigating emotion perception in patients with schizophrenia have used perceptual characteristic manipulations of facial emotions to investigate visual pathway involvement and dysfunction in emotion perception.

The ventral N170 in patients with schizophrenia has been found to be abnormal in a number of studies involving facial affect perception (Caharel et al., 2007; Johnston et al., 2005; Lynn & Salisbury, 2008; Onitsuka et al., 2006; Turetsky et al., 2007). Further, unlike controls, N170 of patients was found to be insensitive to HSF-manipulated emotional faces (Obayashi et al., 2009). Taken together, these data suggest that FG of patients has abnormal activation and/or emotional modulation during emotional face perception. However, like the P1 component, there is no consensus regarding the N170 impairment in schizophrenia and some have found preserved N170 amplitudes (Streit et al., 2001; Wynn et al., 2008).

Further, patients have been found to have abnormal amplitudes of the later affect-related P250 and N250 in some studies (Caharel et al., 2007; Lee, Kim, Kim, & Bae, 2010; Streit et al., 2001; Wynn et al., 2008) but not in others (Johnston et al., 2005; Turetsky et al., 2007).

fMRI studies investigating face-emotion perception in patients with schizophrenia suggest that early visual pathway dysfunction may affect the entire network associated with emotion perception. For instance, studies have shown that in addition to atypical amygdala (Gur et al., 2002; Li et al., 2009), frontal cortex (Habel et al., 2010) and FG (Li et al., 2009; Quintana, Wong, Ortiz-Portillo, Marder, & Mazziotta, 2003; Walther et al., 2009) activation in response to emotional stimuli, there is less activation in visual cortex (Das et al., 2007; Johnston et al., 2005; Takahashi et al., 2004; Taylor, Phan, Britton, & Liberzon, 2005). In addition, Das et al. (2007) found abnormal relationships between both sub-cortical (including superior colliculus and pulvinar of the thalamus) and cortical visual structures, and the amygdala during emotion perception in schizophrenia. This suggests that M-mediated inputs known to rapidly project to the amgydala via sub-cortical and cortical pathways may be impaired. Further Yoon et al. (2006) found preserved functionality of the fusiform face area (part of the FG) in patients when viewing neutral faces (Yoon et al., 2006). Their findings suggest patients have preserved intrinsic ventral stream functionality when emotional characterization is not required.

Overall, there is no current consensus as to when or where emotion perceptual processing breaks down in schizophrenia. The variable findings among behavioral and neurophysiolgical studies within the schizophrenia population may be related to different tasks (gender identification, emotion identification, object identification), perceptual characteristics of stimuli (different contrast, luminance, SF contetnt), analysis techniques (i.e. peak amplitude versus global field power), and electrode locations. Regardless, a number of studies have implicated that problems within the M/dorsal stream may contribute to emotion recognition dysfunction. The second experiment aimed to clarify what occurs in the visual processing stream during emotion perception, and it evaluated possible underlying neuronal pathology during emotion perception in patients with schizophrenia. We implemented a novel approach to study potential early visual pathway contributions to later affect-related emotion processes and overall emotion recognition ability, using contrast manipulated emotional faces within an emotion recognition and a separate ERP paradigm. Previous emotion perception studies in patients with schizophrenia have not yet utilized this type of perceptual manipulation to assist in the examination of when and where processing breaks down in patients. Altering contrast will allow for the assessment of individual visual pathway contribution's to later affect-related processing and emotion recognition, and will allow for the assessment of how low-level visual pathway dysfunction could lead to higher-order processing dysfunction ultimately resulting in emotion recognition impairment in patients with schizophrenia.

1.7 Oscillatory investigation of visual perception in schizophrenia: new avenues of investigation

Recently, researchers have implemented time-frequency (oscillatory) analysis of EEGs in order to further understand the pathophysiology of schizophrenia (Haenschel et al., 2009; Herrmann & Demiralp, 2005; Kwon et al., 1999; Spencer et al., 2004; Uhlhaas & Singer, 2006). Because patients demonstrate widespread dysfunction in several different cortical areas, and connectivity abnormalities within and among these areas, recent theories suggest that patients with schizophrenia may have a 'disconnection syndrome' and/or neural coordination impairment (Friston, 1999; Phillips & Silverstein, 2003; Uhlhaas & Singer, 2010). In turn, neural oscillations, which are thought to be the mechanisms allowing for temporally coordinated and coherent activity within both local and long-range neuronal circuits, are an informative phenomenon to study within schizophrenia (Uhlhaas & Singer, 2010). Further, studies have shown that frequency characteristics of patients' EEG are similar between first-episode and chronic, medicated patients, suggesting that long-term treatment and illness duration have no overall differential effects on these potential trait markers (Sponheim, Clementz, Iacono, & Beiser, 1994). Specifically, this part of the dissertation addresses the differences in oscillatory activity between controls and patients when viewing complex stimuli.

1.7.1 What is measured in time-frequency analysis?

Oscillatory activity is derived by the spectral decomposition of the EEG signal into magnitude and phase information representative of sine-waves of all frequencies present within the EEG over a certain time period. Researchers are able to then quantify the power and phase-synchrony information of a particular frequency (or frequency range) at each time point based on its magnitude and phase information.

The power within a frequency range can be evaluated as either evoked or induced. "Evoked" oscillatory activity refers to oscillations that are phase-locked to a stimulus event over a number of trials. These oscillations have been implicated in the early perceptual processing of visual stimuli (Fries, Reynolds, Rorie, & Desimone, 2001; Tallon-Baudry, Bertrand, Delpuech, & Pernier, 1996). Phase-locked frequencies survive averaging across trials and result in the subsequent ERP waveform. Other frequencies that are not phase locked to the stimulus event however, do not survive averaging over trials, and ultimately sum up to zero. In order to investigate evoked-power therefore, the spectral decomposition is conducted on the averaged ERP waveform. “Induced” activity on the other hand emerges from conducting the spectral decomposition on a single event-trial basis with subsequent averaging of the single event-trial information. Importantly, these oscillations are not strictly phase-locked to the stimulus-event and are thought to reflect internally generated processes related to the stimulus event, but not phase-locked to it.

There are a variety of synchrony and coherence measures used within time-frequency analyses. One of the most prevalent measures within visual perception literature is what is termed “inter-trial phase coherence (ITC)” or the “phase locking factor (PLF)”. These two terms both refer to the consistency in the phase of the oscillation in response to a stimulus event across single trials at an electrode location. The measure specifically reflects the variance of phase across single trials, and is independent of the magnitude or ‘power’ of the oscillation.

1.7.2 Potential functions (and dysfunctions) of distinct frequency bands

From this type of analysis, certain frequency bands have been identified as especially relevant, and evaluated within both healthy and schizophrenia patient populations. Discrete frequency bands are thought to mediate different cognitive and sensory processes. For instance, oscillations within lower-frequencies (delta: 1-3 Hz; theta: 4-8 Hz; alpha: 8-14 Hz) are thought to synchronize neuronal ensembles over long-ranges because they are less susceptible to phase-jitter (Buzsaki & Draguhn, 2004; Lakatos et al., 2008; von Stein, Chiang, & Konig, 2000) while the beta (~15-29 Hz) and gamma (~30-100 Hz) ranges (high-frequency oscillations) are thought to efficiently orchestrate the activity of local neural populations (Gray, Konig, Engel, & Singer, 1989; Womelsdorf et al., 2007).

The delta oscillatory range (~1-3 Hz) has been shown to be an active mechanism that underlies stimulus selection for processing (Lakatos et al., 2008). For instance, during a selective attention paradigm, Lakatos et al. (2008) found that the phase of the delta oscillation (within macaque V1) modulated in response to rhythmically predictable stimuli such that relevant stimuli appeared at the highest peak of the delta oscillation (most excitable state) and the irrelevant stimuli appeared when the oscillation was at its lowest peak (least excitable state). In addition, higher frequency bands exhibited power modulation that was associated with the delta oscillatory phase-shift. Further, delta-band activity has been associated with salience detection and evaluation of visual stimuli (Battaglia, Sutherland, & McNaughton, 2004; Knyazev, 2007; Steriade, 1997).

Event-related delta-frequency oscillations have been shown to be reduced in patients with schizophrenia during information processing studies that have included target-detection, response inhibition, error detection (Bates, Kiehl, Laurens, & Liddle, 2009; Doege et al., 2010), and visual oddball paradigms (Ergen, Marbach, Brand, Basar-Eroglu, & Demiralp, 2008). Researchers have taken these findings to indicate that reduced delta activity may result in the failure to register the saliency of relevant stimuli and inefficient perceptual processing of those stimuli. Further, these rhythms have been found to have elevated spontaneous activity in the schizophrenia population pre-stimulus onset, and throughout the ongoing EEG (Bates et al., 2009; Fehr et al., 2003). In addition, the elevation of spontaneous delta-wave activity has been shown to be associated with general lowered states of consciousness and different forms of brain injury like tumors (Fernandez-Bouzas et al., 1999) and brain lesions (Gilmore & Brenner, 1981).

Oscillations within the theta-band (4-7 Hz) are associated with selective attention, orienting to salient stimuli, and memory encoding and retrieval (Dragoi & Buzsaki, 2006; Pare, 2003; Rizzuto et al., 2003). Their association with memory is bolstered by data showing that stimulation at theta frequencies induces long-term potentiation (LTP) (Larson & Lynch, 1988). Further, LTP has been found to be sensitive to the phase of the ongoing theta oscillation. If stimulation occurs at the peak of the theta oscillation then LTP is induced but if stimulation occurs during the trough of the theta oscillation, depotentiation occurs (Holscher, McGlinchey, Anwyl, & Rowan, 1997; Pavlides, Greenstein, Grudman, & Winson, 1988). This rhythmic band has also been implicated in the gating of incoming information to limbic areas (Vinogradova, 1995).

Theta oscillations have been found in a number of areas within the brain including the hippopcampus, somatosensory, prefrontal and visual cortex and superior colliculus (Raghavachari et al., 2006; Tsujimoto, Shimazu, & Isomura, 2006). Underlying cell types associated with theta oscillatory activity include GABAergic inhibitory interneurons and excitatory glutamatergic neurons (involving NMDA-receptors) (Larson & Lynch, 1988; Leung & Shen, 2007; White, Banks, Pearce, & Kopell, 2000).

Theta-band rhythms have recently been found to be abnormal in the patient population during working memory (Schmiedt, Brand, Hildebrandt, & Basar-Eroglu, 2005), go/no-go (Bates et al., 2009) and simple visual perception tasks (Basar-Eroglu, Schmiedt-Fehr, Marbach, Brand, & Mathes, 2008; Winterer et al., 2004). Like the delta band, its power has also been shown to be relatively elevated compared to controls prior to stimulus onset and during the ongoing EEG (Bates et al., 2009; Winterer et al., 2004; Winterer et al., 2000). Taken together, these findings suggest impaired coordination of slow-wave activity contributes to a break down in information processing in the patient population.

Rhythmic activity within the alpha-band (8-14 Hz) is associated with different states of arousal (Basar & Schurmann, 1994; Klimesch, Doppelmayr, Russegger, Pachinger, & Schwaiger, 1998; Pfurtscheller, 1992; Ramos-Loyo, Gonzalez-Garrido, Amezcua, & Guevara, 2004) and has been shown to have a noticeable increase in power over occipital sites when subjects' eyes are closed. A subsequent reduction in alpha power, when the eyes are open, has been associated with active stimulus processing. In fact, alpha activity has been heavily implicated in suppression and enhancement ('gating') processes of sensory stimuli within striate and extrastriate cortices during intersensory, working memory, and object-discrimination paradigms (Foxe, Simpson, & Ahlfors, 1998; Gomez-Ramirez et al., 2007; Kelly, Gomez-Ramirez, Montesi, & Foxe, 2008; Kelly, Lalor, Reilly, & Foxe, 2006; Sauseng et al., 2006). Importantly, alpha-band activity has also been shown to be predictive of behavioral performance (i.e. reaction time and sensitivity measures) (Kelly et al., 2008; Thut, Nietzel, Brandt, & Pascual-Leone, 2006).

Alpha activity has been found within the thalamus but is also evident over parieto-occipital cortices. Alpha activity is thought to be generated by small groups of localized cells that send distributed activity through cortico-cortical and cortico-thalamic connections (Steriade, Gloor, Llinas, Lopes de Silva, & Mesulam, 1990). Further, its cortical generators have been localized to layers IV and V of visual cortex (Silva, Amitai,

& Connors, 1991; Steriade, 1997). Alpha activity is thought to originate from the interplay of excitatory and inhibitory neuronal interactions involving serotonergic, cholinergic GABAergic and glutamatergic receptors (Millson et al., 1991).

A number of studies have evaluated resting-EEG alpha-activity within the schizophrenia population and found that its power is reduced as compared to controls (Iacono, 1982; Sponheim et al., 1994). Researchers suggested that reduced alpha-activity in patients may result from impaired generation of alpha activity from pacemaker cells in the thalamus, suggesting sub-cortical dysfunction (Sponheim et al., 1994). There are few studies evaluating visual event-related alpha band activity in the patient population. In regards to visual stimuli, patients have exhibited abnormal amplitude modulations over occipital and frontal leads while viewing complex stimuli (Ramos-Loyo, Gonzalez-Garrido, Sanchez-Loyo, Medina, & Basar-Eroglu, 2009), and atypical topographical distribution, but relatively preserved power and synchrony as compared to controls when viewing simple stimuli (Basar-Eroglu et al., 2008). These data indicate possible impairments in visual sensory gating in schizophrenia.

Beta-band oscillations (15-29 Hz) are implicated in sensory gating (Hong, Buchanan, Thaker, Shepard, & Summerfelt, 2008), object recognition (Sehatpour et al., 2008; Uhlhaas et al., 2006), motor control (Alegre et al., 2004; Kilner, Baker, Salenius, Hari, & Lemon, 2000), and emotional perception (Guntekin & Basar, 2010; Marosi et al., 2001). In general, the beta-band, is thought to tag certain stimuli as salient and in need of further evaluation. They have also been implicated in polymodal sensory coordination over long-distances (White et al., 2000). Beta-band activity has been demonstrated in widespread cortical regions and within sub-cortical areas, including: hippocampus, basal ganglia and thalamic nuclei. The beta-range activity has been associated with glutamatergic, NMDA-mediated, GABAergic and dopaminergic receptor complexes (see Uhlhaas, Haenschel, Nikolic, & Singer, 2008).

In addition, patients with schizophrenia have exhibited reduced ability to perceive gestalt stimuli along with a reduction in beta-band phase synchronization (Uhlhaas et al., 2006). Further, ssVEP generation involving beta-frequencies was found to be reduced as compared to controls, indicating dysfunction of basic visual responses (Krishnan et al., 2005).

Finally, gamma-band rhythms are thought to play a major role in visual perception and visual feature binding, coordinating activity in both striate and extrastriate cortices (Gray et al., 1989; Singer & Gray, 1995). They have been shown to modulate in response to changes in perceptual characteristics of stimuli as well, such as size and eccentricity (Busch, Debener, Kranczioch, Engel, & Herrmann, 2004). Along these lines, coordinated rhythmic activity within this band has been shown to help with object recognition processes (Yuval-Greenberg & Deouell, 2007) including the processing of a coherent percept (‘gestalt’) (Keil, Muller, Ray, Gruber, & Elbert, 1999). Gamma-band activity has also been implicated in higher-order processes such as working memory (Colgin et al., 2009; Siegel, Warden, & Miller, 2009). Gamma-activity has been observed in widespread regions of cortex, including visual cortex and the retina subsequent to visual stimulation. Gamma-frequencies have been shown to originate from the activity of GABAergic, glutamatergic, and cholinergic neurotransmitter systems (Atallah & Scanziani, 2009; Traub, Bibbig, LeBeau, Buhl, & Whittington, 2004).

Because gamma synchrony is implicated as a mechanism for the integration of neuronal processes throughout distributed brain regions and is thought to ultimately lead to coherent perceptions, the majority of visual perceptual studies within the schizophrenia literature have focused on its dysfunction (Herrmann & Demiralp, 2005; Schnitzler & Gross, 2005; Spencer et al., 2003; Spencer et al., 2004). Specifically, visual perceptual gamma-activity impairment has been shown in the patient population during visual backward masking, visual oddball, illusory contour, and gestalt and emotional face perception paradigms (Spencer, 2008; Spencer et al., 2003; Spencer et al., 2004; Spencer, Niznikiewicz, Shenton, & McCarley, 2008; Symond, Harris, Gordon, & Williams, 2005; Uhlhaas et al., 2006; Williams, Whitford, Nagy et al., 2009; Wynn, Light, Breitmeyer, Nuechterlein, & Green, 2005), suggesting that abnormal visual gamma-band activity within occipital regions may be a general sensory-level pathology. Further support for this hypothesis comes from data demonstrating gamma-band alterations in unmedicated, first-episode and chronic patients (Gallinat, Winterer, Herrmann, & Senkowski, 2004; Spencer, 2008; Spencer et al., 2008; Williams, Whitford, Gordon et al., 2009; Williams, Whitford, Nagy et al., 2009). In addition, atypical gamma-band activity has also been found in patients when they performed higher cognitive tasks involving executive functions like working memory (Basar-Eroglu et al., 2007) and emotion discrimination (Williams, Whitford, Nagy et al., 2009).

However, visual perceptual dysfunction in patients cannot solely be explained by altered gamma-band activity. Further, oscillations that occur within different frequency bands do not function in isolation from one another and the nature of their interaction is thought to be critical in assisting the brain perform sensory, perceptual and higher-level cognitive functions. Therefore, it is important to investigate the function and dysfunction of other frequency-bands within the patient population during visual perception.

To this end, Experiment 3 will conduct frequency and time-frequency analyses on EEG data collected in response to the perception of complex face stimuli in patients and controls. The study will specifically evaluate between-group differences in delta, theta and alpha band induced activity averaged across time, and then unfolded across time as these bands have been relatively unexplored during visual perception in patients.

1.8 Objectives

The overarching goal of this dissertation is to further the understanding of early visual pathway pathology in the schizophrenia patient population and how this impairment affects a higher-order cognitive process like emotion recognition.

Experiment 1 (Chapter 2) was conducted in order to further clarify M-stream impairment in patients with schizophrenia. Their preferential impairment is still a matter of debate within the literature. We utilized a well-validated contrast threshold paradigm using different SF stimuli that were presented at different luminance levels. Scotopic levels were included in order to try to isolate M-pathway function and minimize P-pathway involvement in vision. Photopic luminance levels, and HSFs were utilized to push the visual system to saturate the M-stream in order to evaluate P-pathway processes. **This particular approach has not been yet utilized within the schizophrenia literature.** We hypothesized that; (1) during the scotopic conditions, the M-stream would be successfully isolated, and we would see between-group differences in contrast-thresholds, indicative of a sub-cortical M-stream dysfunction, and; (2) patients would improve their contrast thresholds similarly to controls as contrast increased indicating that P-biased information was being used effectively.

Experiment 2 (Chapter 3) was conducted in order to investigate early visual pathway deficits and their contribution to emotion recognition impairment in schizophrenia. Recent studies have associated M/dorsal stream impairments in schizophrenia patients with emotion recognition, implying that the deficit is a general consequence of early visual pathway dysfunction.

We conducted separate behavioral and ERP investigations with contrast-manipulated stimuli in order to investigate dichotomous visual pathway contributions to later affect-related processes. We evaluated low-level visual-emotion processing integrity in patients using contrast response functions of the dorsal P1 and the ventral N170. We also evaluated the relationship of the dorsal and ventral components to the later affect-related P250, and each component's relation to behavioral performance. The main hypotheses were that; (1) patients would demonstrate emotion recognition deficits; (2) the dorsal P1 component would show a typical M-related contrast response curve, and patients would show robust differences compared to controls; (3) the ventral N170 would remain relatively intact in the patient population; (4) patients would show a deficit in the later affect-related P250 component; and (5) the dorsal P1 component would be related to affect-related processing (P250) and emotion recognition performance.

Experiment 3 (Chapter 4) examined lower-frequency-band characteristics (delta, theta, alpha) within the patient population when viewing complex face stimuli and performing an implicit task. Most visual perceptual paradigms investigating frequency-band activity have focused on evoked-power and synchrony differences within the gamma-band in the patient population. However, each frequency band does not function in isolation and lower frequency-activity has been shown to be important in visual perception. Therefore, Experiment 3 will analyze lower-frequency band activity in patients and controls during an implicit event-related visual paradigm.

CHAPTER 2

Psychophysical assessment of magnocellular and parvocellular visual pathway function in schizophrenia via a luminance altered contrast threshold paradigm

1. Abstract

A growing literature has focused specifically on low-level visual processing impairment in patients with schizophrenia. Data reveal that patients have preferential magnocellular (M) versus parvocellular (P) dysfunction. The purpose of the current study was to further characterize M-stream impairment in the patient population using a novel approach. Contrast thresholds at varying luminance levels (from scotopic to photopic) were investigated. M-biased responses were examined by using scotopic luminance conditions, while P-biased responses were examined using photopic luminance conditions. Patients exhibited contrast threshold deficits during scotopic luminance conditions, indicative of M-stream dysfunction. Further, as luminance increased to photopic levels and the P-stream was activated, both patients and controls improved their contrast thresholds similarly, suggesting relatively preserved P-pathway function.

2. Introduction

Patients with schizophrenia exhibit low-level visual processing dysfunction that is now considered a central element of their pathology (Butler et al., 2009; Kraepelin, 1904). A growing literature has focused on visual processing impairment and its contribution to functional outcome, implicating its clinical importance (Brenner et al., 2002; Butler, Zemon et al., 2005; Keri, Kiss et al., 2005; Laycock et al., 2007; Sergi & Green, 2003; Sergi et al., 2006). Clinical visual processing studies have been based upon a model of the visual system in which distinct perceptual attributes of visual stimuli are processed in parallel via two separate sub-cortical pathways: the magnocellular (M) and parvocellular (P). These previous studies have attempted to manipulate perceptual attributes of stimuli in order to bias processing to the M- and P- pathways and subsequently look at potential compromise within each (Butler, Gur et al., 2005; Butler et al., 2001; Keri et al., 2002; Keri & Benedek, 2007; Saccuzzo, Cadenhead, & Braff, 1996). Indeed, a number of neurophysiological studies have demonstrated deficits within both the sub-cortical M-stream and corresponding cortical dorsal visual pathway of patients (Butler et al., 2007; Butler et al., 2001; Butler, Zemon et al., 2005; Keri et al., 2002; Kim et al., 2006; Kim et al., 2005; Martinez et al., 2008; Slaghuis & Bishop, 2001). Further, these data lend support to behavioral findings of preferential M- versus P-pathway visual perceptual dysfunction in schizophrenia (Butler et al., 2001; Cadenhead et al., 1998; Keri et al., 2002; Keri et al., 2004; Kim et al., 2006; Schechter et al., 2003; Slaghuis & Bishop, 2001). However, it remains difficult to effectively bias processing towards the M- versus P- pathway. This study will use a novel approach using luminance manipulation to evaluate visual pathway function in patients.

The visual system is divided into two main sub-cortical pathways (M and P) that project discretely and in parallel from the retina, via the lateral geniculate nucleus (LGN) of the thalamus to primary visual cortex (V1). From there, the M-system projects to the dorsal visual stream (located within parieto-occipital cortex), while the P-stream projects to the ventral visual stream (located within temporo-occipital cortex). Substantial cross-over between pathways occurs beginning in V1 (Liddell et al., 2005; Lund, 1973; Merigan & Maunsell, 1993; Schiller et al., 1979; Schroeder et al., 1998).

These pathways also differ functionally by preferred stimulus attributes. M-neurons are larger, quickly conducting and prefer low/scotopic-luminance levels (<1 cd/m^2) and high temporal frequencies of stimuli. M-neurons receive input from larger areas of the visual field, resulting in sensitivity to larger stimuli (low-spatial frequency, LSFs). Alternatively, P-neurons are smaller and more slowly conducting. They are sensitive to higher mesopic (~1-30 cd/m^2) and photopic luminance levels (>30 cd/ m^2), slower temporal frequencies and smaller stimuli (high-spatial frequencies, HSFs) (Dacey & Petersen, 1992; Derrington & Lennie, 1984; Kaplan, 1991; Tootell, Silverman et al., 1988). Further, both pathways respond differentially to different levels of contrast. The M-system exhibits a non-linear response function over low to mid-range contrasts. There is high, initial gain, indicating an amplification of neuronal response at low contrasts (1-10% contrast), with a saturation of response occurring around 16-32% contrast. On the other hand, P-neurons do not begin responding until about 10% contrast, and their response pattern is fairly linear as contrast increases (Kaplan, 1991; Tootell, Hamilton, & Switkes, 1988).

An efficient method used to evaluate visual system functionality is to determine the contrast needed (contrast threshold) for the reliable detection of different spatial frequency (SF) gratings at threshold (Butler, Gur et al., 2005; Chen, Levy, Sheremata, & Holzman, 2004; Slaghuis, 2004; Slaghuis & Bishop, 2001; Slaghuis & Thompson, 2003). By plotting threshold as a function of SF under specific conditions, human M- and P-pathway properties can be examined (e.g. Figure 5) (Slaghuis, 1998). SF gratings are commonly used to elicit contrast threshold curves because their perceptual traits, including average luminance, contrast, SF, phase, and temporal frequency can be varied to bias processing towards M- and P- pathways.

Overall, patients with schizophrenia have demonstrated deficits in contrast threshold for LSF and high temporal frequency stimuli, supporting evidence of M-stream dysfunction (Butler, Zemon et al., 2005; Keri et al., 2002; Slaghuis, 1998, 2004). However, these previous studies used mid to high background luminance-levels which may not have optimally biased processing to the M- versus P-pathway during SF contrast threshold detection. In this way, a sensitive enough paradigm to evaluate visual pathway dysfunction in schizopnrenia may not be currently available. To further clarify potential visual pathway abnormalities in schizophrenia, we propose to use luminance-level manipulation during a contrast threshold paradigm.

Indeed, luminance manipulation may be exploited to heavily bias processing towards the M-pathway. Evidence suggests that rod photoreceptors mediate scotopic vision, sending information primarily to M-ganglion cells. Alternatively, at higher luminance levels, both rod and cone signals have been shown to converge on the same ganglion cell (Enroth-Cugell, Hertz, & Lennie, 1977; Gouras & Link, 1966; Lee et al.,

1997) and overlap via gap junctions, sending their information to a mixture of M- and P-retinal cells (Abd-El-Barr et al., 2009; Dowling, 1987). Regardless, Purpura et al. (1988) demonstrated that M-ganglion cells in the non-human primate retina were solely activated in response to SF stimuli presented at scotopic luminance levels. Further, higher luminance levels appeared to saturate M-neuronal responses. In this way, it seems that scotopic luminance may be an appropriate way to bias processing towards the M-stream, while higher luminance levels may help investigate P-stream function as M-neurons saturate in their response.

Benedek et al. (2003) implemented a contrast threshold paradigm using SF gratings presented at a range of luminance levels and SFs to investigate the feasibility of using scotopic luminance conditions to bias processing towards the M- or P-system in healthy controls. They elicited behavioral and neurophysiological contrast threshold functions in humans during scotopic and photopic vision that paralleled those found in animal neuronal-recordings within M- and P-neurons, respectively. These data suggest that the scotopic luminance condition successfully parsed the M- from the P- pathway while high photopic conditions were able to bias processing towards the P-stream, indicating these manipulations could be used in clinical populations for visual pathway assessment purposes.

To our knowledge, only one other study has used a range of luminance levels during a contrast threshold paradigm to investigate visual pathway compromise within the schizophrenia patient population. Slaghuis and Bishop (2001) conducted a contrast threshold paradigm with flicker stimuli of varying temporal frequencies presented at 3 cd/m^2, 33 cd/m^2, and 66 cd/m^2 luminance levels. They concluded that contrast threshold impairment found in the schizophrenia population at mid-high temporal frequencies and mesopic luminance levels indicated a possible preferential M-stream dysfunction. However, the lowest luminance level used was within the mesopic range (1-30 cd/m^2), and SF gratings were not utilized in the contrast threshold paradigm.

The current study evaluates M- versus P- pathway function by implementing a reliable contrast threshold paradigm, using SFs presented at different luminance levels ranging from scotopic to photopic (see Benedek et al., 2003). We will also utilize two stimulus durations (32 ms and 500 ms) to avoid ceiling contrast threshold effects at low-luminance and floor contrast threshold effects at high luminance. Our goals for the study are two-fold. First, we would like to evaluate the integrity of the M-pathway in patients with schizophrenia using scotopic luminance levels. Scotopic luminance will prevent the introduction of dominant P-pathway processing, and bias processing towards the M-pathway. Secondly, we would like to investigate whether any differential benefit in contrast threshold is obtained for controls versus patients through the introduction of P-information during mesopic and photopic luminance conditions. Similar between-group improvements in performance due to the ability to utilize P-biased information would indicate relatively preserved P-pathway functionality.

3. Methods

Participants

Overall, 24 patients and 20 controls participated in this study. In the 32 ms condition, there were 23 patients (21 male) (one male patient did not complete this condition), and in the 500 ms condition, 22 patients (20 male; two male patients did not complete testing) participated. Patients met the Diagnostic and Statistical Manual of

Mental Disorder (Fourth Edition) (DSM-IV) criteria for schizophrenia (n = 21) or schizoaffective (n = 3) disorder. There were also 19 healthy volunteers in the 32 ms condition (15 male; one male control did not complete this condition) and 20 (16 male) healthy volunteers in the 500 ms condition.

Patients were recruited from inpatient (n = 8) and outpatient (n = 16) facilities associated with the Nathan Kline Institute for Psychiatric Research. Diagnoses were obtained using the Structured Clinical Interview for DSM-IV *(*SCID) and all available clinical information. Controls were recruited through the Volunteer Recruitment Pool at the Nathan Kline Institute. Healthy volunteers with a history of SCID-defined Axis I psychiatric disorder were excluded if they had any neurological or ophthalmologic disorders that might affect performance or met criteria for alcohol or substance dependence within the last 6 months or abuse within the last month. All participants provided informed consent according to the Declaration of Helsinki. This study was approved by the Nathan Kline Institute for Psychiatric Research/Rockland Psychiatric Center and Rockland County Department of Mental Health Institutional Review Boards.

Clinical and demographic information are included in Table 1. The patient and control groups did not differ significantly in age (32 ms: t_{40} = -.3, p =.77; 500 ms: t_{40} = -.08, p =.94), gender (Fisher's exact test, 32 ms: p = .38; 500 ms: p = .4), or parental socioeconimc status (32 ms: t_{35} = .12, p = .90; 500 ms: t_{34} = .2, p= .84). All patients were receiving antipsychotic medication at the time of testing. Chlorpromazine equivalents were calculated using conversion factors described previously (Hyman SE, 1995; Jibson & Tandon, 1998; Peuskens & Link, 1997). All participants had 20/32 or better corrected visual acuity on the Logarithmic Visual Acuity Chart (Precision Vision, LaSalle, IL).

Apparatus

Patterns were generated using the VENUS system (Neuroscientific Corporation, Farmingdale, NY) on a red-green-blue monitor with a frame rate of approximately 119 Hz (non-interlaced). At a viewing distance of 150 cm, the stimulus fields subtended 5.7 x 5.7 degrees of visual angle. The space-average luminance was altered, depending on condition.

A chin rest was used to ensure stability of the participants' heads during testing. Attached to the chin rest was a 50.8 cm x 50.8 cm black plastic board with a 13.34 cm x 13.34 cm square opening cut in the center. Neutral density filters were placed in front of the opening to achieve varying levels of luminance throughout testing. Experimenters ensured that participants could see the viewing screen through the opening with each eye individually, in addition to binocularly to ensure there was no obstruction of view.

Luminance Levels

To investigate scotopic, mesopic and photopic visual functionality, the contrast threshold paradigm was administered at 5 luminance levels (.01, 0.1, 1, 10, and 100 candelas per meter squared, cd/m^2). The decrease in luminance was achieved by Kodak Wratten Neutral Density Filter Gelatins of 2 and 1 log units. Without any filters, the luminance of the screen was 100 cd/m^2. Using two 2 filters produced .01 cd/m^2; a 2 and a 1 filter produced .1 cd/m^2; a 2 filter produced 1 cd/m^2; a 1 filter produced 10 cd/m^2. Luminance levels of .01 cd/m^2 and .1 cd/m^2 were considered scotopic, 1 cd/m^2 and 10 cd/m^2 were considered mesopic and 100 cd/m^2 was considered photopic based on previous literature (i.e. Benedek et al., 2003; Slaghuis & Bishop, 2001). The paradigm began with the lowest luminance (.01 cd/m^2) and participants were dark adapted for 20 minutes before any testing began. Participants were given 2 minute breaks between each luminance level to allow for adaptation to the new lighting condition.

Stimuli and Procedure

Log threshold functions, which are the reciprocal of log-contrast sensitivity functions (as previously described by Butler et al. 2005), were obtained. Horizontal sine-wave gratings were presented for 32 ms and 500 ms in separately conducted paradigms (Figure 1). Contrast thresholds were measured at 3 different spatial frequencies (.56, 4.47, and 11.18 cycles per degree, c/deg) and at 5 different luminance levels (.01, .1, 1, 10, and 100 cd/m^2). Stimuli were administered by the Venus system.

A spatial 2-alternative forced-choice procedure was used. SF gratings were presented randomly on one-half (either the right or left side) of the visual display, with the other side having a constant uniform field. Participants stated on which side they saw the grating appear, and the experimenter recorded the answer with a key-pad to minimize response errors. An up-down transformed response method (UDTR) was implemented to obtain contrast thresholds for participants with a criterion of 70.7% correct responses for each SF grating at each luminance level. For each SF, contrast was changed in 3 dB steps for each correct (decrease) or incorrect (increase) response until 2 errors were made. Then, the UDTR rule began, and contrast was changed in 1.5 dB steps. The mean of 10 reversals was used to obtain contrast thresholds. Results were plotted as the log-transform of the contrast threshold versus SF. Lower thresholds indicate better performance.

Statistical Analysis

For the 32 ms condition, the.01 cd/m^2 condition elicited a ceiling effect of a threshold at ~100% contrast for each SF in both groups (Figure 2A). Because of the ceiling effect, this luminance level will be excluded from further analysis for the 32 ms condition. For the 32 ms condition, an overall 2 Group (controls, patients) x 4 Luminance level (.1, 1, 10, 100 cd/m^2) x 3 Spatial Frequency (.56, 4.47, and 11.18 c/deg) mixed-design ANOVA was conducted. For the 500 ms condition, the same mixed-design ANOVA was conducted, however there were 5 Luminance levels (.01, .1, 1, 10, 100 cd/m^2). Appropriate follow up ANOVAs and post-hoc t-tests were applied when the analyses of variance revealed significant main effects or interactions.

Significance everywhere was judged at a two-sided level of significance α=0.05. Analyses were conducted using SPSS software (Chicago, Ill).

4. Results

32 ms

For the 32 ms condition, threshold response functions at the scotopic luminance reflected characteristic M-stream characteristics with lowest threshold (best performance) at the lowest SF, indicating that processing was successfully biased towards the M-pathway. In addition, there was a main effect of Group ($F_{1,40} = 17.2$, $p < .001$) with controls having lower thresholds/better performance versus patients. There was also a main effect Luminance ($F_{3,38} = 517$, $p < .001$) with decreased thresholds as luminance increased (Figure 3). Finally, there was a main effect of SF ($F_{2,39} = 392$, $p < .001$) that resulted from increased thresholds as cycles per degree increased (Figure 2). In addition, there was a Luminance x SF interaction ($F_{6,35} = 19.35$, $p < .001$), and a Group x Luminance x SF interaction ($F_{6,35} = 2.69$, $p = .03$).

Follow-up repeated measures ANOVAs were conducted at each Luminance with Group as the between-subjects factor and SF as the within-subjects factor to investigate the 3-way interaction. There was a main effect of Group ($F_{1,40} = 9.6 - 24$, P = .003 - <.001) and SF ($F_{2,39} = 39.8 - 393.9$, P <.001) at each luminance level. There was a Group x SF interaction only at .1 cd/m^2 ($F_{2,39} = 13.3$, P <.001). Patients showed a robust deficit at the scotopic luminance (.1 cd/m^2) for .56 and 4.47 c/deg ($t_{40} = 5.2$, p < .001; $t_{40} = 3.8$, p = .001 respectively) (Figure 2B). The convergence of threshold at ceiling levels at .1 cd/m^2 and 11.18 c/deg may be due to the greatly reduced efficiency of the M-system at resolving HSFs during scotopic conditions (Savage & Banks, 1992). Conversely, at the higher luminance conditions (1, 10, 100 cd/m^2), between-group differences were similar across SFs (p >.11) (Figure 2C-E).

Effects across higher luminance levels (once P-biased information was introduced) were then evaluated within each SF (Figure 3). A repeated measures ANOVA was conducted with Group as the between-subjects variable and Luminance (1, 10, 100 cd/ m^2 only) as the within-subjects variable at each SF. There were Group ($F_{1,40} = 3 – 18.7$, p = .005 - <.001) and Luminance ($F_{2,39} = 117.2 - 128.4$, p = <.001) main effects but no Group x Luminance interactions for each SF (p > .08). These data indicate that the deficit in threshold in patients was similar across mesopic and photopic conditions for all three SFs (Figure 3A-C). Both patients and controls were able to use P-biased information effectively to improve their performance similarly, indicating relatively preserved P-pathway function in patients.

500 ms

The 500 ms condition was conducted in order to look at contrast thresholds at the lowest scotopic luminance (.01 cd/m^2) while avoiding ceiling effects elicited in the 32 ms condition. Threshold response functions reflected M-stream characteristics during the scotopic .01 cd/m^2 and .1 cd/m^2 conditions, with lowest threshold (best performance) at the lowest SF, indicating that processing was successfully biased towards the M-stream. There was a main effect of Group ($F_{1,40}$ = 25.6, p <.001), SF ($F_{2,39}$ = 193.7, p <.001) and Luminance ($F_{4,37}$ = 187, p <.001). In addition, there was a Group x Luminance ($F_{4, 37}$ = 3.23, p =.023), Luminance x SF ($F_{8,33}$ = 35.4,p <.001), and a Group x Luminance x SF interaction ($F_{8,33}$ = 2.29, p = .045).

Follow up repeated measures ANOVAs were conducted at each Luminance with Group as the between-subjects factor and SF as the within-subjects factor to investigate the 3-way interaction. There was a Group ($F_{1,40}$ = 13.5 – 27.3, p = .001 - <.001) and SF ($F_{2,39}$ = 51.6 – 272.7, p <.001) main effect at each luminance level. There was a Group x SF interaction at .01 cd/ m^2 ($F_{2,39}$ = 8.9, p = .001). Follow-up independent sample t-tests conducted at .01 cd/m^2 demonstrated that patients showed a robust deficit in threshold for .56 c/deg and 4.47 c/deg (t_{40} = 4.3, p < .001; t_{40} = 2.2, p = .038, respectively), indicative of an M-stream deficit (Figure 4A). The convergence of threshold at .01 cd/m^2 and 11.18 c/deg, may be due to the lack in efficiency of the system in resolving HSFs at scotopic luminance levels. There were deficits across all SFs at the other scotopic luminance (.1 cd/ m^2) as well (t_{40} = 3.8-5.2, p < .001) (Figure 4B). In addition, there were consistent between-group differences across SFs at higher luminance levels (1, 10 and 100 cd/m^2) (Figure 4C- E).

Effects across higher luminance levels were then evaluated within each SF (Figure 5). A repeated measures ANOVA was conducted with Group as the between-subjects variable and Luminance (1, 10, 100 cd/ m^2 only) as the within-subjects variable at each SF. The data showed that for each SF, there was a Group ($F_{1,40}$ = 13.4 – 15.6, p =

.001 - <.001) and Luminance ($F_{2,39}$ = 27.3 – 161.8, p <.001) main effect, with no interactions, indicating that the deficit in threshold of patients was similar across mesopic and photopic luminance levels (p > .11) (Fig 5A-C). These data suggest that patients and controls improved their thresholds similarly as P-biased information was introduced indicating relatively preserved P-stream function in patients.

Benefits of Duration- 500 ms versus 32 ms

An overall 2 Group (controls, patients) x 4 Luminance (0.1, 1, 10, 100 cd.m2) x 3 SF (.56, 4.47, 11.18 c/deg) x 2 Duration (32, 500 ms) ANOVA was conducted to look at differential group benefits of stimulus duration on contrast thresholds. There were no interactions involving Group and Duration, indicating that patients were able to take advantage of the stimulus duration increase similarly to controls. This is illustrated in Figure 6 where the change in threshold from 32 ms to 500 ms (500 ms threshold – 32 ms threshold) was plotted for each luminance at each SF separately for controls and patients.

Medication effects

There was no significant correlation with CPZ equivalents in patients and any dependent contrast threshold measure (P>.12).

5. Discussion

To evaluate visual pathway integrity in patients with schizophrenia, we implemented a typical contrast threshold paradigm using five different levels of luminance and a range of SFs. Scotopic luminance levels were implemented in the current study to help further bias processing towards the M-stream, and higher levels of luminance were used to investigate P-pathway function. The results indicate robust M-stream impairment with relatively intact P-pathway functioning.

In the current study, the shape of the threshold functions of both groups at scotopic levels (for both 32 ms and 500 ms) reflected M-stream characteristics (Figure 2B, Figure 4A-B). These response functions demonstrated maximal sensitivity (lowest threshold) occurring at the lowest SF. These data, mirror responses recorded from M-cells during scotopic viewing conditions in animal studies, and replicate psychophysical contrast response curves elicited during scotopic conditions in healthy controls (Benedek et al., 2003; Daitch & Green, 1969; Hawken & Parker, 1984; Hicks et al., 1983; Hofmann, Barnes, & Hallett, 1990; Kelly, 1972; Patel, 1966; Purpura et al., 1988). This suggests that in the current study, processing was successfully biased towards the M-pathway and P-pathway effects were minimized.

Further, during scotopic conditions, patients exhibited a large deficit in their contrast thresholds as compared to controls. The impairment was most pronounced at LSFs. In fact, previous data have shown that the M-pathway is more sensitive to LSFs versus mid- or HSFs in general, and LSF detection by the M-pathway is most efficient during scotopic luminance conditions (Savage & Banks, 1992). Therefore, it may only be appropriate to evaluate between-group differences in M-pathway function at .56 c/deg during scotopic vision, when the M-pathways of both groups were at their maximum sensitivity. Along these lines, the convergence of thresholds in both groups at ceiling for the 11.18 c/deg stimuli at .1 cd/m^2 (32 ms condition) and .01 cd/m^2 (500 ms condition) may be due to the lack of efficiency of the M-pathway at resolving such HSFs during scotopic vision.

The second goal of the current study was to investigate between-group differences in threshold across higher luminance levels, when P-information was introduced to the system via increasing luminance. At each SF, patients maintained similar levels of deficit between mesopic and photopic conditions for both stimulus durations (Figures 3 & 5). This indicates that patients were able to improve their contrast thresholds, by way of utilization of P-information, in the same manner as controls. While some could argue that similar magnitude deficits across mesopic and photopic conditions are suggestive of possible P-pathway dysfunction, this is not necessarily true. While scotopic luminance levels can prevent the P-stream from processing stimulus attributes, studies have shown that both the M- and P-pathways are simultaneously engaged as P-biased information is introduced into the system in the form of increasing luminance (Abd-El-Barr et al., 2009; Kaplan, Lee, & Shapley, 1990; Slaghuis & Bishop, 2001). Further, the M-pathway has been shown to be pushed to response saturation at high photopic luminance levels across a range of contrasts (Purpura et al., 1988). Thus, any enhanced deficit obtained at higher luminance levels, when the M-stream is reaching saturation would essentially be due to P-pathway dysfunction. In the current study, there was no enhanced impairment, suggesting deficits in patients at higher luminance levels were a result of a compromised M- not P-pathway.

In addition, we used two different stimulus durations in order to circumvent potential threshold ceiling or floor effects. The 32 ms condition elicited a ceiling threshold effect for all SFs at the lowest luminance (thresholds were ~100%), but this was avoided during the 500 ms condition. The data showed that patients were able to utilize increased duration time at each SF and luminance (.1, 1, 10, 100 cd/m^2) in the same manner as controls to help improve their performance (Figure 6). However, longer durations were not compensatory, and patients exhibited threshold deficits throughout the

500 ms condition. Although the goal of the current study did not include finding stimulus duration thresholds, our results are in-line with previous duration threshold studies that have demonstrated the ability of patients to employ increased stimulus length to improve performance (Braff & Saccuzzo, 1985; Butler, Tambini et al., 2008; Cattapan-Ludewig, Hilti, Ludewig, Vollenweider, & Feldon, 2005; Saccuzzo & Braff, 1981; Schwartz, Evans, Sautter, Pena, & Winstead, 1992; Slaghuis & Bakker, 1995; Weiner, Opler, Kay, Merriam, & Papouchis, 1990). It has been proposed that patients are less able to process rapidly presented stimuli due to M-neuronal abnormalities. The ability of patients to benefit from increasing stimulus duration may therefore be a result of a relatively intact P-pathway.

Scotopic luminance restricts P-pathway activation, and the impairment found during this condition strongly suggests it originates at the sub-cortical level within the M-stream, although Gutherie et al. (2006) suggested it occurs post-photoreceptor. Our results are also in line with a number of other studies suggesting abnormalities originate at low-levels of the visual pathway (Butler et al. 2004, 2005, 2007; Gutherie et al. 2006; Keri et al. 2002, 2004; Kim et al. 2005; Martinez et al. 2008; Schechter et al. 2005; Slaghuis, 1998; Slaghuis & Bishop 2001). For instance, patients have exhibited reduced white matter integrity within optic radiations that project from LGN to V1 (Butler, Zemon et al., 2005). Studies have also implemented paradigms using steady-state visual evoked potentials (ssVEPs) to specifically investigate sub-cortical dysfunction. Indeed, patients have demonstrated reduced ssVEP generation in response to M- versus P-biased stimuli, and this reduction was subsequently associated with compromised white matter in the sub-cortical optic radiations (Butler, Zemon et al., 2005). Further, the contrast response curves of control ssVEPs in the M-biased condition mimicked those measured from single M-neurons in monkey LGN (Kaplan, 1991). However, curves of patients in response to M-biased stimuli were similar to those elicited from cat LGN and visual cortex subsequent to microinfusion of N-methyl D-aspartate (NMDA) antagonist. Taken together, the previous and current data provide evidence that M-stream deficits occur at low-levels of the visual system, and may involve impairment at the level of the NMDA receptor, consistent with glutamatergic theories of schizophrenia (Fox et al., 1990; Javitt & Zukin, 1991; Kwon, Esguerra, & Sur, 1991; Olney & Farber, 1995; Tsai & Coyle, 2002).

A limitation of this study was that all patients were receiving medications at the time of testing. However, no significant correlation was found between contrast threshold and chlorpromazine equivalents for the 32 ms ($p>.065$) or 500 ms ($p>.15$) condition. In addition, a number of studies have found visual processing deficits in both medicated and unmedicated patients (Braff & Saccuzzo, 1982; Butler et al., 1996; Cadenhead et al., 1997; Harvey et al., 1990) and first-degree relatives (Chen, Nakayama, Levy, Matthysse, & Holzman, 1999; Green, Nuechterlein, & Breitmeyer, 1997; Keri et al., 2004; Yeap et al., 2006).

In conclusion the use of scotopic luminance levels allowed for us to confidently restrict P-pathway function, and heavily bias processing to the M-pathway in order to investigate its integrity. The present study revealed that patients with schizophrenia exhibit robust sub-cortical M-pathway impairments. Further, patients were able to utilize P-biased information similarly to controls in order to improve their performance, indicating relatively unimpaired P-pathway function.

6. References

Abd-El-Barr, M. M., Pennesi, M. E., Saszik, S. M., Barrow, A. J., Lem, J., Bramblett, D. E., et al. (2009). Genetic dissection of rod and cone pathways in the dark-adapted mouse retina. *J Neurophysiol, 102*(3), 1945-1955.

Andreasen, N. C. (1984). *The scale for the assessment of negative symptoms (SANS).* Iowa City: The University of Iowa.

Benedek, G., Benedek, K., Keri, S., & Janaky, M. (2003). The scotopic low-frequency spatial contrast sensitivity develops in children between the ages of 5 and 14 years. *Neurosci Lett, 345*(3), 161-164.

Braff, D. L., & Saccuzzo, D. P. (1982). Effect of antipsychotic medication on speed of information processing in schizophrenic patients. *Am J Psychiatry, 139*(9), 1127-1130.

Braff, D. L., & Saccuzzo, D. P. (1985). The time course of information-processing deficits in schizophrenia. *Am J Psychiatry, 142*(2), 170-174.

Brenner, C. A., Lysaker, P. H., Wilt, M. A., & O'Donnell, B. F. (2002). Visual processing and neuropsychological function in schizophrenia and schizoaffective disorder. *Psychiatry Res, 111*(2-3), 125-136.

Butler, P. D., Abeles, I. Y., Weiskopf, N. G., Tambini, A., Jalbrzikowski, M., Legatt, M. E., et al. (2009). Sensory contributions to impaired emotion processing in schizophrenia. *Schizophr Bull, 35*(6), 1095-1107.

Butler, P. D., Gur, R. C., Jalbrzikowski, M., Loughead, J., Saperstein, A. M., Schechter, I., et al. (2005). Visual processing impairment and emotion recognition dysfunction in schizophrenia. *Internation Congress on Schizophrenia Research Abstract, Savannah, Georgia.*

Butler, P. D., Harkavy-Friedman, J. M., Amador, X. F., & Gorman, J. M. (1996). Backward masking in schizophrenia: relationship to medication status, neuropsychological functioning, and dopamine metabolism. *Biol Psychiatry, 40*(4), 295-298.

Butler, P. D., Martinez, A., Foxe, J. J., Kim, D., Zemon, V., Silipo, G., et al. (2007). Subcortical visual dysfunction in schizophrenia drives secondary cortical impairments. *Brain, 130*, 417-430.

Butler, P. D., Schechter, I., Zemon, V., Schwartz, S. G., Greenstein, V. C., Gordon, J., et al. (2001). Dysfunction of early stage visual processing in schizophrenia. *Am J Psychiatry, 158*(7), 1126-1133.

Butler, P. D., Tambini, A., Yovel, G., Jalbrzikowski, M., Ziwich, R., Silipo, G., et al. (2008). What's in a face? Effects of stimulus duration and inversion on face processing in schizophrenia. *Schizophr Res*.

Butler, P. D., Zemon, V., Schechter, I., Saperstein, A. M., Hoptman, M. J., Lim, K. O., et al. (2005). Early-stage visual processing and cortical amplification deficits in schizophrenia. *Arch Gen Psychiatry, 62*(5), 495-504.

Cadenhead, K. S., Geyer, M. A., Butler, R. W., Perry, W., Sprock, J., & Braff, D. L. (1997). Information processing deficits of schizophrenia patients: relationship to clinical ratings, gender and medication status. *Schizophr Res, 28*(1), 51-62.

Cadenhead, K. S., Serper, Y., & Braff, D. L. (1998). Transient versus sustained visual channels in the visual backward masking deficits of schizophrenia patients. *Biol Psychiatry, 43*(2), 132-138.

Cattapan-Ludewig, K., Hilti, C. C., Ludewig, S., Vollenweider, F. X., & Feldon, J. (2005). Rapid visual information processing in schizophrenic patients: the impact of cognitive load and duration of stimulus presentation. A pilot study. *Neuropsychobiology, 52*(3), 130-134.

Chen, Y., Levy, D. L., Sheremata, S., & Holzman, P. S. (2004). Compromised late-stage motion processing in schizophrenia. *Biol Psychiatry, 55*(8), 834-841.

Chen, Y., Nakayama, K., Levy, D. L., Matthysse, S., & Holzman, P. S. (1999). Psychophysical isolation of a motion-processing deficit in schizophrenics and their relatives and its association with impaired smooth pursuit. *Proc Natl Acad Sci U S A, 96*(8), 4724-4729.

Dacey, D. M., & Petersen, M. R. (1992). Dendritic field size and morphology of midget and parasol ganglion cells of the human retina. *Proc Natl Acad Sci U S A, 89*(20), 9666-9670.

Daitch, J. M., & Green, D. G. (1969). Contrast sensitivity of the human peripheral retina. *Vision Res, 9*(8), 947-952.

Derrington, A. M., & Lennie, P. (1984). Spatial and temporal contrast sensitivities of neurones in lateral geniculate nucleus of macaque. *J Physiol, 357*, 219-240.

Dowling, J. E. (Ed.). (1987). *The Retina, an Approachable Part of the Brain*. Cambridge: Harvard University Press.

Enroth-Cugell, C., Hertz, B. G., & Lennie, P. (1977). Convergence of rod and cone signals in the cat's retina. *J Physiol, 269*(2), 297-318.

Fox, K., Sato, H., & Daw, N. (1990). The effect of varying stimulus intensity on NMDA-receptor activity in cat visual cortex. *J Neurophysiol, 64*(5), 1413-1428.

Gouras, P., & Link, K. (1966). Rod and cone interaction in dark-adapted monkey ganglion cells. *J Physiol, 184*(2), 499-510.

Green, M. F., Nuechterlein, K. H., & Breitmeyer, B. (1997). Backward masking performance in unaffected siblings of schizophrenic patients. Evidence for a vulnerability indicator [published erratum appears in Arch Gen Psychiatry 1997 Sep;54(9):846]. *Arch Gen Psychiatry, 54*(5), 465-472.

Harvey, P. D., Keefe, R. S., Moskowitz, J., Putnam, K. M., Mohs, R. C., & Davis, K. L. (1990). Attentional markers of vulnerability to schizophrenia: performance of medicated and unmedicated patients and normals. *Psychiatry Res, 33*(2), 179-188.

Hawken, M. J., & Parker, A. J. (1984). Contrast sensitivity and orientation selectivity in lamina IV of the striate cortex of Old World monkeys. *Exp Brain Res, 54*(2), 367-372.

Hicks, T. P., Lee, B. B., & Vidyasagar, T. R. (1983). The responses of cells in macaque lateral geniculate nucleus to sinusoidal gratings. *J Physiol, 337*, 183-200.

Hofmann, M. I., Barnes, C. S., & Hallett, P. E. (1990). Detection of briefly flashed sine-gratings in dark-adapted vision. *Vision Res, 30*(10), 1453-1466.

Hollingshead, A. (1975). Four Factor Index of Social Status. Yale University Department of Sociology.

Hyman SE, A. G., Rosenbaum JF (Ed.). (1995). *Handbook of Psychiatric Drug Therapy*. Boston: Little, Brown and Company.

Javitt, D. C., & Zukin, S. R. (1991). Recent advances in the phencyclidine model of schizophrenia. *Am J Psychiatry, 148*(10), 1301-1308.

Jibson, M. D., & Tandon, R. (1998). New atypical antipsychotic medications. *J Psychiatr Res, 32*(3-4), 215-228.

Kaplan, E. (1991). The receptive field structure of retinal ganglion cells in cat and monkey. In A. G. Leventhal (Ed.), *Vision and Visual Dysfunction* (pp. 10-40). Boston: CRC Press.

Kaplan, E., Lee, B., & Shapley, R. (1990). *New Views of primate retinal function.* (Vol. 9). Oxford: Pergamon.

Kelly, D. H. (1972). Adaptation effects on spatio-temporal sine-wave thresholds. *Vision Res, 12*(1), 89-101.

Keri, S., Antal, A., Szekeres, G., Benedek, G., & Janka, Z. (2002). Spatiotemporal visual processing in schizophrenia. *J Neuropsychiatry Clin Neurosci, 14*(2), 190-196.

Keri, S., & Benedek, G. (2007). Visual contrast sensitivity alterations in inferred magnocellular pathways and anomalous perceptual experiences in people at high-risk for psychosis. *Vis Neurosci, 24*(2), 183-189.

Keri, S., Kelemen, O., Benedek, G., & Janka, Z. (2004). Vernier threshold in patients with schizophrenia and in their unaffected siblings. *Neuropsychology, 18*(3), 537-542.

Keri, S., Kiss, I., Kelemen, O., Benedek, G., & Janka, Z. (2005). Anomalous visual experiences, negative symptoms, perceptual organization and the magnocellular pathway in schizophrenia: a shared construct? *Psychol Med, 35*(10), 1445-1455.

Kim, D., Wylie, G., Pasternak, R., Butler, P. D., & Javitt, D. C. (2006). Magnocellular contributions to impaired motion processing in schizophrenia. *Schizophr Res, 82*(1), 1-8.

Kim, D., Zemon, V., Saperstein, A., Butler, P. D., & Javitt, D. C. (2005). Dysfunction of early-stage visual processing in schizophrenia: harmonic analysis. *Schizophr Res, 76*(1), 55-65.

Kraepelin, E. (1904). *Psychiatrie ein lehrbuch for studierende und arzte*. Liepzig: Verlag von Johann Ambrosius Barth.

Kwon, Y. H., Esguerra, M., & Sur, M. (1991). NMDA and non-NMDA receptors mediate visual responses of neurons in the cat's lateral geniculate nucleus. *J Neurophysiol, 66*(2), 414-428.

Laycock, R., Crewther, S. G., & Crewther, D. P. (2007). A role for the 'magnocellular advantage' in visual impairments in neurodevelopmental and psychiatric disorders. *Neurosci Biobehav Rev, 31*(3), 363-376.

Lee, B. B., Smith, V. C., Pokorny, J., & Kremers, J. (1997). Rod inputs to macaque ganglion cells. *Vision Res, 37*(20), 2813-2828.

Liddell, B. J., Brown, K. J., Kemp, A. H., Barton, M. J., Das, P., Peduto, A., et al. (2005). A direct brainstem-amygdala-cortical 'alarm' system for subliminal signals of fear. *Neuroimage, 24*(1), 235-243.

Lund, J. S. (1973). Organization of neurons in the visual cortex, area 17, of the monkey (Macaca mulatta). *J Comp Neurol, 147*(4), 455-496.

Martinez, A., Hillyard, S. A., Dias, E. C., Hagler, D. J., Butler, P. D., Guilfoyle, D. N., et al. (2008). Magnocellular pathway impairment in schizophrenia: evidence from fMRI. *J Neuroscience, 28*(30), 7492-7500.

Merigan, W. H., & Maunsell, J. H. R. (1993). How parallel are the primate visual pathways? In W. M. Cowan, E. M. Shooter, C. F. Stevens & R. F. Thompson

(Eds.), *Ann Rev Neuroscience* (pp. 369-402). Palo Alto, CA: Annual Reviews, Inc.

Olney, J. W., & Farber, N. B. (1995). Glutamate receptor dysfunction and schizophrenia. *Arch Gen Psychiatry, 52*(12), 998-1007.

Overall, J. E., & Gorham, D. R. (1962). The brief psychiatric rating scale. *Psychological Reports, 10*, 799-812.

Patel, A. S. (1966). Spatial resolution by the human visual system. The effect of mean retinal illuminance. *J Opt Soc Am, 56*(5), 689-694.

Peuskens, J., & Link, C. G. (1997). A comparison of quetiapine and chlorpromazine in the treatment of schizophrenia. *Acta Psychiatr Scand, 96*(4), 265-273.

Purpura, K., Kaplan, E., & Shapley, R. M. (1988). Background light and the contrast gain of primate P and M retinal ganglion cells. *Proc Natl Acad Sci U S A, 85*(12), 4534-4537.

Saccuzzo, D. P., & Braff, D. L. (1981). Early information processing deficit in schizophrenia. New findings using schizophrenic subgroups and manic control subjects. *Arch Gen Psychiatry, 38*(2), 175-179.

Saccuzzo, D. S., Cadenhead, K. S., & Braff, D. L. (1996). Backward versus forward visual masking deficits in schizophrenic patients: centrally, not peripherally, mediated? *Am J Psychiatry, 153*(12), 1564-1570.

Savage, G. L., & Banks, M. S. (1992). Scotopic visual efficiency: constraints by optics, receptor properties, and rod pooling. *Vision Res, 32*(4), 645-656.

Schechter, I., Butler, P. D., Silipo, G., Zemon, V., & Javitt, D. C. (2003). Magnocellular and parvocellular contributions to backward masking dysfunction in schizophrenia. *Schizophrenia Research, 64*, 91-101.

Schiller, P. H., Malpeli, J. G., & Schein, S. J. (1979). Composition of geniculostriate input ot superior colliculus of the rhesus monkey. *J Neurophysiol, 42*(4), 1124-1133.

Schroeder, C. E., Mehta, A. D., & Givre, S. J. (1998). A spatiotemporal profile of visual system activation revealed by current source density analysis in the awake macaque. *Cereb Cortex, 8*(7), 575-592.

Schwartz, B. D., Evans, W. J., Sautter, F., Pena, J. M., & Winstead, D. K. (1992). Deficits in initial feature registration of schizophrenics and substance abusers. *Schizophr Res, 7*(3), 217-224.

Sergi, M. J., & Green, M. F. (2003). Social perception and early visual processing in schizophrenia. *Schizophr Res, 59*(2-3), 233-241.

Sergi, M. J., Rassovsky, Y., Nuechterlein, K. H., & Green, M. F. (2006). Social perception as a mediator of the influence of early visual processing on functional status in schizophrenia. *Am J Psychiatry, 163*(3), 448-454.

Slaghuis, W. L. (1998). Contrast sensitivity for stationary and drifting spatial frequency gratings in positive- and negative-symptom schizophrenia. *J Abnorm Psychol, 107*(1), 49-62.

Slaghuis, W. L. (2004). Spatio-temporal luminance contrast sensitivity and visual backward masking in schizophrenia. *Exp Brain Res, 156*(2), 196-211.

Slaghuis, W. L., & Bakker, V. J. (1995). Forward and backward visual masking of contour by light in positive- and negative-symptom schizophrenia. *J Abnorm Psychol, 104*(1), 41-54.

Slaghuis, W. L., & Bishop, A. M. (2001). Luminance flicker sensitivity in positive- and negative-symptom schizophrenia. *Exp Brain Res, 138*(1), 88-99.

Slaghuis, W. L., & Thompson, A. K. (2003). The effect of peripheral visual motion on focal contrast sensitivity in positive- and negative-symptom schizophrenia. *Neuropsychologia, 41*(8), 968-980.

Tootell, R. B., Hamilton, S. L., & Switkes, E. (1988). Functional anatomy of macaque striate cortex. IV. Contrast and magno-parvo streams. *J Neurosci, 8*(5), 1594-1609.

Tootell, R. B., Silverman, M. S., Hamilton, S. L., Switkes, E., & De Valois, R. L. (1988). Functional anatomy of macaque striate cortex. V. Spatial frequency. *J Neurosci, 8*(5), 1610-1624.

Tsai, G., & Coyle, J. T. (2002). Glutamatergic mechanisms in schizophrenia. *Annu Rev Pharmacol Toxicol, 42*, 165-179.

Weiner, R. U., Opler, L. A., Kay, S. R., Merriam, A. E., & Papouchis, N. (1990). Visual information processing in positive, mixed, and negative schizophrenic syndromes. *J Nerv Ment Dis, 178*(10), 616-626.

Yeap, S., Kelly, S. P., Sehatpour, P., Magno, E., Javitt, D. C., Garavan, H., et al. (2006). Early visual sensory deficits as endophenotypes for schizophrenia: high-density electrical mapping in clinically unaffected first-degree relatives. *Arch Gen Psychiatry, 63*(11), 1180-1188.

9. Tables

Table 1

Demographic and Clinical Characteristics of Healthy Controls and Patients with Schizophrenia

Characteristic	**Controls 32 ms (n=19)**	**Controls 500 ms (n=20)**	**Patients 32 ms (n=23)**	**Patients 500 ms (n=22)**
Age	38.8 ± 12.1	38 ± 12.2	37.7 ± 10.9	37.7 ± 11.2
Gender (M/F)	15/4	16/4	21/2	20/2
Chlorpromazine daily equivalent, mg			1036 ± 890	1069±893
Antipsychotics				
Atypical			20	19
Typical				
Both			3	3
Parental socioeconomic status	39.36± 14.1 (n=16)	38.3 ± 14.2 (n=16)	40.7 ± 40.1 (n=22)	40.5 ± 41.6 (n=20)
BPRS total score			37.5±10.3 (n=23)	35.7±9.7 (n=22)
SANS total score (including global Scores)			28.2 ± 10.6 (n=23)	27.4 ± 10.2 (n=22)
Duration of illness (years)			16.1 ± 10.1 (n=23)	16.6 ± 9.8 (n=22)

Note: Values are SD. Numbers of subjects per group are noted when there is missing data. Socioeconomic status was measured by the 4-factor Hollingshead Scale (Hollingshead, 1975). M, male; F, Female; BPRS, Brief Psychiatric Rating Scale (Overall & Gorham, 1962); SANS, Schedule for Assessment of Negative Symptoms (Andreasen, 1984).

7. Figure Legends

Figure 1: Examples of spatial frequency gratings processed by different visual pathways. Left: Low-spatial frequency (LSF) grating against a controlled luminance background. LSFs are processed by the magnocellular pathway. Right: High-spatial frequency (HSF) grating against a controlled luminance background. HSFs are processed by the parvocellular pathway.

Figure 2*:* 32 ms condition**:** Contrast threshold curves plotted at each luminance level. Error bars represent 95% confidence intervals. Blue: Controls. Red: Patients. A) At the lowest scotopic luminance there were ceiling effects (100% contrast needed) for both groups. B) At .1 cd/m^2 (scotopic luminance) there were robust deficits at the lower SFs. This indicates M-pathway dysfunction. C)-E) At 1, 10 and 100 cd/m^2, all between-group differences were similar across SFs within each luminance condition (P>.07).

Figure 3: 32 ms condition: Contrast threshold curves plotted at each luminance level. Error bars represent 95% confidence intervals. Blue: Controls. Red: Patients. For A) .56 c/deg and B) 4.47 c/deg, and C) 11.18 c/deg there were similar between-group differences across the mesopic to photopic luminance levels (1, 10 and 100 cd/m^2), indicating controls and patients similarly improved their contrast thresholds through the use of P-biased information.

Figure 4: 500 ms condition: Contrast threshold curves plotted at each luminance level. Error bars represent 95% confidence intervals. Blue: Controls. Red: Patients. A) At .01 cd/m^2 there were robust deficits at the lower SFs indicative of M-stream dysfunction. At B) .1, C) 1 D) 10 and E) 100 cd/m^2 there were consistently similar between-group differences across SFs.

Figure 5: 500 ms condition: Contrast threshold curves plotted at each luminance level. Error bars represent 95% confidence intervals. Blue: Controls. Red: Patients. A-C) Between-group differences were similar across mesopic and photopic luminance levels indicative of relatively preserved P-stream functionality.

Figure 6: The change in threshold from 32 ms to 500 ms is plotted (500 ms threshold – 32 ms threshold). The greater the change in threshold, the more benefit participants gained from increased duration. Controls and patients benefitted from increased duration similarly. At LSFs, duration benefitted the lowest luminance the most whereas at HSF, duration benefitted the lowest luminance the least.

8. Figures

<u>Figure 1:</u>
Stimulus examples:

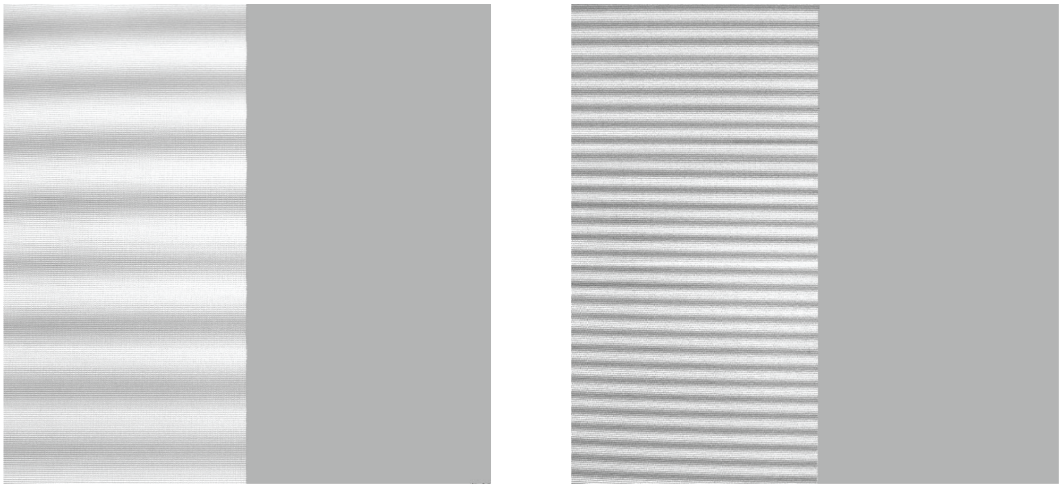


Figure 2:
Contrast thresholds separated by luminance (32 ms condition)

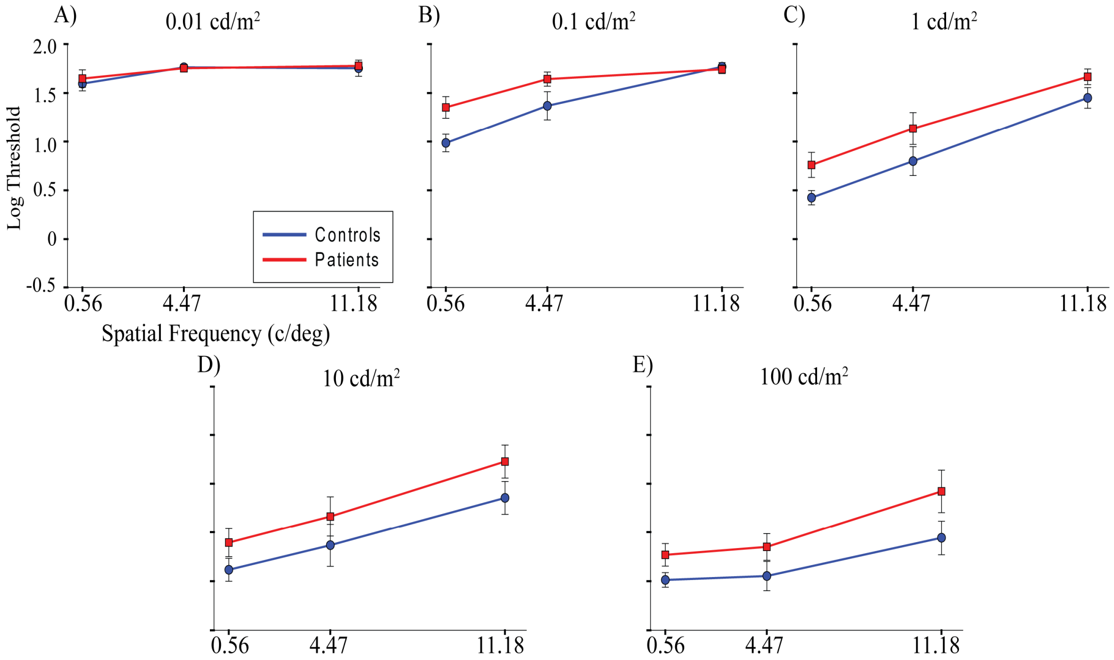


Figure 3:
Contrast thresholds separated by spatial frequency (32 ms condition)

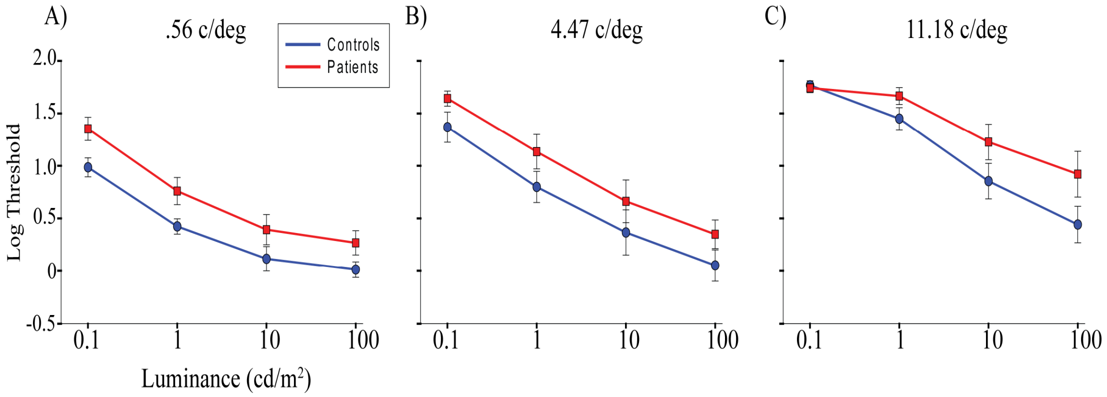


Figure 4:
Contrast thresholds separated by luminance (500 ms condition)

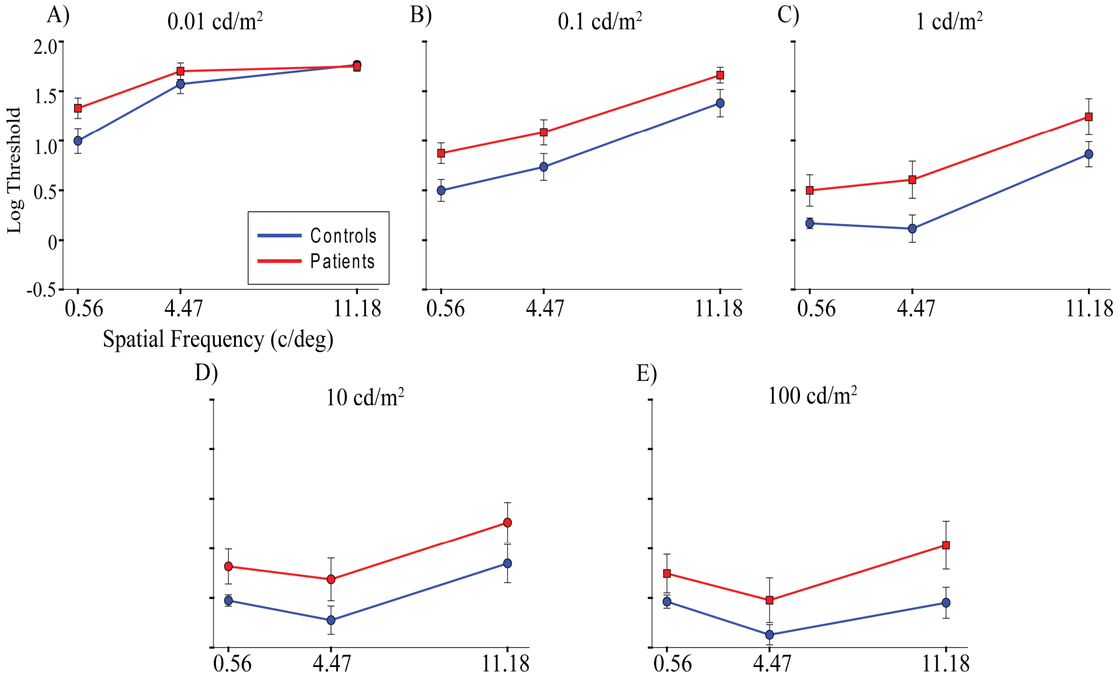


Figure 5:
Contrast thresholds separated by spatial frequency (500 ms condition)

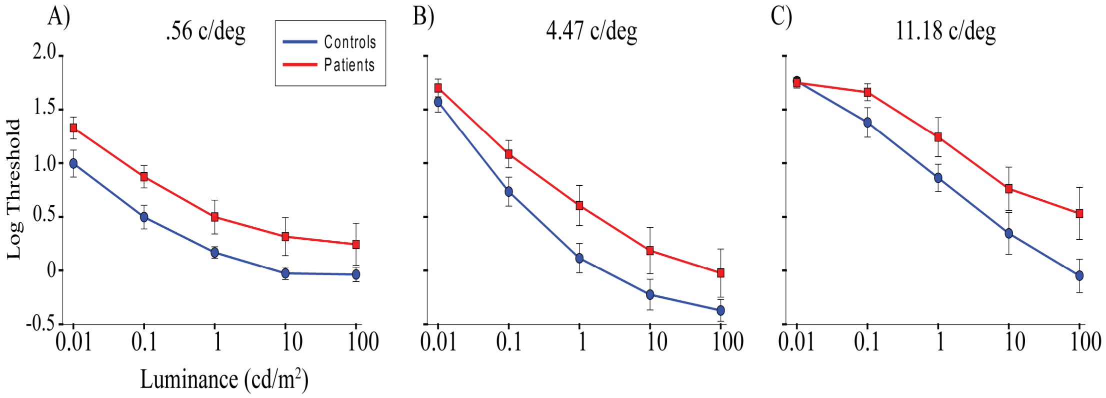
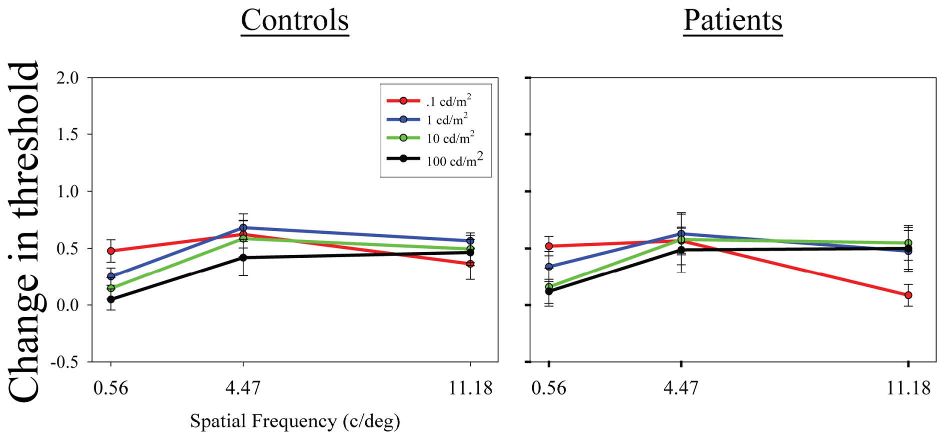


Figure 6:
Changes in threshold due to stimulus duration increase



CHAPTER 3

An event-related potential investigation of the contribution of early visual processing dysfunction to emotion recognition deficits in schizophrenia

1. Abstract

The present study used a behavioral and electrophysiological paradigm to investigate contributions of low-level visual pathway dysfunction to emotion perceptual processing deficits in schizophrenia by altering contrasts of faces. Contrast response curves for the dorsal (P1) and ventral (N170) pathways were elicited in response to contrast-manipulated stimuli in order to evaluate visual pathway integrity in patients. Results showed that the P1 contrast response curves in controls reflected M-stream characteristics, and patients exhibited robust deficits in their pattern of response, suggesting impaired M-input to the dorsal pathway. Conversely, the N170 amplitude remained intact. Contributions of low-level visual pathways to emotion recognition and later emotion-related processing (as indexed by the P250) were also assessed. P250 activity in patients was reduced at all contrasts. Further, the P1 predicted the P250 component, and both P1 and P250 components predicted emotion recognition ability during M-biased contrasts across groups. Taken together, these data support the hypothesis that emotion recognition and emotion perceptual processing deficits in schizophrenia result from early-stage visual processing impairments.

2. Introduction

Deficits in facial emotion recognition are among the best-documented impairments in schizophrenia (Edwards et al., 2002; Heimberg et al., 1992; Kerr & Neale, 1993; Kohler et al., 2000; Mandal, Pandey, & Prasad, 1998; Penn, Corrigan, Bentall, Racenstein, & Newman, 1997). These deficits, found in first-episode and chronic patients (Addington, Addington, & Gasbarre, 2001; Edwards, Pattison, Jackson, & Wales, 2001; Kohler et al., 2003; Streit, Wolwer, & Gaebel, 1997), contribute to impaired social competence (Brekke, Kay, Lee, & Green, 2005; Kee, Green, Mintz, & Brekke, 2003; Mueser et al., 1996) and poor functional outcome (Sergi et al., 2006). Thus, understanding the neural basis of face emotion processing deficits is important for developing intervention and remediation strategies.

There are alternative theories of emotion processing dysfunction in schizophrenia. Impaired emotion recognition may result from deficits in activation of limbic structures, which are known to be involved in emotion processing (Borod, Martin, Alpert, Brozgold, & Welkowitz, 1993; Edwards et al., 2002; Gur et al., 2002; Gur et al., 2000; Holt et al., 2006; Li et al., 2009; Walker, McGuire, & Bettes, 1984). On the other hand, patients have intact internal representations of emotion (Herbener et al., 2007; Horan et al., 2006; Kring et al., 1993; Kring & Moran, 2008) and patient deficits are not specific to emotion but are also found during non-emotional face processing tasks (Addington & Addington, 1998; Edwards et al., 2002; Feinberg et al., 1986; Kerr & Neale, 1993). A number of studies also show dysfunction in early stage visual processing in schizophrenia (Brenner, Wilt, Lysaker, Koyfman, & O'Donnell, 2003; Butler et al., 2007; Butler, Silverstein et al., 2008; Chen et al., 2003; Keri et al., 2004). Thus, impaired ability to accurately perceive emotion may result from generalized visual processing deficits.

The human visual system contains magnocellular (M) and parvocellular (P) pathways which project from the retina to primary visual cortex via the lateral geniculate nucleus. M-neurons are large, specialized for rapid responding, and preferentially project to dorsal visual stream areas. There are also M-projections through superior colliculus and pulvinar to amygdala (Liddell et al., 2005; Schiller et al., 1979). P-neurons are smaller, more slowly conducting and project preferentially to ventral visual stream areas.

The two pathways have different, but overlapping properties. For instance, the M-pathway is preferentially activated by large (low spatial frequency, LSF) stimuli that convey global/configural information. The P-pathway is preferentially activated by small (high spatial frequency, HSF) stimuli that convey detailed information. Integration of information from both pathways is important in such complex visual processes as object recognition and perceptual closure (Doniger et al., 2002; Sehatpour et al., 2010).

The two pathways are also differentially affected by contrast. The M-pathway shows a nonlinear response to contrast, with a steep increase in response to increases in low-levels of contrast. As contrast reaches approximately 16%, responses reach saturation-levels. Conversely, P-neurons do not begin to respond until stimuli reach approximately 10% contrast and show a linear rise in response to increases in contrast. Thus, low contrast can bias stimuli towards the M-pathway and the shape of the contrast response functions can be used to differentiate between M- and P-biased function. Patients with schizophrenia exhibit preferential impairment in M-function as seen in their behavioral and neurophysiological contrast response functions, with decreased initial slope at low-contrasts and decreased plateau of response at higher contrasts in response to simple visual stimuli (Butler et al., 2009; Butler et al., 2007; Butler, Zemon et al., 2005; Kim et al., 2005; Schechter et al., 2003; Schechter et al., 2005; Slaghuis, 2004), but P-stream deficits may be present as well (Keri et al., 2002; Slaghuis, 1998; Slaghuis & Thompson, 2003).

Studies in healthy controls show a role for the M-pathway in emotion processing (Bar, Neta et al., 2006; Gosselin & Schyns, 2001; Pourtois, Dan, Grandjean, Sander, & Vuilleumier, 2005; Schyns & Oliva, 1999; Vuilleumier et al., 2003). Several recent psychophysical studies have shown relationships between visual perceptual deficits and impaired emotion recognition in schizophrenia (Butler et al., 2009; Lee, Gosselin et al., 2010; Norton et al., 2009). In a psychophysical study, we manipulated the contrast of face emotion stimuli and found contrast response functions in controls that were similar to those found in controls in response to simple stimuli and to those found in M-neurons in animal physiological studies (see Butler et al., 2009). Further, patients with schizophrenia had decreased initial slope and decreased plateau of their contrast response curves, indicative of involvement of M-impairment in emotion processing deficits. The present study examines event-related potentials (ERP) to contrast-manipulated emotional face stimuli in order to specifically examine the early sensory deficits that potentially contribute to later emotion processing dysfunction and underlie our previous behavioral findings.

The three ERP components examined in the current study were the P1, N170, and P250. The P1 component occurs at ~100 ms post-stimulus over dorsal occipital sites, and has a dorsal stream generator that appears to be primarily driven by M-stream input

(Butler et al., 2007). The P1 is generally thought to reflect global processing and the assessment of early-stage visual information. While the P1 is relatively understudied with regard to face processing, it has been shown to be enhanced to LSF emotion versus neutral stimuli (Obayashi et al., 2009; Pourtois et al., 2005; Vlamings et al., 2009) and has been found to vary by emotion in a number of studies (Keil et al., 2001; Lee, Gosselin et al., 2010; Pizzagalli et al., 1999; Pizzagalli et al., 2002; Turetsky et al., 2007) but see, (Eimer & Holmes, 2007), suggesting it may be sensitive to sensory aspects of emotional stimuli. Studies of P1 deficits in schizophrenia to non-face stimuli have been instrumental in identifying dorsal stream deficits in this disorder (Butler et al., 2007; Doniger et al., 2002; Haenschel et al., 2004; Schechter et al., 2005; Yeap et al., 2006). However, results have been mixed in response to face emotion stimuli with some studies showing deficits in patients (Caharel et al., 2007; Campanella et al., 2006), including lack of increased P1 response to LSF face emotion stimuli (Obayashi et al., 2009), while others do not show impaired P1 amplitude (Johnston et al., 2005; Lee, Gosselin et al., 2010; Turetsky et al., 2007; Wynn et al., 2008).

The N170 occurs at ~170 ms post-stimulus over ventral occipitotemporal sites, and is thought to have a generator in fusiform gyrus (Herrmann, Ehlis, Muehlberger, & Fallgatter, 2005; Shibata et al., 2002), an area associated with face processing, though a generator in superior temporal sulcus has also been found (Itier & Taylor, 2004; Joyce & Rossion, 2005). The N170 has been extensively studied in face processing and is thought to be involved in the structural encoding of faces (Bentin, Allison, Puce, Perez, & McCarthy, 1996; Eimer, 2000). Its amplitude has also been shown to be sensitive to spatial frequency manipulations (Goffaux et al., 2003; Halit, de Haan, Schyns, &

Johnson, 2006; Nakashima et al., 2008; Obayashi et al., 2009). Further, it has been found to vary by emotion in some (Blau et al., 2007; Caharel et al., 2007; Caharel et al., 2005; Campanella et al., 2006; Campanella, Quinet, Bruyer, Crommelinck, & Guerit, 2002; Lynn & Salisbury, 2008; Turetsky et al., 2007) but not other face-emotion paradigms (Eimer & Holmes, 2002; Eimer, Holmes, & McGlone, 2003; Holmes et al., 2005; Obayashi et al., 2009). Studies of non-face stimuli in schizophrenia generally show that the N1 is not impaired (Butler et al., 2007; Doniger et al., 2002; Foxe et al., 2001; Sehatpour et al., 2010), indicating intact P-input to the ventral stream (Doniger et al., 2002; Foxe et al., 2005), but see (Galletly, Clark, & McFarlane, 2005; Neuhaus et al., 2011). Results have been mixed in response to face emotion stimuli with some studies showing intact N170 amplitudes in schizophrenia (Streit et al., 2001; Wynn et al., 2008), while other studies show reductions in amplitude (Caharel et al., 2007; Campanella et al., 2006; Johnston et al., 2005; Lee, Gosselin et al., 2010; Turetsky et al., 2007).

The affect-related N250 peaks at approximately 250 ms over fronto-central sites (Lee, Gosselin et al., 2010; Tanaka, Curran, Porterfield, & Collins, 2006; Turetsky et al., 2007; Wynn et al., 2008), and its posterior counterpart, the P250, is found over occipito-parietal and temporal sites (Caharel et al., 2007; Krolak-Salmon, Fischer, Vighetto, & Mauguiere, 2001; Streit et al., 2001). These components are less well understood but have been found to be affected by emotional content of faces (Caharel et al., 2007; Krolak-Salmon et al., 2001; Streit et al., 2001). Studies finding decreased P1 and/or N170 but normal P250/N250 amplitudes have suggested that facial affect recognition deficits are secondary or “flow-on” effects of a generalized visual processing impairment in schizophrenia (Caharel et al., 2007; Johnston et al., 2005; Turetsky et al., 2007).

Conversely, several studies have found a deficit only in the later N250 but not the earlier components, suggesting specific emotional processing impairment (Lee, Gosselin et al., 2010; Streit et al., 2001; Wynn et al., 2008).

The present study investigated contributions of early sensory processing dysfunction to emotion recognition deficits in schizophrenia by altering contrasts of faces themselves. Subsequent examination of contrast response functions allowed us to assess the integrity of dorsal and ventral visual streams, and distinguished between early perceptual and later stages of emotion processing. Dorsal and ventral pathway contributions to emotion recognition and affect-related processing, as indexed by the P250, were also evaluated. The overall hypothesis was that emotion identification impairment in schizophrenia would reflect deficits in early stages of sensory processing, particularly involving M-stream dysfunction. The following specific predictions were tested: 1) patients would demonstrate impaired emotion recognition ability including at the M-biased contrast; 2) controls would show P1 amplitude contrast response functions typical of an M-pattern of response; 3) patients would show P1 deficits including decreased initial gain and lower plateau of their contrast response functions indicative of M/dorsal stream dysfunction; 4) the N170 component would be intact in patients reflecting preserved ventral stream function; and 5) impaired P1 amplitude would be related to decreased amplitude of the later emotion-related P250 component and to behavioral performance in patients, reflecting contributions of impaired early-stage dorsal pathway processing to later emotion processing.

3. Methods

Participants

Participants were 25 patients (23 male) meeting Diagnostic and Statistical Manual of Mental Disorder (Fourth Edition) (DSM-IV) criteria for schizophrenia (n= 21) or schizoaffective disorder (n=4) and 25 healthy volunteers (16 male). Patients were recruited from inpatient (n=14) and outpatient (n=11) facilities associated with the Nathan Kline Institute for Psychiatric Research. Diagnoses were obtained using the Structured Clinical Interview for DSM-IV (SCID) (First, Spitzer, Gibbon, & Williams, 1997) and all available clinical information. Controls were recruited through the Volunteer Recruitment Pool at the Nathan Kline Institute. Healthy volunteers with a history of SCID-defined Axis I psychiatric disorders were excluded. Patients and controls were excluded if they had any neurological or ophthalmologic disorders that might affect performance or met criteria for alcohol or substance dependence within the last six months or abuse within the last month. All participants provided informed consent according to the Declaration of Helsinki. This study was approved by the Nathan Kline Institute for Psychiatric Research/Rockland Psychiatric Center and Rockland County Department of Mental Health, and by the City College of the City University of New York Institutional Review Boards.

Clinical and demographic information are included in Table 1. The patient and control groups did not differ significantly in age ($t_{48} = 0.3$, $p = .73$), or parental socioeconomic status ($t_{39} = -0.5$, $p = .62$). All patients were receiving antipsychotic medication at the time of testing. Chlorpromazine equivalents were calculated using conversion factors described previously (Hyman SE, 1995; Jibson & Tandon, 1998; Peuskens & Link, 1997; Woods, 2003). All participants had 20/32 or better corrected visual acuity on the Logarithmic Visual Acuity Chart (Precision Vision, LaSalle, IL).

Stimuli

Facial images were from the Ekman and Friesen (Ekman & Friesen, 1976) stimulus database and included fear, happy, sad, and neutral faces from 11 different individuals, for a total of 11 different stimuli per emotion and 44 total stimuli (for e.g., Figure 1). An oval was placed around the facial image in order to exclude extraneous information, such as hair. Only the gray levels within the oval aperture were considered in computing contrast. Root- mean-square (RMS) contrast is frequently reported for complex images such as faces (Ojanpaa & Nasanen, 2003) and it was set at 2%, 8% and 57%. The same stimuli were used in the behavioral and ERP studies. Stimuli were presented on a Phillips CRT monitor located 114 cm from the participants. Major and minor axes of the images subtended 5 x 7 degrees of visual angle. Mean luminance was held constant for each contrast condition, and for the background screen.

Behavioral experiment - procedure

Each of the 44 stimuli was presented three times at each contrast level, with emotion type and contrast level randomly intermixed, for a total of 132 stimuli per contrast level. Stimuli were shown for 500 milliseconds followed by a screen asking the participant to choose fear, happy, sad, or neutral as a response. The response screen remained present until the experimenter pressed the key corresponding to the verbal response of the participant. The outcome measure was percent correct for each emotion at each contrast.

Electrophysiological experiment - procedure

Each of the 44 stimuli was presented with emotion type and contrast level randomly intermixed. A target flower, which was also enclosed in the same sized oval and had the same overall mean luminance as the facial images, was presented 10% of the time. Stimuli were shown for 500 milliseconds with an interstimulus interval (ISI) that was jittered with a mean of 1000 ms (900 and 1100 ms were the lower and upper bounds). Participants were asked to press a button every time they saw the target flower. Requiring participants to attend to the flower rather than identify emotions was intended to enhance investigation of sensory responses to the non-target stimuli. Blocks were ~3 minutes long and 30 blocks were run to achieve ~300 trials for each emotion at each contrast. The electrophysiological outcome measures were amplitudes of the three components P1, N170 and P250 for each emotion at each contrast which were obtained as follows:

Electrophysiological experiment - data acquisition and processing

High-density continuous EEG was acquired from 64 surface electrode sites arranged geodesically, using the BioSemi Active II system (BioSemi, Amsterdam, The Netherlands), along with digital stimulus timing-tags. Data were digitized online at 512 Hz. All data were recorded relative to a common-reference online and algebraically re-referenced offline to a standard reference, which was the average of all electrodes, before further analyses.

For all participants, EEG epochs were constructed off-line (-100 to 500 ms post-stimulus onset). Data were baseline corrected from -100 ms to stimulus onset. Automated artifact rejection with a criterion of ±120 μv was conducted to exclude any trials that contained eye-blinks, physical movement or electrical artifacts. Trials containing eye-movements, identified as deflections of >10 μV lasting >25 ms appearing on both eye channels, were rejected offline. There were no between-group significant differences in percentage of sweeps accepted (t_{48} = .76, p = .45). Epochs were then averaged separately for each stimulus type for each participant and subjected to statistical analyses. Grand average waveforms were constructed separately for each stimulus type for patients and controls. Figure 4 shows filtered waveforms (50 Hz low-pass, 0.5 Hz high-pass, 24 dB/octave roll-off).

Voltage topography maps were used to select the electrode sites with maximal amplitude for the P1, N170 and P250 components. P1 was maximal over dorsal electrodes (right hemisphere: O2, PO8; left hemisphere: O1, PO7) (Figure 2a). N170 was maximal over lateral, ventral-occipital sites (right hemisphere: PO8, PO10; left hemisphere: PO7, PO9) (Figure 2b). P250 was maximal over dorsal electrode sites (right hemisphere: O2, PO8, P8; left hemisphere: O1, PO7, P7) (Figure 2c).

Latency windows 20 ms before and 20 ms after peak amplitude were identified for each component. The mean voltage within each specified latency window was obtained for each electrode. Mean amplitudes for each electrode of interest for a specific component were then averaged together for each participant. The same latency windows were used for patients and controls, but they differed according to contrast. The P1 latency window was 85-125 ms for 57% contrast; 105-145 ms for 8% contrast; and 125-165 ms for 2% contrast. The N170 latency window was 144-185 ms for 57% contrast; 165-205 ms for 8% contrast; and 183-223 ms for 2% contrast. Finally, the P250 latency window was 215-255 ms at 57%; 230-270 ms for 8% contrast; and 255-295 ms for 2% contrast.

Statistical analysis

Between group analyses for the psychophysical measure (percent correct) and each ERP component were performed separately using mixed-model analyses of variance (ANOVAs) with Group (patient, control) as the between-subjects factor, and with RMS Contrast (2, 8, 57%), and Emotion (fear, happy, sad, neutral) as within-subject factors. Percent correct, P1, N170, or P250 amplitude were the dependent variables. Appropriate follow-up ANOVAs, contrasts, and independent sample t-tests were conducted to further assess main effects and interactions. Data for ERP analyses were collapsed across hemisphere because the same pattern of between-group effects was found for each hemisphere for each component. The comparison group included a significantly higher proportion of female participants than the patient group (p=.037, Fisher's exact test). Gender was therefore included as a covariate in between-group ANCOVAs.

ERP components as predictors of behavior were also examined. Mixed-effects model regressions were used because the relationship between ERP components and behavior may depend on diagnostic Group, and/or Emotion. The models were conducted separately for each of the three ERP measures and each of the three contrast levels. Behavior was modeled as a function of the ERP component (P1, N170 or P250) (entered into the model as the predictor), Group, Emotion and all 2- and 3-way interactions between them. The model selection strategy was as follows: if the 3-way interaction term (a 3 d.f. test) was not significant, it was omitted and the model was refit and the significance of the 2-way interactions were subsequently assessed. In such a way, non-significant terms were eliminated one-by-one while following the hierarchical principle that if a higher order interaction term is significant, all lower order terms contained in it are retained in the model regardless of their significance. Subsequent correlational analyses were conducted according to the results of the final model.

Earlier ERP components were also investigated as predictors of the later component. Specifically, the relationships between P1 and P250, and N170 and P250 were examined. The models were conducted separately for each of the three contrasts. Because these relationships may depend on Group and/or Emotion, the later ERP component (P250) was modeled as a function of the earlier component (P1 or N170 entered as the predictor), Group, Emotion, and all 2- and 3-way interactions between them. The same model selection strategy was used as described above. Subsequent correlational analyses were conducted according to the results of the final model.

Significance everywhere was judged at a two-sided level of significance $\alpha=0.05$. Analyses were conducted using SPSS software (Chicago, Ill).

4. Results

Behavior

Contrast response curves were plotted for the two diagnostic groups for each emotion condition (Figure 3a). Patients showed behavioral deficits in emotion recognition compared to controls at each emotion and contrast as indicated by a main effect of Group ($F_{1,48} = 44.5$, $p < .001$). The group effect remained strongly significant even when gender was included as a factor ($F_{1,47} = 34.5$, $p < .001$).

It should be noted that steep slopes at low contrasts were generally not seen for controls because correct responses at 2% RMS contrast were already substantially elevated. Thus, for behavior, differences in initial gain between controls and patients could not be examined. The finding that controls performed relatively well at the low, M-biased contrast indicates that magnocellular information may be sufficient for emotion recognition (controls: 78.7% correct overall). However, patients needed the addition of parvocellular information at high contrast (i.e., 57% RMS contrast) to reach the same level of performance as controls at low contrast (i.e., 2% RMS contrast; Figure 3a), for all emotions except neutral. Further, similar between-group differences were seen across contrasts as indicated by the lack of a significant Group x Contrast interaction ($F_{2,47} = .52$, $p = .6$), indicating that behavioral performance of patients improved similarly to that of controls as contrast increased, and P-biased information was introduced.

As seen in Figure 3b, the smallest between group differences were seen to happy faces, particularly at 57% RMS contrast, potentially due to ceiling effects in controls, as indicated by a trend towards a significant Group x Emotion x Contrast interaction ($F_{6,43} = 2.3$, $p = .053$).

P1

Group-averaged waveforms were plotted for P1 amplitude at each contrast, collapsed across emotions (Figure 4a). In addition, contrast response functions were plotted for the two diagnostic groups for each emotion condition (Figure 5a). Patients demonstrated significantly decreased P1 amplitudes compared to controls for each emotion at each contrast, as seen by a significant main effect of Group ($F_{1,48} = 9.5$, $p = .003$). The group effect remained strongly significant even when gender was included as a factor ($F_{1,47} = 12$, $p = .001$).

As hypothesized, contrast response curves for P1 amplitude in controls showed a pattern characteristic of magnocellular neurons – i.e., a sharp rise in response as contrast increased from 2% to 8% and plateau thereafter. The shape of the contrast response functions differed between patients and controls as seen by a significant Group x Contrast interaction ($F_{2,47} = 5$, $p = .01$). Patients exhibited shallower slopes than controls between 2% and 8% RMS contrast ($F_{1,48} = 5.8$, $p = .02$). For both groups, a plateau was reached at 8% RMS contrast, as seen by little change in P1 amplitude as contrast was increased from 8% to 57% ($F_{1,48} = 1.56$, $p = .22$). In addition, at plateau, the P1 amplitude was significantly lower for patients than controls (Figure 5a). Patients required the addition of parvocellular information (57% RMS contrast images) to reach similar P1 amplitudes as controls at the M-biased contrast for each emotion ($p > .11$) (Figure 5a). This is also demonstrated in voltage topography maps (Figure 2a).

P1 amplitude varied by emotion in controls at 2% RMS contrast only but did not vary for patients at any contrast (Figure 5b), as indicated by a Group x Emotion x Contrast interaction ($F_{6,43} = 2.6$, $p = .03$). Follow-up ANOVAs were conducted at each contrast, and indeed, a significant Group x Emotion interaction was only seen at 2% RMS contrast ($F_{3,46} = 5.56$, $p = .002$). Follow-up univariate ANOVAs conducted for each group separately at 2% RMS contrast revealed a main effect of Emotion for controls ($F_{3,22} = 17.88$, $p < .001$) but not patients ($F_{3,22} = 1.31$, $p = .29$). For controls, the P1 amplitude was lower for fear than for the other three emotions and lower for happy than sad ($p < . 016$).

N170

Group-average waveforms were plotted for N170 amplitude at each contrast, collapsed across emotions (Fig 4b). In addition, contrast response functions were plotted for the two diagnostic groups for each emotion condition (Figure 6a). Patients did not show significantly decreased N170 amplitudes compared to controls, as seen by a non-significant main effect of Group ($F_{1,48}$ = .12, p = .73). The group effect remained non-significant even when gender was included as a factor ($F_{1,47}$ = .24, p = .64).

N170 amplitude contrast response functions, for both groups, increased linearly with contrast and did not plateau. Indeed, both groups exhibited steep slopes between 2% and 8% RMS contrast ($F_{1,48}$ = 89.69, p < .001), as well as between 8% and 57% RMS contrast ($F_{1,48}$ = 29.92, p < .001).

The N170 pattern of response to emotion was different between groups at 2% and 57%, but not 8 % RMS contrast (Figure 6b), as indicated by a Group x Emotion x Contrast interaction ($F_{6,43}$ = 2.74, P = .024). Follow-up ANOVAs at each contrast revealed significant Group x Emotion interactions at 2% ($F_{3,46}$ = 2.95, p = .043) and 57% RMS contrast ($F_{3,46}$ = 3.24, p = .03), whereas at 8% RMS contrast there was only a main effect of Emotion ($F_{3,46}$ = 11.85, p < .001).

Specific patterns of emotion for each contrast were then examined. At 2% RMS contrast, within group univariate ANOVAs revealed significant main effects of Emotion for both controls ($F_{3,22}$ = 2.98, p = .05) and patients ($F_{3,22}$ = 4.63, p = .012). For controls, the N170 amplitude was more negative for happy than fear or sad (p = .05). For patients, the N170 amplitude was more negative for sad than fear and neutral (p < .021). At 8% RMS contrast, across groups, N170 amplitude to fear was more negative than for the other three emotions (p < .018), and happy was more negative than sad and neutral (p < .04). Lastly, at 57% RMS contrast, within group univariate ANOVAs revealed a main effect of Emotion for controls ($F_{3,22}$ = 4.42, p = .014) but not patients ($F_{3,22}$ = 1.4, p = .27). For controls, the N170 amplitude for neutral was less negative than for the other three emotions (p < .03).

P250

Group-average waveforms were plotted for P250 amplitude at each contrast, collapsed across emotion (Figure 4c). In addition, contrast response functions were plotted for the two diagnostic groups for each emotion condition (Figure 7a). Patients demonstrated significantly decreased P250 amplitudes for each emotion and contrast compared to controls, as seen by a significant main effect of Group ($F_{1,48} = 9.5$, $p = .003$). The group effect remained strongly significant even when gender was included as a factor ($F_{1,47} = 14.9$, $p < .001$).

P250 amplitude contrast response functions increased linearly with contrast and did not plateau (Figure 7a). Across groups, there were large slopes between 2% and 8% RMS contrast ($F_{1,48} = 44.01$, $p < .001$) and between 8% and 57% RMS contrast ($F_{1,48} = 37.97$, $p < .001$). Like the P1, patients needed the addition of P-biased information (57% contrast images) to reach similar P250 amplitudes as controls at the M-biased 2% RMS contrast for each emotion ($p > .14$). This is also demonstrated via voltage topography maps (Figure 2c).

P250 amplitude varied by emotion, and the pattern was similar across groups and contrasts as seen by an overall significant main effect of Emotion ($F_{3,46} = 20$, $p < .001$) and no significant interactions (Figure 7b). P250 amplitude was higher for neutral than for the other three emotions ($p < .005$). In addition, P250 amplitude to sad was higher than to happy or fear ($p < .001$) and P250 amplitude to happy was higher than to fear ($p < .001$).

Relationships between behavior and electrophysiology

Examination of ERP components as predictors of behavior was carried out using mixed effects model regressions and the best-fitting model was obtained as described in the statistical analysis section.

The best-fitting models for 2% and 8% RMS contrast showed that P1 amplitude predicted behavior based on emotion, not diagnosis, as seen by significant Emotion x P1 interactions (2%: p = .003; 8%: p =.03). P1 amplitude at 57% RMS contrast was not related to behavior. The associations between P1 and behavior at 2% and 8 % RMS contrast were subsequently assessed separately for each emotion across groups. P1 amplitude was associated with behavior for all emotions other than neutral. Correlations are shown in Table 2a.

The N170 predicted behavior at 2% and 57% RMS contrast based on diagnosis, as seen by significant Group x N170 interactions (2%: p = .001; 57%: p = .033). Subsequent within-group correlations at 2% and 57% RMS contrast revealed that behavior was associated with N170 for patients, but not controls (Table 2b). Conversely, the best fitting model at 8% RMS contrast demonstrated a main effect of N170 (p = .009), indicating that the N170 predicted behavior regardless of group and emotion. Subsequently, a significant correlation between N170 amplitude and behavior across groups and emotions at 8% RMS contrast was found (Table 2b).

The P250 amplitude predicted behavior based on emotion at 2% RMS contrast, as seen by a significant Emotion x P250 interaction (p=.003). The association between P250 amplitude and behavior at 2% RMS contrast was thus assessed separately for each emotion across groups. P250 amplitude was associated with behavior, but to a differing degree, for all emotions at 2% RMS contrast. Correlations are shown in Table 2c.

Relationships between electrophysiological components

The best fitting models at 2%, 8% and 57% RMS contrast showed that the P1 predicted the P250 amplitude regardless of group or emotion as seen by a main effect of P1 amplitude at all three contrasts ($p < .001$). Subsequent correlations between P1 and P250 conducted across groups and emotions were significant at each contrast (Table 3).

The best fitting model for 2% RMS contrast showed that the relationship between N170 and P250 was based on Group and Emotion as seen via a Group x Emotion x N170 interaction ($p = .04$). Subsequent analysis found that the within-group correlations between N170 and P250 were significantly different from each other for sad and neutral faces ($p < .05$). That is, controls showed stronger positive correlations between components while patients showed weaker, negative correlations. However, no within-group correlations between the N170 and P250 components for any emotion reached significance ($p > .07$), indicating that the N170 was not significantly associated with the P250. The best fitting model at 8% and 57% RMS contrast showed that the N170 predicted the P250 component regardless of group or emotion as seen by a main effect of N170 amplitude ($p = .02$, $p=0.03$, respectively). However, follow-up correlations between N170 and P250 across groups and emotions were not significant. Because of this apparent paradox, we investigated correlations between N170 and P250 for each participant separately, across emotions, and found significant effects (2% and 8% RMS contrast: $p = .008$). This suggests that the main effect in the model was due to the N170 and P250 peaks originating from same waveform of each individual. However, unlike the association between P1 and P250, the relationship between N170 and P250 was not found across individuals. Therefore, the N170 may not be truly contributing to the P250 component.

Clinical ratings versus neurophysiology and behavior

For patients, significant correlations were observed between SANS total including global ratings and P1 amplitude at 2% contrast for fear, sad and neutral (n = 22, r = -.5--.44, p = .02-.04), 8% contrast for fear, happy and sad (n = 22, r = -.5--.44, p = .02-.04) and 57% contrast for fear and sad (n = 22, r = -.44--.43, p = .04-.05). No significant correlations were observed between N170 and any clinical measures. Significant correlations were also observed between GAF scores and P250 amplitude at 2% RMS contrast for happy, sad and neutral (n = 20, r = .5-.6, p = .02-.005) and 8% contrast for fear, happy and sad (n = 20, r = .45-.54, p = .047-.015). Significant correlations were observed between ILS scaled scores and behavioral recognition of happy and sad at 2% RMS contrast (n = 24, r = .46-.51, p = 0.024-.011).

Gender

There were significantly more females in the control than the patient group (Fisher's exact test, p = .037). Gender effects in the control group were examined as this group contained 16 males and 9 females. A mixed-model ANOVA with Gender (male, female) as the between-subjects factor, Contrast (2, 8, 57%), and Emotion (fear, happy, sad, neutral) as within-subject factors, and Behavior (percent correct), P1, N170, or P250 amplitude as the dependent variable did not show a significant main effect of gender (p > .078).

5. Discussion

This study was based on the findings that the M/dorsal stream is involved in face emotion recognition (Adolphs, Tranel, & Buchanan, 2005; Amaral, Behniea, & Kelly, 2003; Calder et al., 2000; Kveraga et al., 2007; Morris et al., 2001; Schyns & Oliva, 1999; Vuilleumier et al., 2003; Whalen et al., 2004; Winston et al., 2003) and that deficits in early stage visual sensory processing, particularly involving the M-pathway, have become increasingly well-documented in schizophrenia (Butler et al., 2007; Doniger et al., 2002; Foxe et al., 2001; Martinez et al., 2008; O'Donnell et al., 2002; Schechter et al., 2005; Slaghuis, 2004). The present study examined the pattern of behavioral and ERP responses across contrast levels in patients with schizophrenia in order to evaluate impaired M/dorsal stream contributions to face emotion processing deficits in schizophrenia. While we have previously performed a similar behavioral experiment (Butler et al., 2009) this is the first ERP study to evaluate emotion processing across contrast levels.

For the behavioral task, controls performed well during the low contrast condition suggesting that information necessary for emotion recognition can be carried primarily by the M-system. This is consistent with previous findings showing that configural (global) and low spatial frequency (course) information are vital for emotion recognition in controls (Adolphs et al., 2005; Calder et al., 2000; Morris, deBonis, & Dolan, 2002; Schyns & Oliva, 1999). Patients showed significant deficits in emotion recognition compared to controls for each emotion at each contrast. The deficit at low contrast indicates that patients have difficulty using the M-pathway in emotion recognition. Indeed, patients needed the addition of high contrast information to perform similarly to controls at low contrast. These results are similar to our previous behavioral findings

(Butler et al., 2009). However, because controls performed well even at 2% RMS contrast in the present study, it was difficult to examine the shape of the contrast response functions.

For the P1 amplitude, controls exhibited non-linear contrast response functions with steep increase at low contrast and plateau at higher contrasts, reflecting a characteristic M-pattern of response to the emotion-based stimuli. Schizophrenia patients not only showed a decrease in P1 amplitude compared to controls for each contrast and emotion, but also showed shallower initial gain than controls and a lower amplitude of response at plateau, consistent with M/dorsal pathway impairment (Butler et al., 2007). While patients have shown similar contrast response functions to simple check stimuli in ERP and steady-state visual evoked potential studies (Butler et al., 2009; Butler et al., 2007; Butler, Zemon et al., 2005), the present results are the first to extend these findings to more complex emotion-based stimuli. This non-linear response pattern reflecting amplification of responses at low-contrast is thought to be mediated by NMDA receptors and is decreased by NMDA antagonists (Kwon et al., 1992). The deficit in patients is consistent with NMDA receptor dysfunction in schizophrenia (Javitt & Zukin, 1991).

Reduced P1 amplitude (Caharel et al., 2007; Campanella et al., 2006; Obayashi et al., 2009) and longer P1 latencies (Lee, Gosselin et al., 2010; Wynn et al., 2008) have been found in several, but not all (Herrmann et al., 2004; Johnston et al., 2005; Turetsky et al., 2007; Wynn et al., 2008) previous face emotion studies. Studies that have showed a decrease in P1 amplitude (Caharel et al., 2007; Campanella et al., 2006), including ours, used tasks unrelated to emotion identification. Thus, the decrease in P1 amplitude may be associated with the use of an implicit task which may enhance the sensory nature of the neuronal response. Our results are also in accord with numerous studies showing P1 reductions to non-face stimuli in schizophrenia (Butler et al., 2004; Caharel et al., 2007; Campanella et al., 2006; Doniger et al., 2002; Foxe et al., 2001; Foxe et al., 2005; Haenschel et al., 2004; Schechter et al., 2005; Spencer et al., 2003; Yeap et al., 2006) and suggest that impaired emotional processing is a general consequence of a deficit in processing incoming sensory stimuli.

Further, we found that P1 amplitude varied by emotion in the 2% RMS contrast condition for controls but not patients. Studies in controls have shown that P1 amplitude varies by emotion when presentation time is short or low spatial frequency stimuli are used (Pourtois et al., 2005; Turetsky et al., 2007; Vuilleumier et al., 2003; Winston et al., 2003). Thus, sensory characteristics mediated by the M-pathway may underlie emotion differentiation at this early stage of processing. This may be most pronounced in response to the low contrast manipulation that emphasizes the M-pathway in the present study.

Indeed, the P1 has been shown to be modulated by both direct M-stream input to the dorsal stream (Butler et al., 2007) and by fast M-stream input via tecto-pulvinar projections to the amygdala which then feedback to extrastriate visual areas affecting processing at the level of the P1 (Aggleton, Burton, & Passingham, 1980; Amaral et al., 2003; Cowey & Stoerig, 1991; Morris et al., 2001; Morris et al., 1998; Morris, Ohman, & Dolan, 1999; Vuilleumier et al., 2003; Winston et al., 2003). Later emotion processing deficits in schizophrenia may arise from this early input dysfunction.

N170 contrast response functions showed a linear relationship in patients and controls, similar to P-pathway functions. Indeed, the N170 is thought to have a generator in the ventral stream (e.g., fusiform gyrus) (Herrmann et al., 2005; Shibata et al., 2002) which is known to receive P-stream inputs (Schroeder et al., 1998). In addition, patients did not show N170 deficits for any emotion at any contrast. Mixed results have previously been found in face-emotion studies, with some showing intact N170 amplitudes during facial affect processing (Lee, Kim et al., 2010; Streit et al., 2001; Wynn et al., 2008) while a number of others showed that patients had N170 deficits (Caharel et al., 2007; Campanella et al., 2006; Johnston et al., 2005; Lee, Kim et al., 2010; Turetsky et al., 2007). The reason for the discrepancy among studies is unclear and may be related to differences including stimulus presentation durations, analysis methods, and different electrode locations used. However, differences do not appear to be related to the implicit versus explicit nature of the task. In addition, some studies looking at non-face stimuli show normal N1 amplitudes in patients with schizophrenia (Doniger et al., 2002; Foxe et al., 2001). The intact N170 to face emotion stimuli in the present study, like the N1 to non-face stimuli, may reflect preserved P-pathway input to the ventral stream (e.g. fusiform gyrus). Indeed, intact function of the fusiform face area has been reported in several schizophrenia studies (Butler, Tambini et al., 2008; Yoon et al., 2006).

The N170 response varied by emotion (at all three contrasts) for controls, consistent with a number of previous studies (Batty & Taylor, 2003; Blau et al., 2007; Campanella et al., 2006; Campanella et al., 2002), but see (Eimer & Holmes, 2002; Eimer et al., 2003), supporting a role for the N170 in affect modulation rather than simply in structural encoding of facial features. In the present study, patients with schizophrenia showed differential N170 amplitude emotion response profiles compared to controls, as previous findings also demonstrate (Lynn & Salisbury, 2008; Turetsky et al., 2007). Since N710 amplitude itself was intact in the present study, the aberrant pattern of N170 modulation in patients could be due to impaired M-stream input to both, ventral stream areas via dorsal stream crossover (as is thought to underlie object processing deficits in schizophrenia, see Sehatpour et al., 2010), and the amygdala which heavily projects to and influences fusiform gyrus (Fukuda, Ono, & Nakamura, 1987; Iwai, Yukie, Suyama, & Shirakawa, 1987; Iwai et al., 1990; Spiegler & Mishkin, 1981).

The P250 has been shown to be modulated by emotional content (Balconi & Pozzoli, 2003; Caharel et al., 2007; Carretie, Martin-Loeches et al., 2001; Carretie, Mercado et al., 2001; Horley et al., 2001; Schutter et al., 2004; Streit et al., 2001). Indeed, in the current study, the P250 differentiated among emotions in both groups, including at low-contrast supporting previous data indicating that emotion discrimination is in-part achieved through M-mediated information (Calder et al., 2000; Schyns & Oliva, 1999). However, patients exhibited deficits in P250 amplitude at each emotion and each contrast. The deficit seen in patients at low-contrast and the significant relationship between P1 and P250 components, which was absent between N170 and P250 components, supports the hypothesis that early sensory deficits involving the M/dorsal pathway contribute to later emotion processing dysfunction.

With the exception of one previous study which examined the P250 (Caharel et al., 2007), previous ERP studies of face emotion processing in schizophrenia have examined the N250 (Johnston et al., 2005; Lee, Kim et al., 2010; Streit et al., 2001; Turetsky et al., 2007; Wynn et al., 2008). The topographic distribution of voltage guided our choice to focus on the posterior P250 (see Figure 2). The emphasis of activity occurring within dorsal occipital cortex in our study may be related to our use of an implicit task that enhanced sensory/perceptual processes.

The posterior P250 component is not well understood, but may reflect recursive visual cortical processing that plays a role in enhancing the saliency of emotional stimuli. Indeed previous neuroimaging studies have shown that projections from ventral visual areas feedback onto extrastriate cortices at later time-points in the visual processing pathway in order to assist in emotion discrimination (Freese & Amaral, 2005; Sabatinelli et al., 2009; Vuilleumier, Richardson, Armony, Driver, & Dolan, 2004). The P250 may represent this process electrophysiologically, and its drastic reduction in patients may reflect its association with the early dorsal P1 impairment seen in the current study.

P1, N170, and P250 amplitude were each correlated with ability to identify emotion in the psychophysical study. For the P1 and P250 this relationship depended on emotion and was not based on general group differences. In addition, for the P1 and P250, the relationships with behavior were seen at the lower contrasts. This may be because performance at high contrast had less variability than at the lower contrasts, particularly for controls. N170 amplitude predicted behavior in patients only at 2% and 57% RMS contrast. These data indicate that overall, patients may additionally rely on their ventrally generated N170 for emotion processing as they have deficits in processes mediated by the early dorsal component. Relationships between ERP components and behavior in the present study highlight the importance of early stage processing (i.e., the P1) in the ability to identify emotion.

The present finding of significant relationships between greater P1 amplitude and decreased negative symptoms indicates a relationship between early visual processing dysfunction and emotion processing in people with negative symptoms. In addition, relationships between increased P250 and increased GAF scores, indicative of higher functioning, are consistent with behavioral studies showing the relevance of emotion processing to overall ability to function in schizophrenia (Brekke et al., 2005; Kee et al., 2003; Sergi et al., 2006).

Limitations of the study include all patients being on medication and a much larger number of females in the control than patient group. However, visual processing deficits have been found in both medicated and unmedicated patient populations (Braff and Sacuzzo, 1982; Harvey et al., 1990; Butler et al., 1996; Cadenhead et al., 1997; Butler et al., 2002) and unmedicated first-degree relatives (Green et al., 1997; Chen et al., 1999; Keri et al., 2004). In addition, there were no correlations found between the chlorpromazine (CPZ) equivalents and P1, and P250 amplitudes across contrasts ($p>.3$). However, the N170 for fear, happy and neutral at 57% RMS contrast was correlated with CPZ equivalents ($p = .04$, $p = .03$, $p =.04$, respectively) so effects of medication on this component cannot be ruled out. While there were more females in the control versus the patient group, gender did not affect the results.

In conclusion, the finding of impaired P1 amplitude in schizophrenia to face emotion stimuli provides evidence that emotion recognition deficits in schizophrenia occur at an early stage of visual processing. The P1 contrast response functions maintained M-stream characteristics and patients showed a decreased initial slope and a lower plateau of neuronal response. This pattern of response suggests that the reduced P1 amplitude is at least in-part due to M-pathway dysfunction in schizophrenia, and the relationship between P1 and emotion recognition ability implies P1 deficits contribute to emotion recognition deficits in the patient population. Lastly, a normal N170 but impaired dorsal stream P250, along with a significant relationship between P1 and P250 amplitudes suggest M/dorsal stream involvement in emotion processing deficits and indicate the importance of early deficits for later processing.

6. References

Addington, J., & Addington, D. (1998). Facial affect recognition and information processing in schizophrenia and bipolar disorder. *Schizophr Res, 32*(3), 171-181.

Addington, J., Addington, D., & Gasbarre, L. (2001). Neurocognitive and social functioning in schizophrenia and other diagnoses. *Schizophr Res, 48*(2-3), 367-368.

Adolphs, R., Tranel, D., & Buchanan, T. W. (2005). Amygdala damage impairs emotional memory for gist but not details of complex stimuli. *Nat Neurosci, 8*(4), 512-518.

Aggleton, J. P., Burton, M. J., & Passingham, R. E. (1980). Cortical and subcortical afferents to the amygdala of the rhesus monkey (Macaca mulatta). *Brain Res, 190*(2), 347-368.

Amaral, D. G., Behniea, H., & Kelly, J. L. (2003). Topographic organization of projections from the amygdala to the visual cortex in the macaque monkey. *Neuroscience, 118*(4), 1099-1120.

Andreasen, N. C. (1984). *The scale for the assessment of negative symptoms (SANS).* Iowa City: The University of Iowa.

Balconi, M., & Pozzoli, U. (2003). Face-selective processing and the effect of pleasant and unpleasant emotional expressions on ERP correlates. *Int J Psychophysiol, 49*(1), 67-74.

Bar, M., Neta, M., & Linz, H. (2006). Very first impressions. *Emotion, 6*(2), 269-278.

Batty, M., & Taylor, M. J. (2003). Early processing of the six basic facial emotional expressions. *Brain Res Cogn Brain Res, 17*(3), 613-620.

Bentin, S., Allison, T., Puce, A., Perez, E., & McCarthy, G. (1996). Electrophysiological studies of face perception in humans. *Journal of Cognitive Neuroscience, 8*, 551-565.

Blau, V. C., Maurer, U., Tottenham, N., & McCandliss, B. D. (2007). The face-specific N170 component is modulated by emotional facial expression. *Behav Brain Funct, 3*, 7.

Borod, J. C., Martin, C. C., Alpert, M., Brozgold, A., & Welkowitz, J. (1993). Perception of facial emotion in schizophrenic and right brain-damaged patients. *J Nerv Ment Dis, 181*(8), 494-502.

Brekke, J., Kay, D. D., Lee, K. S., & Green, M. F. (2005). Biosocial pathways to functional outcome in schizophrenia. *Schizophr Res, 80*(2-3), 213-225.

Brenner, C. A., Wilt, M. A., Lysaker, P. H., Koyfman, A., & O'Donnell, B. F. (2003). Psychometrically matched visual-processing tasks in schizophrenia spectrum disorders. *J Abnorm Psychol, 112*(1), 28-37.

Butler, P. D., Abeles, I. Y., Weiskopf, N. G., Tambini, A., Jalbrzikowski, M., Legatt, M. E., et al. (2009). Sensory contributions to impaired emotion processing in schizophrenia. *Schizophr Bull, 35*(6), 1095-1107.

Butler, P. D., Kim, D., Foxe, J. J., Piesco, J. R., Hoptman, M. J., Lim, K. O., et al. (2004). Decreased signal amplification in schizophrenia: evidence from visual studies. *Society for Neuroscience Abstracts*, Program No. 348.341.

Butler, P. D., Martinez, A., Foxe, J. J., Kim, D., Zemon, V., Silipo, G., et al. (2007). Subcortical visual dysfunction in schizophrenia drives secondary cortical impairments. *Brain, 130*, 417-430.

Butler, P. D., Silverstein, S. M., & Dakin, S. C. (2008). Visual perception and its impairment in schizophrenia. *Biol Psychiatry, 64*(1), 40-47.

Butler, P. D., Tambini, A., Yovel, G., Jalbrzikowski, M., Ziwich, R., Silipo, G., et al. (2008). What's in a face? Effects of stimulus duration and inversion on face processing in schizophrenia. *Schizophr Res*.

Butler, P. D., Zemon, V., Schechter, I., Saperstein, A. M., Hoptman, M. J., Lim, K. O., et al. (2005). Early-stage visual processing and cortical amplification deficits in schizophrenia. *Arch Gen Psychiatry, 62*(5), 495-504.

Caharel, S., Bernard, C., Thibaut, F., Haouzir, S., Di Maggio-Clozel, C., Allio, G., et al. (2007). The effects of familiarity and emotional expression on face processing examined by ERPs in patients with schizophrenia. *Schizophr Res, 95*(1-3), 186-196.

Caharel, S., Courtay, N., Bernard, C., Lalonde, R., & Rebai, M. (2005). Familiarity and emotional expression influence an early stage of face processing: an electrophysiological study. *Brain Cogn, 59*(1), 96-100.

Calder, A. J., Rowland, D., Young, A. W., Nimmo-Smith, I., Keane, J., & Perrett, D. I. (2000). Caricaturing facial expressions. *Cognition, 76*(2), 105-146.

Campanella, S., Montedoro, C., Streel, E., Verbanck, P., & Rosier, V. (2006). Early visual components (P100, N170) are disrupted in chronic schizophrenic patients: an event-related potentials study. *Neurophysiol Clin, 36*(2), 71-78.

Campanella, S., Quinet, P., Bruyer, R., Crommelinck, M., & Guerit, J. M. (2002). Categorical perception of happiness and fear facial expressions: an ERP study. *J Cogn Neurosci, 14*(2), 210-227.

Carretie, L., Martin-Loeches, M., Hinojosa, J. A., & Mercado, F. (2001). Emotion and attention interaction studied through event-related potentials. *J Cogn Neurosci, 13*(8), 1109-1128.

Carretie, L., Mercado, F., Tapia, M., & Hinojosa, J. A. (2001). Emotion, attention, and the 'negativity bias', studied through event-related potentials. *Int J Psychophysiol, 41*(1), 75-85.

Chen, Y., Nakayama, K., Levy, D., Matthysse, S., & Holzman, P. (2003). Processing of global, but not local, motion direction is deficient in schizophrenia. *Schizophr Res, 61*(2-3), 215-227.

Cowey, A., & Stoerig, P. (1991). The neurobiology of blindsight. *Trends Neurosci, 14*(4), 140-145.

Doniger, G. M., Foxe, J. J., Murrary, M. M., Higgins, B. A., & Javitt, D. C. (2002). Impaired visual object recogntion and dorsal/ventral stream interaction in schizophrenia. *Arch Gen Psychiatry, 59*, 1011-1020.

Edwards, J., Jackson, H. J., & Pattison, P. E. (2002). Emotion recognition via facial expression and affective prosody in schizophrenia: a methodological review. *Clin Psychol Rev, 22*, 789-832.

Edwards, J., Pattison, P. E., Jackson, H. J., & Wales, R. J. (2001). Facial affect and affective prosody recognition in first-episode schizophrenia. *Schizophr Res, 48*(2-3), 235-253.

Eimer, M. (2000). The face-specific N170 component reflects late stages in the structural encoding of faces. *Neuroreport, 11*(10), 2319-2324.

Eimer, M., & Holmes, A. (2002). An ERP study on the time course of emotional face processing. *Neuroreport, 13*(4), 427-431.

Eimer, M., & Holmes, A. (2007). Event-related brain potential correlates of emotional face processing. *Neuropsychologia, 45*(1), 15-31.

Eimer, M., Holmes, A., & McGlone, F. P. (2003). The role of spatial attention in the processing of facial expression: an ERP study of rapid brain responses to six basic emotions. *Cogn Affect Behav Neurosci, 3*(2), 97-110.

Ekman, P., & Friesen, W. V. (1976). *Pictures of facial affect*. Palo Alto: Consulting Psychologists Press.

Feinberg, T. E., Rifkin, A., Schaffer, C., & Walker, E. (1986). Facial discrimination and emotional recognition in schizophrenia and affective disorders. *Arch Gen Psychiatry, 43*(3), 276-279.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (1997). *Structured Clinical Interview for DSM-IV Axis I Disorders- Patient Edition*. New York: New York State Psychiatric Institute.

Foxe, J. J., Doniger, G. M., & Javitt, D. C. (2001). Early visual processing deficits in schizophrenia: impaired PI generation revealed by high-density electrical mapping. *NeuroReport, 12*(17).

Foxe, J. J., Murray, M. M., & Javitt, D. C. (2005). Filling-in in Schizophrenia: a High-density Electrical Mapping and Source-analysis Investigation of Illusory Contour Processing. *Cereb Cortex, 15*(12), 1914-1927.

Freese, J. L., & Amaral, D. G. (2005). The organization of projections from the amygdala to visual cortical areas TE and V1 in the macaque monkey. *J Comp Neurol, 486*(4), 295-317.

Fukuda, M., Ono, T., & Nakamura, K. (1987). Functional relations among inferotemporal cortex, amygdala, and lateral hypothalamus in monkey operant feeding behavior. *J Neurophysiol, 57*(4), 1060-1077.

Galletly, C. A., Clark, C. R., & McFarlane, A. C. (2005). Clozapine improves working memory updating in schizophrenia. *Eur Neuropsychopharmacol, 15*(6), 601-608.

Goffaux, V., Gauthier, I., & Rossion, B. (2003). Spatial scale contribution to early visual differences between face and object processing. *Brain Res Cogn Brain Res, 16*(3), 416-424.

Gosselin, F., & Schyns, P. G. (2001). Bubbles: a technique to reveal the use of information in recognition tasks. *Vision Res, 41*(17), 2261-2271.

Gur, R. E., McGrath, C., Chan, R. M., Schroeder, L., Turner, T., Turetsky, B. I., et al. (2002). An fMRI study of facial emotion processing in patients with schizophrenia. *Am J Psychiatry, 159*(12), 1992-1999.

Gur, R. E., Turetsky, B. I., Cowell, P. E., Finkelman, C., Maany, V., Grossman, R. I., et al. (2000). Temporolimbic volume reductions in schizophrenia. *Arch Gen Psychiatry, 57*(8), 769-775.

Haenschel, C., Waltz, J., Bittner, R. A., Hartling, F., Rotarska-Jagiela, A., Maurer, K., et al. (2004). Intertrial synchronization deficits account for reduced P1 and high-frequency EEG activity in schizophrenia. *Society for Neuroscience Abstracts*, Program No. 348.343.

Halit, H., de Haan, M., Schyns, P. G., & Johnson, M. H. (2006). Is high-spatial frequency information used in the early stages of face detection? *Brain Res, 1117*(1), 154-161.

Heimberg, C., Gur, R. E., Erwin, R. J., Shtasel, D. L., & Gur, R. C. (1992). Facial emotion discrimination: III. Behavioral findings in schizophrenia. *Psychiatry Res, 42*(3), 253-265.

Herbener, E. S., Rosen, C., Khine, T., & Sweeney, J. A. (2007). Failure of positive but not negative emotional valence to enhance memory in schizophrenia. *J Abnorm Psychol, 116*(1), 43-55.

Herrmann, M. J., Ehlis, A. C., Muehlberger, A., & Fallgatter, A. J. (2005). Source localization of early stages of face processing. *Brain Topogr, 18*(2), 77-85.

Herrmann, M. J., Ellgring, H., & Fallgatter, A. J. (2004). Early-Stage face processing dysfunction in patients with schizophrenia. *Am J Psychiatry, 161*(5), 915-917.

Holmes, A., Winston, J. S., & Eimer, M. (2005). The role of spatial frequency information for ERP components sensitive to faces and emotional facial expression. *Brain Res Cogn Brain Res, 25*(2), 508-520.

Hollingshead, A. (1975). Four Factor Index of Social Status. Yale University Department of Sociology.

Holt, D. J., Kunkel, L., Weiss, A. P., Goff, D. C., Wright, C. I., Shin, L. M., et al. (2006). Increased medial temporal lobe activation during the passive viewing of emotional and neutral facial expressions in schizophrenia. *Schizophr Res, 82*(2-3), 153-162.

Horan, W. P., Green, M. F., Kring, A. M., & Nuechterlein, K. H. (2006). Does anhedonia in schizophrenia reflect faulty memory for subjectively experienced emotions? *J Abnorm Psychol, 115*(3), 496-508.

Horley, K., Gonsalvez, C., Williams, L., Lazzaro, I., Bahramali, H., & Gordon, E. (2001). Event-related potentials to threat-related faces in schizophrenia. *Int J Neurosci, 107*(1-2), 113-130.

Hyman SE, A. G., Rosenbaum JF (Ed.). (1995). *Handbook of Psychiatric Drug Therapy*. Boston: Little, Brown and Company.

Itier, R. J., & Taylor, M. J. (2004). Source analysis of the N170 to faces and objects. *Neuroreport, 15*(8), 1261-1265.

Iwai, E., Yukie, M., Suyama, H., & Shirakawa, S. (1987). Amygdalar connections with middle and inferior temporal gyri of the monkey. *Neurosci Lett, 83*(1-2), 25-29.

Iwai, E., Yukie, M., Watanabe, J., Hikosaka, K., Suyama, H., & Ishikawa, S. (1990). A role of amygdala in visual perception and cognition in macaque monkeys (Macaca fuscata and Macaca mulatta). *Tohoku J Exp Med, 161 Suppl*, 95-120.

Javitt, D. C., & Zukin, S. R. (1991). Recent advances in the phencyclidine model of schizophrenia. *Am J Psychiatry, 148*(10), 1301-1308.

Jibson, M. D., & Tandon, R. (1998). New atypical antipsychotic medications. *J Psychiatr Res, 32*(3-4), 215-228.

Johnston, P. J., Stojanov, W., Devir, H., & Schall, U. (2005). Functional MRI of facial emotion recognition deficits in schizophrenia and their electrophysiological correlates. *Eur J Neurosci, 22*(5), 1221-1232.

Joyce, C., & Rossion, B. (2005). The face-sensitive N170 and VPP components manifest the same brain processes: the effect of reference electrode site. *Clin Neurophysiol, 116*(11), 2613-2631.

Kee, K. S., Green, M. F., Mintz, J., & Brekke, J. S. (2003). Is emotion processing a predictor of functional outcome in schizophrenia? *Schizophr Bull, 29*(3), 487-497.

Keil, A., Muller, M. M., Gruber, T., Wienbruch, C., Stolarova, M., & Elbert, T. (2001). Effects of emotional arousal in the cerebral hemispheres: a study of oscillatory brain activity and event-related potentials. *Clin Neurophysiol, 112*(11), 2057-2068.

Keri, S., Antal, A., Szekeres, G., Benedek, G., & Janka, Z. (2002). Spatiotemporal visual processing in schizophrenia. *J Neuropsychiatry Clin Neurosci, 14*(2), 190-196.

Keri, S., Kelemen, O., Benedek, G., & Janka, Z. (2004). Vernier threshold in patients with schizophrenia and in their unaffected siblings. *Neuropsychology, 18*(3), 537-542.

Kerr, S. L., & Neale, J. M. (1993). Emotion perception in schizophrenia: specific deficit or further evidence of generalized poor performance? *J Abnorm Psychol, 102*(2), 312-318.

Kim, D., Zemon, V., Saperstein, A., Butler, P. D., & Javitt, D. C. (2005). Dysfunction of early-stage visual processing in schizophrenia: harmonic analysis. *Schizophr Res, 76*(1), 55-65.

Kohler, C. G., Bilker, W., Hagendoorn, M., Gur, R. E., & Gur, R. C. (2000). Emotion recognition deficit in schizophrenia: association with symptomatology and cognition. *Biol Psychiatry, 48*(2), 127-136.

Kohler, C. G., Turner, T. H., Bilker, W. B., Brensinger, C. M., Siegel, S. J., Kanes, S. J., et al. (2003). Facial emotion recognition in schizophrenia: intensity effects and error pattern. *Am J Psychiatry, 160*(10), 1768-1774.

Kring, A. M., Kerr, S. L., Smith, D. A., & Neale, J. M. (1993). Flat affect in schizophrenia does not reflect diminished subjective experience of emotion. *J Abnorm Psychol, 102*(4), 507-517.

Kring, A. M., & Moran, E. K. (2008). Emotional response deficits in schizophrenia: insights from affective science. *Schizophr Bull, 34*(5), 819-834.

Krolak-Salmon, P., Fischer, C., Vighetto, A., & Mauguiere, F. (2001). Processing of facial emotional expression: spatio-temporal data as assessed by scalp event-related potentials. *Eur J Neurosci, 13*(5), 987-994.

Kveraga, K., Boshyan, J., & Bar, M. (2007). Magnocellular projections as the trigger of top-down facilitation in recognition. *J Neurosci, 27*(48), 13232-13240.

Kwon, Y. H., Nelson, S. B., Toth, L. J., & Sur, M. (1992). Effect of stimulus contrast and size on NMDA receptor activity in cat lateral geniculate nucleus. *J Neurophysiol, 68*(1), 182-196.

Lee, J., Gosselin, F., Wynn, J. K., & Green, M. F. (2010). How Do Schizophrenia Patients Use Visual Information to Decode Facial Emotion? *Schizophr Bull*.

Lee, S. H., Kim, E. Y., Kim, S., & Bae, S. M. (2010). Event-related potential patterns and gender effects underlying facial affect processing in schizophrenia patients. *Neurosci Res, 67*(2), 172-180.

Li, H., Chan, R. C., McAlonan, G. M., & Gong, Q. Y. (2009). Facial emotion processing in schizophrenia: a meta-analysis of functional neuroimaging data. *Schizophr Bull, 36*(5), 1029-1039.

Liddell, B. J., Brown, K. J., Kemp, A. H., Barton, M. J., Das, P., Peduto, A., et al. (2005). A direct brainstem-amygdala-cortical 'alarm' system for subliminal signals of fear. *Neuroimage, 24*(1), 235-243.

Lynn, S. K., & Salisbury, D. F. (2008). Attenuated modulation of the N170 ERP by facial expressions in schizophrenia. *Clin EEG Neurosci, 39*(2), 108-111.

Mandal, M. K., Pandey, R., & Prasad, A. B. (1998). Facial expressions of emotions and schizophrenia: a review. *Schizophr Bull, 24*(3), 399-412.

Martinez, A., Hillyard, S. A., Dias, E. C., Hagler, D. J., Butler, P. D., Guilfoyle, D. N., et al. (2008). Magnocellular pathway impairment in schizophrenia: evidence from fMRI. *J Neuroscience, 28*(30), 7492-7500.

Morris, J. S., deBonis, M., & Dolan, R. J. (2002). Human amygdala responses to fearful eyes. *Neuroimage, 17*(1), 214-222.

Morris, J. S., DeGelder, B., Weiskrantz, L., & Dolan, R. J. (2001). Differential extrageniculostriate and amygdala responses to presentation of emotional faces in a cortically blind field. *Brain, 124*(Pt 6), 1241-1252.

Morris, J. S., Ohman, A., & Dolan, R. J. (1998). Conscious and unconscious emotional learning in the human amygdala. *Nature, 393*(6684), 467-470.

Morris, J. S., Ohman, A., & Dolan, R. J. (1999). A subcortical pathway to the right amygdala mediating "unseen" fear. *Proc Natl Acad Sci U S A, 96*(4), 1680-1685.

Mueser, K. T., Doonan, R., Penn, D. L., Blanchard, J. J., Bellack, A. S., Nishith, P., et al. (1996). Emotion recognition and social competence in chronic schizophrenia. *J Abnorm Psychol, 105*(2), 271-275.

Nakashima, T., Kaneko, K., Goto, Y., Abe, T., Mitsudo, T., Ogata, K., et al. (2008). Early ERP components differentially extract facial features: evidence for spatial frequency-and-contrast detectors. *Neurosci Res, 62*(4), 225-235.

Neuhaus, A. H., Karl, C., Hahn, E., Trempler, N. R., Opgen-Rhein, C., Urbanek, C., et al. (2011). Dissection of early bottom-up and top-down deficits during visual attention in schizophrenia. *Clin Neurophysiol, 122*(1), 90-98.

Norton, D., McBain, R., Holt, D. J., Ongur, D., & Chen, Y. (2009). Association of impaired facial affect recognition with basic facial and visual processing deficits in schizophrenia. *Biol Psychiatry, 65*(12), 1094-1098.

O'Donnell, B. F., Potts, G. F., Nestor, P. G., Stylianopoulos, K. C., Shenton, M. E., & McCarley, R. W. (2002). Spatial frequency discrimination in schizophrenia. *J Abnorm Psychol, 111*(4), 620-625.

Obayashi, C., Nakashima, T., Onitsuka, T., Maekawa, T., Hirano, Y., Hirano, S., et al. (2009). Decreased spatial frequency sensitivities for processing faces in male patients with chronic schizophrenia. *Clin Neurophysiol, 120*(8), 1525-1533.

Ojanpaa, H., & Nasanen, R. (2003). Utilisation of spatial frequency information in face search. *Vision Res, 43*(24), 2505-2515.

Overall, J. E., & Gorham, D. R. (1962). The brief psychiatric rating scale. *Psychological Reports, 10*, 799-812.

Penn, D. L., Corrigan, P. W., Bentall, R. P., Racenstein, J. M., & Newman, L. (1997). Social cognition in schizophrenia. *Psychol Bull, 121*, 114-132.

Peuskens, J., & Link, C. G. (1997). A comparison of quetiapine and chlorpromazine in the treatment of schizophrenia. *Acta Psychiatr Scand, 96*(4), 265-273.

Pizzagalli, D., Regard, M., & Lehmann, D. (1999). Rapid emotional face processing in the human right and left brain hemispheres: an ERP study. *Neuroreport, 10*(13), 2691-2698.

Pizzagalli, D. A., Lehmann, D., Hendrick, A. M., Regard, M., Pascual-Marqui, R. D., & Davidson, R. J. (2002). Affective judgments of faces modulate early activity (approximately 160 ms) within the fusiform gyri. *Neuroimage, 16*(3 Pt 1), 663-677.

Pourtois, G., Dan, E. S., Grandjean, D., Sander, D., & Vuilleumier, P. (2005). Enhanced extrastriate visual response to bandpass spatial frequency filtered fearful faces: time course and topographic evoked-potentials mapping. *Hum Brain Mapp, 26*(1), 65-79.

Sabatinelli, D., Lang, P. J., Bradley, M. M., Costa, V. D., & Keil, A. (2009). The timing of emotional discrimination in human amygdala and ventral visual cortex. *J Neurosci, 29*(47), 14864-14868.

Schechter, I., Butler, P. D., Silipo, G., Zemon, V., & Javitt, D. C. (2003). Magnocellular and parvocellular contributions to backward masking dysfunction in schizophrenia. *Schizophrenia Research, 64*, 91-101.

Schechter, I., Butler, P. D., Zemon, V. M., Revheim, N., Saperstein, A. M., Jalbrzikowski, M., et al. (2005). Impairments in generation of early-stage transient visual evoked potentials to magno- and parvocellular-selective stimuli in schizophrenia. *Clin Neurophysiol, 116*(9), 2204-2215.

Schiller, P. H., Malpeli, J. G., & Schein, S. J. (1979). Composition of geniculostriate input ot superior colliculus of the rhesus monkey. *J Neurophysiol, 42*(4), 1124-1133.

Schroeder, C. E., Mehta, A. D., & Givre, S. J. (1998). A spatiotemporal profile of visual system activation revealed by current source density analysis in the awake macaque. *Cereb Cortex, 8*(7), 575-592.

Schutter, D. J., de Haan, E. H., & van Honk, J. (2004). Functionally dissociated aspects in anterior and posterior electrocortical processing of facial threat. *Int J Psychophysiol, 53*(1), 29-36.

Schyns, P. G., & Oliva, A. (1999). Dr. Angry and Mr. Smile: when categorization flexibly modifies the perception of faces in rapid visual presentations. *Cognition, 69*(3), 243-265.

Sehatpour, P., Dias, E. C., Butler, P. D., Revheim, N., Guilfoyle, D. N., Foxe, J. J., et al. (2010). Impaired visual object processing across an occipital-frontal-hippocampal brain network in schizophrenia: an integrated neuroimaging study. *Arch Gen Psychiatry, 67*(8), 772-782.

Sergi, M. J., Rassovsky, Y., Nuechterlein, K. H., & Green, M. F. (2006). Social perception as a mediator of the influence of early visual processing on functional status in schizophrenia. *Am J Psychiatry, 163*(3), 448-454.

Shibata, T., Nishijo, H., Tamura, R., Miyamoto, K., Eifuku, S., Endo, S., et al. (2002). Generators of visual evoked potentials for faces and eyes in the human brain as determined by dipole localization. *Brain Topogr, 15*(1), 51-63.

Slaghuis, W. L. (1998). Contrast sensitivity for stationary and drifting spatial frequency gratings in positive- and negative-symptom schizophrenia. *J Abnorm Psychol, 107*(1), 49-62.

Slaghuis, W. L. (2004). Spatio-temporal luminance contrast sensitivity and visual backward masking in schizophrenia. *Exp Brain Res, 156*(2), 196-211.

Slaghuis, W. L., & Thompson, A. K. (2003). The effect of peripheral visual motion on focal contrast sensitivity in positive- and negative-symptom schizophrenia. *Neuropsychologia, 41*(8), 968-980.

Spencer, K. M., Nestor, P. G., Niznikiewicz, M. A., Salisbury, D. F., Shenton, M. E., & McCarley, R. W. (2003). Abnormal neural synchrony in schizophrenia. *J Neurosci, 23*(19), 7407-7411.

Spiegler, B. J., & Mishkin, M. (1981). Evidence for the sequential participation of inferior temporal cortex and amygdala in the acquisition of stimulus-reward associations. *Behav Brain Res, 3*(3), 303-317.

Streit, M., Wolwer, W., Brinkmeyer, J., Ihl, R., & Gaebel, W. (2001). EEG-correlates of facial affect recognition and categorisation of blurred faces in schizophrenic patients and healthy volunteers. *Schizophr Res, 49*(1-2), 145-155.

Streit, M., Wolwer, W., & Gaebel, W. (1997). Facial-affect recognition and visual scanning behaviour in the course of schizophrenia. *Schizophr Res, 24*(3), 311-317.

Tanaka, J. W., Curran, T., Porterfield, A. L., & Collins, D. (2006). Activation of preexisting and acquired face representations: the N250 event-related potential as an index of face familiarity. *J Cogn Neurosci, 18*(9), 1488-1497.

Turetsky, B. I., Kohler, C. G., Indersmitten, T., Bhati, M. T., Charbonnier, D., & Gur, R. C. (2007). Facial emotion recognition in schizophrenia: when and why does it go awry? *Schizophr Res, 94*(1-3), 253-263.

Vlamings, P. H., Goffaux, V., & Kemner, C. (2009). Is the early modulation of brain activity by fearful facial expressions primarily mediated by coarse low spatial frequency information? *J Vis, 9*(5), 12 11-13.

Vuilleumier, P., Armony, J. L., Driver, J., & Dolan, R. J. (2003). Distinct spatial frequency sensitivities for processing faces and emotional expressions. *Nat Neurosci, 6*(6), 624-631.

Vuilleumier, P., Richardson, M. P., Armony, J. L., Driver, J., & Dolan, R. J. (2004). Distant influences of amygdala lesion on visual cortical activation during emotional face processing. *Nat Neurosci, 7*(11), 1271-1278.

Walker, E., McGuire, M., & Bettes, B. (1984). Recognition and identification of facial stimuli by schizophrenics and patients with affective disorders. *Br J Clin Psychol, 23 (Pt 1)*, 37-44.

Whalen, P. J., Kagan, J., Cook, R. G., Davis, F. C., Kim, H., Polis, S., et al. (2004). Human amygdala responsivity to masked fearful eye whites. *Science, 306*(5704), 2061.

Winston, J. S., Vuilleumier, P., & Dolan, R. J. (2003). Effects of low-spatial frequency components of fearful faces on fusiform cortex activity. *Curr Biol, 13*(20), 1824-1829.

Woods, S. W. (2003). Chlorpromazine equivalent doses for the newer atypical antipsychotics. *J Clin Psychiatry, 64*(6), 663-667.

Wynn, J. K., Lee, J., Horan, W. P., & Green, M. F. (2008). Using event related potentials to explore stages of facial affect recognition deficits in schizophrenia. *Schizophr Bull, 34*(4), 679-687.

Yeap, S., Kelly, S. P., Sehatpour, P., Magno, E., Javitt, D. C., Garavan, H., et al. (2006). Early visual sensory deficits as endophenotypes for schizophrenia: high-density electrical mapping in clinically unaffected first-degree relatives. *Arch Gen Psychiatry, 63*(11), 1180-1188.

Yoon, J. H., D'Esposito, M., & Carter, C. S. (2006). Preserved function of the fusiform face area in schizophrenia as revealed by fMRI. *Psychiatry Res, 148*(2-3), 205-216.

9. Tables

Table 1

Demographic and Clinical Characteristics of Healthy Controls and Patients with Schizophrenia

Characteristic	**Controls (n=25)**	**Patients (n=25)**
Age	39.5 ± 12.8	40.7 ± 11
Gender (M/F)	16/9	23/2*
Chlorpromazine daily equivalent, mg		1093 ± 580.7
Antipsychotics		
Atypical		20
Typical		
Both		5
Parental socioeconomic status	41.1 ± 17.3 (n=23)	38.9 ± 14.6 (n=18)
BPRS total score		37.6 ± 6.9 (n =22)
SANS total score (including global Scores)		36.4 ± 13.1 (n =22)
Duration of illness (years)		15.1 ± 9.1 (n=25)

Note: Values are mean ± SD. Numbers of subjects per group are noted when there is missing data. Socioeconomic status was measured by the 4-factor Hollingshead Scale (Hollingshead, 1975). M, male; F, female; BPRS, Brief Psychiatric Rating Scale (Overall & Gorham, 1962); SANS, Schedule for Assessment of Negative Symptoms (Andreasen, 1984).

*p<.05

**p<.001

Table 2a

P1 and behavior	**Fear**	**Happy**	**Sad**	**Neutral**
2% Contrast				
R	.43*	.42*	.38*	.11
8% Contrast				
R	.54**	.41*	.44*	.26

Table 2a: P1's relationship with behavior. +<.05; *: <.01; **<.001

Table 2b

N170 and behavior	**Collapsed on Emotion**
2% Contrast Controls:	
R	-.004
Patients:	
R	-.24+
8%Contrast	
R	-.18*
57%Contrast Controls:	
R	-.018
Patients:	
R	-.25+

Table 2b: N170's relationship with behavior. +<.05; *: <.01; **<.001

Table 2c

P250 and behavior	**Fear**	**Happy**	**Sad**	**Neutral**
2% Contrast				
R	.46**	.28^{+}	.31^{+}	.39*

Table 2c: P250's relationship with behavior. +<.05; *: <.01; **<.001

Table 3

P1 and P250	**Collapsed on Emotion**
2% Contrast	
R	.38**
8% Contrast	
R	.53**
57% Contrast	
R	.5**

Table 3: P1’s relationship with P250. +<.05; *: <.01; **<.001; combined groups

7. Figure Legends

Figure 1: Examples of contrast-manipulated emotional face-stimuli. Emotions used were: Fear, Happy, Sad and Neutral. Left: 2% RMS Contrast. Middle: 8% RMS Contrast. Right: 57% RMS Contrast. Bottom: Target flower. Luminance was equalized across all stimuli, and was used as the background luminance.

Figure 2: Voltage topographic maps at each contrast and collapsed across emotion. A) Voltage topography for the P1 component. Voltage topography of patients at 57% RMS contrast was similar to that of controls at 2% RMS contrast. B) Voltage topography for the N170 component. Voltage topographies of controls and patients were similar. C) Voltage topography for the, Left: P250 component. Voltage topography of patients at 57% RMS contrast was similar to that of controls at 2% RMS contrast. Right: Voltage topography for the N250, which has been investigated in previous studies, failed to show as large of an effect as was seen at posterior sites.

Figure 3: Behavioral results. Red: Controls. Blue: Patients. Error bars represent 95% confidence intervals. A) Percent correct contrast response curves for each emotion separately. B) Percent correct emotion response profiles at each contrast separately.

Figure 4: Grand-averaged waveforms for controls and patients collapsed on emotion. Electrode sites for each component are indicated on the voltage topographic maps below (maps represent 57% RMS contrast). Red: Controls. Blue: Patients. A) P1 grand-averaged waveforms for all three contrasts. B) N170 grand-averaged waveforms for all three contrasts. C) P250 grand–averaged waveforms for all three contrasts.

Figure 5: Red: Controls. Blue: Patients. Error bars represent 95% confidence intervals.

A) Dorsal P1 amplitude contrast response curves in controls and patients for each emotion separately. Contrast response curves in controls reflected M-pathway characteristics. Patients exhibited a blunted slope from 2% to 8% RMS contrast and a significantly reduced plateau in response from 8% to 57% RMS contrast as compared to controls. This pattern of response suggests the P1 reflects dorsal visual stream activity that is influenced by M-pathway input and supports evidence for preferential M/dorsal stream dysfunction in patients. B) Emotion response profiles for the P1 amplitude in controls and patients for each contrast separately. At 2% RMS contrast, P1 amplitude of controls varied by emotion, while P1 amplitude of patients did not.

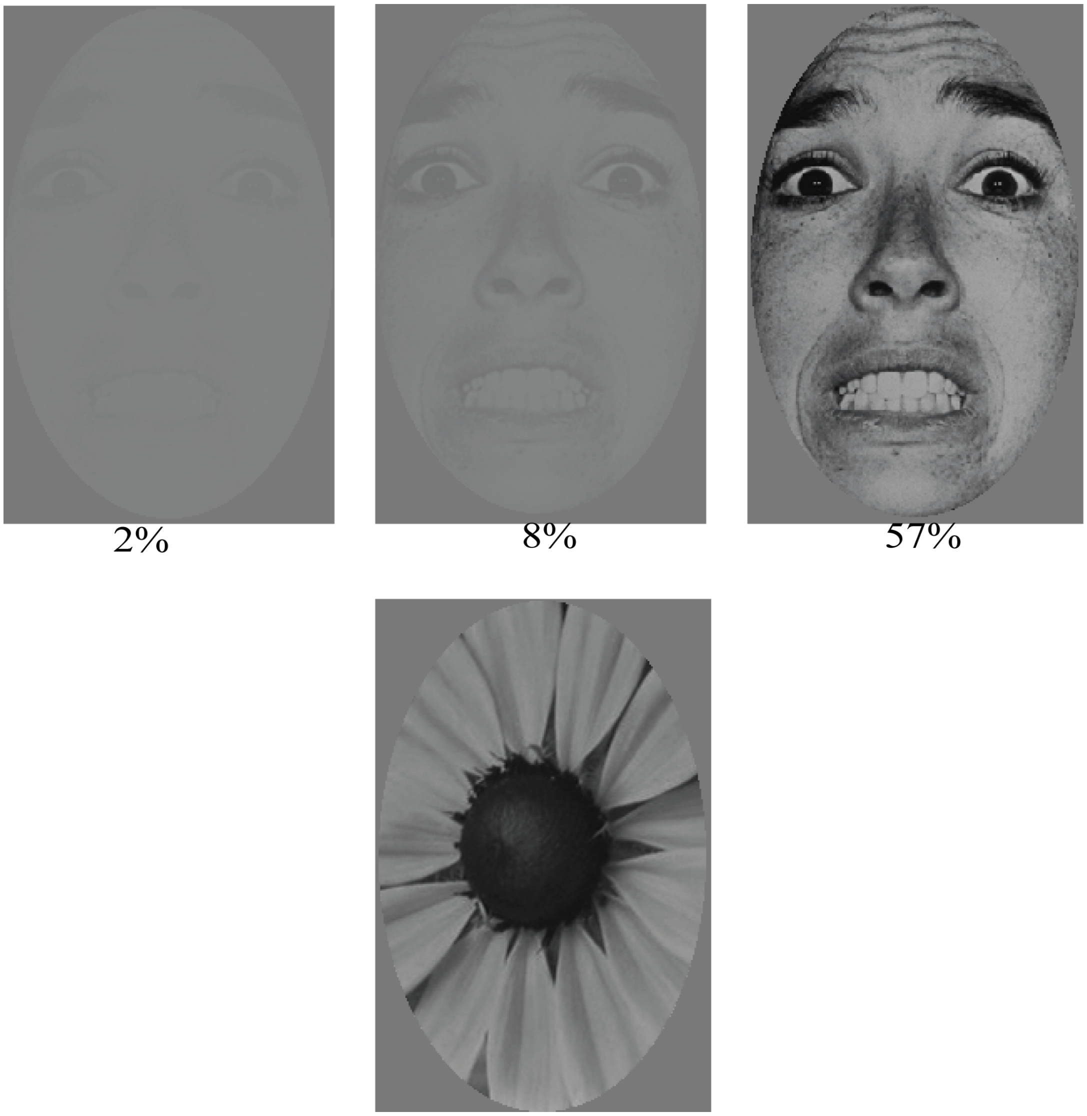
Figure 6: Red: Controls. Blue: Patients. Error bars represent 95% confidence intervals. A) Ventral N170 amplitude contrast response curves in controls and patients for each emotion separately. The N170 pattern of response suggests the component reflects ventral visual stream activity, influenced by P-pathway input and supports evidence for relatively intact P-stream function in patients. B) Emotion response profiles for the N170 amplitude in controls and patients for each contrast separately. At 2% and 57% RMS contrast, there emotion response profiles for controls and patients were significantly different from one another.

Figure 7: Red: Controls. Blue: Patients. Error bars represent 95% confidence intervals. A) Dorsal P250 amplitude contrast response curves in controls and patients for each emotion separately. Note: The P250 occurs later within the visual processing stream and reflects a confluence of dorsal and ventral inputs, making its contrast response curves less valid to interpret as reflecting separate visual pathway function. B) Emotion response profiles for the P250 amplitude in controls and patients for each contrast separately. Both

controls and patients exhibited similar emotion response profiles, but amplitudes in patients were drastically reduced.

8. Figures

<u>Figure 1 :</u>
Stimulus examples



2% 8% 57%

Figure 2 :

Voltage topography maps

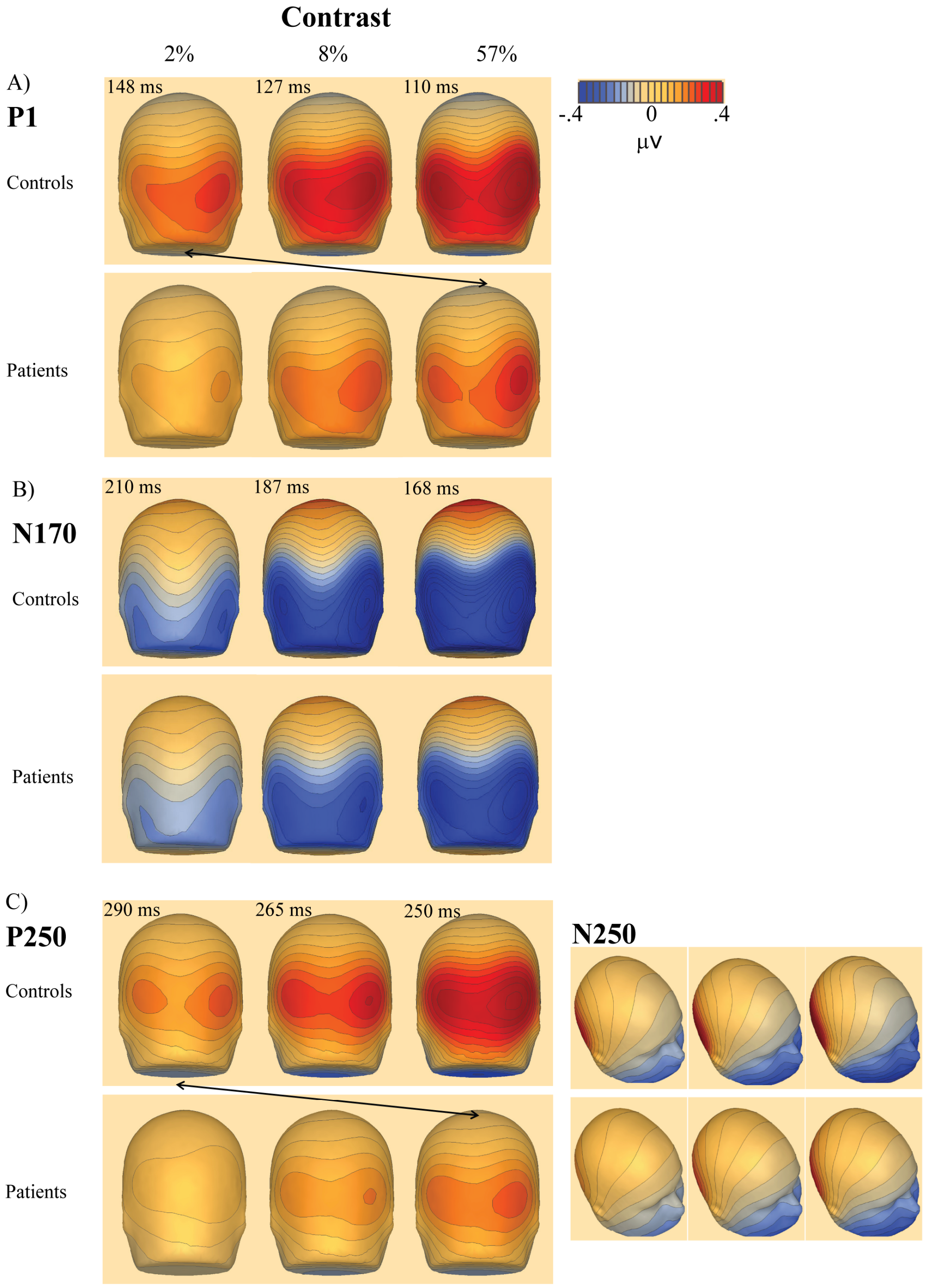
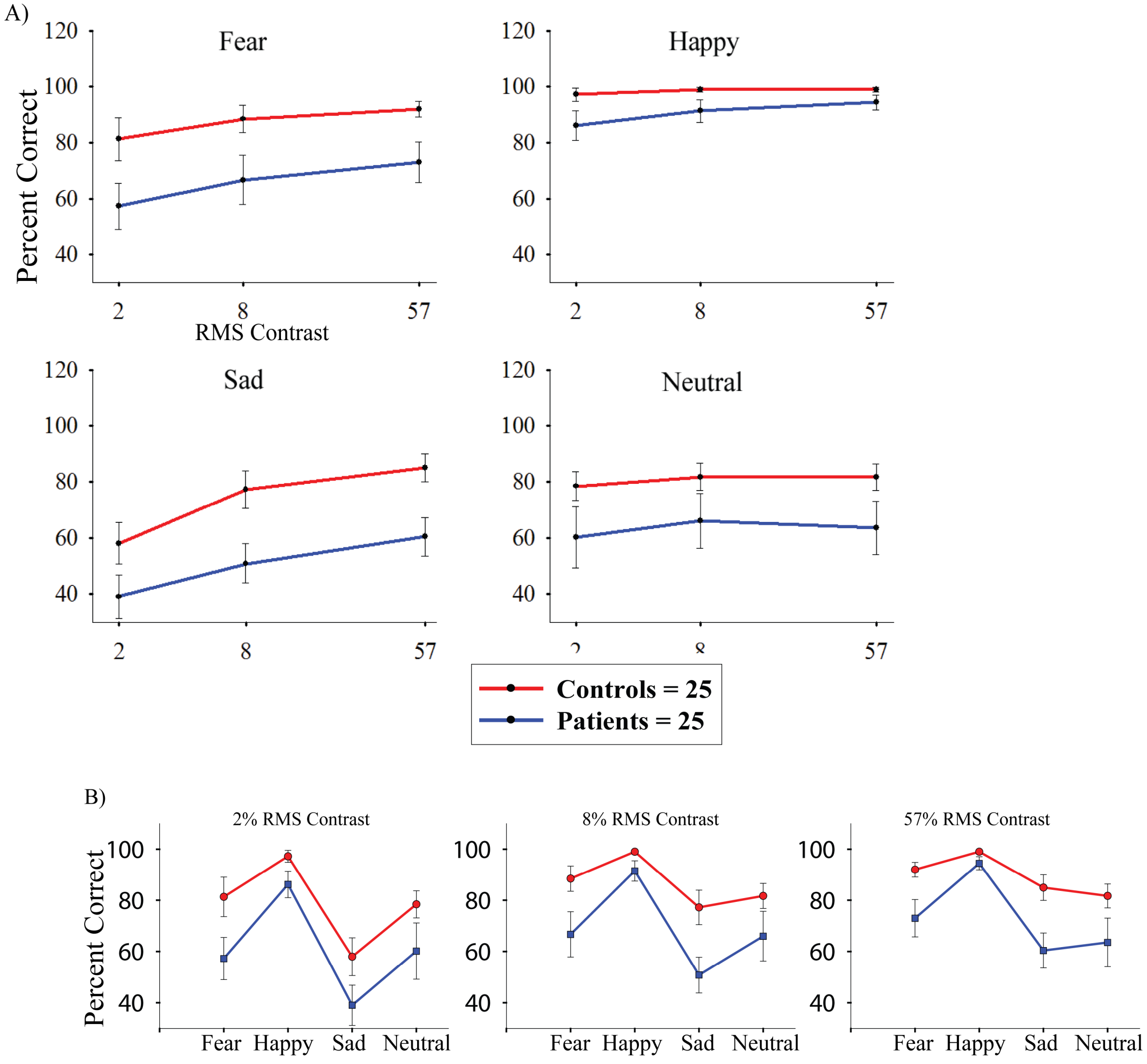


Figure 3:
Behavioral contrast response curves and emotion response profiles



<u>Figure 4:</u>

Grand-averaged waveforms

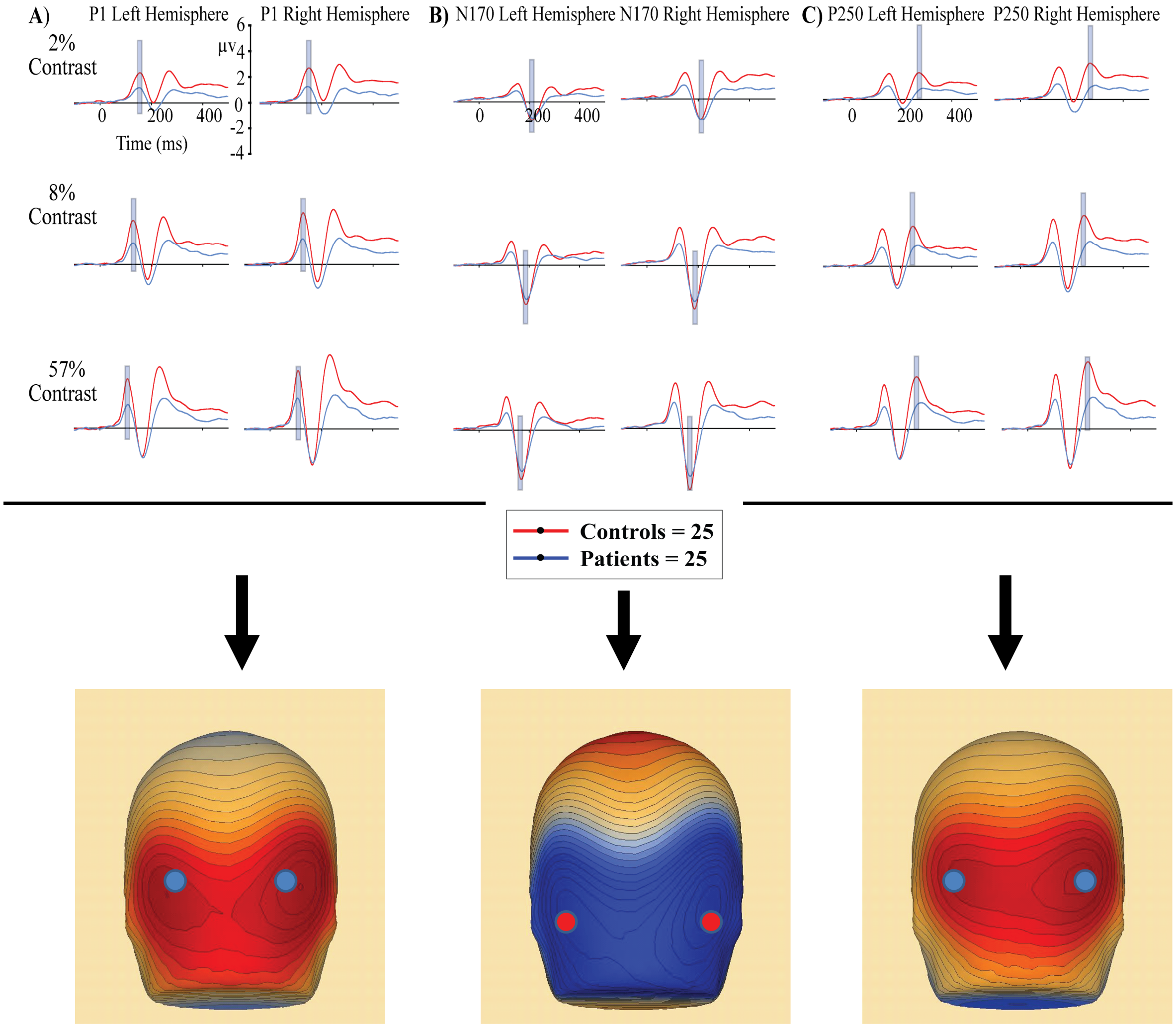


Figure 5:

P1 contrast response curves and emotion response profiles

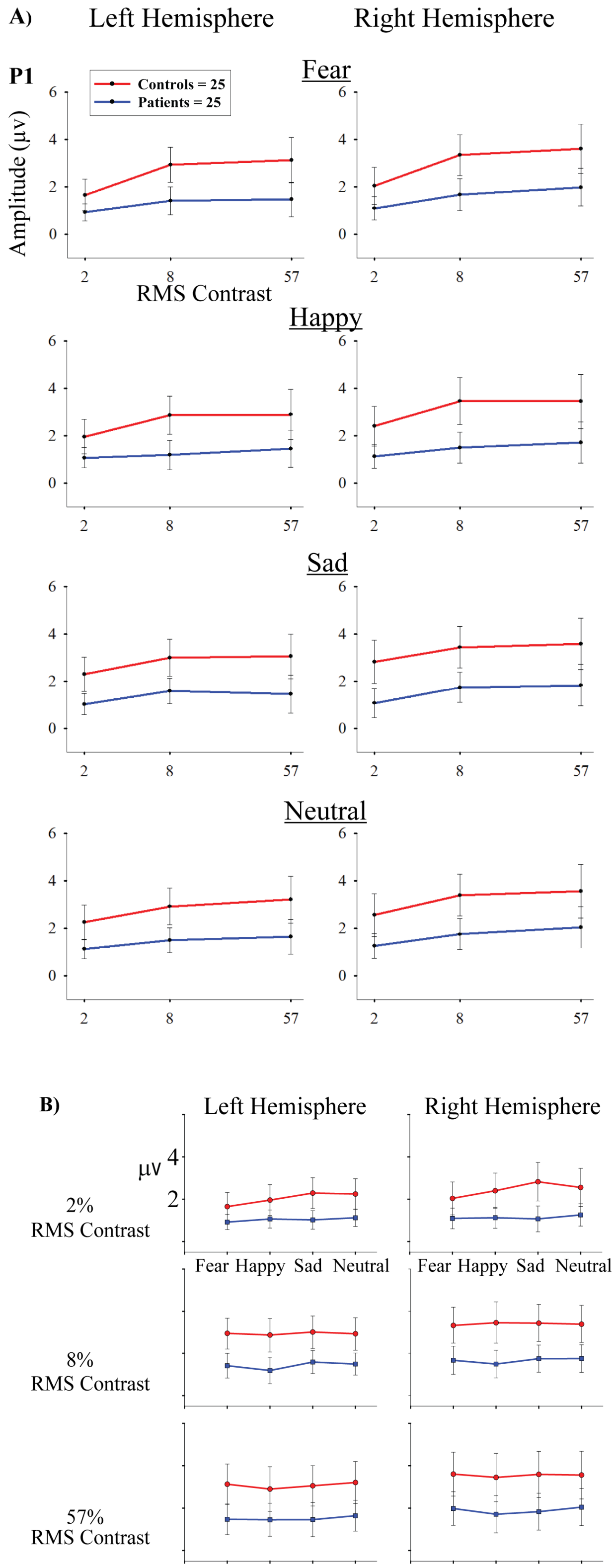


Figure 6:
N170 contrast response curves and emotion response profiles

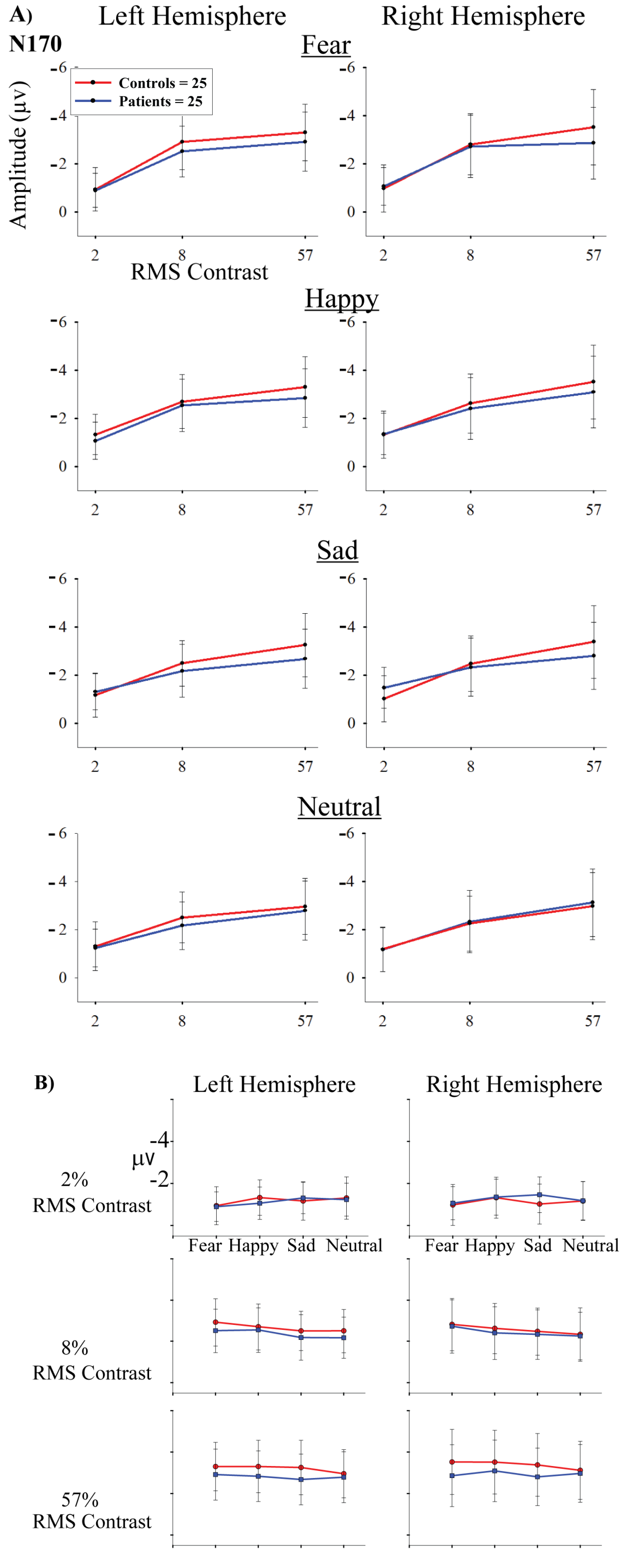
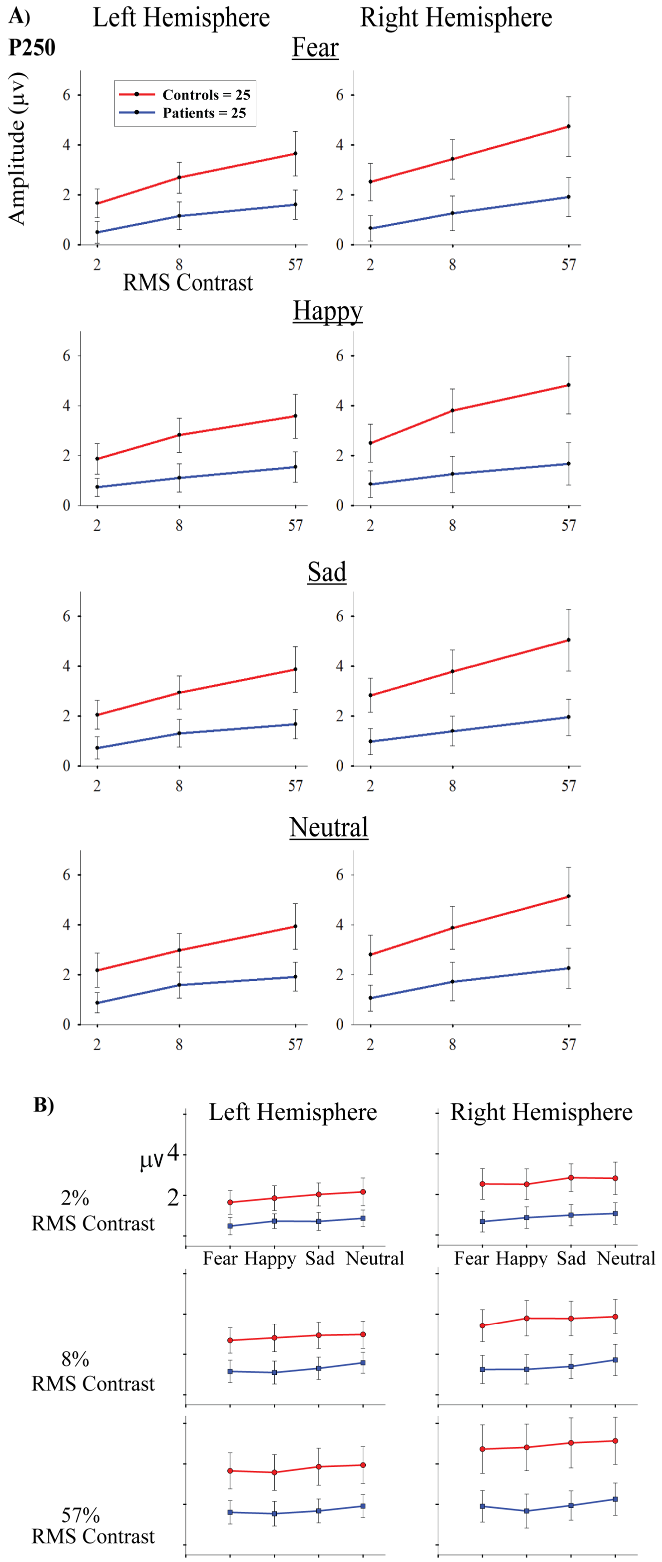


Figure 7:
P250 contrast response curves and emotion response profiles



CHAPTER 4

Lower-frequency band activity during visual perception in schizophrenia

1. Abstract

The present study examined the spatial-temporal oscillatory dynamics in schizophrenia patients, during processing of complex visual stimuli. We evaluated activity in the FFT-spectrum and assessed differences in the putative underlying generators of the delta, theta and alpha oscillatory frequencies. Further, we examined activity in the pre and post-stimulus intervals, and the ratio between them (so-called event-related synchronization and/or desynchronization). The FFT-data revealed controls had significantly greater alpha band activation in posterior electrodes as compared to patients. The FFT-data also revealed a trend towards between-group significance in the theta-band over anterior electrodes, driven by patients exhibiting greater activation compared to controls. Moreover, the topographical analysis showed significantly different distributions in both bands, suggesting that patients and controls have distinct sets of generators underlying these oscillatory rhythms. The analyses conducted on the instantaneous delta-band activity revealed that patients have significantly greater power during the pre and post-stimulus intervals, but the modulating-ratio between them (i.e. the ERS) was similar across groups. Finally, the data revealed that patients had a substantially reduced alpha-ERD compared to controls, thus highlighting their impairment in cortical gating mechanisms during processing of visual sensory inputs.

2. Introduction

Recordings in sub-cortical and cortical areas have shown that neural responses can be manifested in periodic cycles (oscillations) depending on the behavioral state of the animal or subject (see Buzsaki, 2006 for a review). The leading tenet proposes that ongoing cyclical signals are fundamental for controlling and coordinating activity within a local neural circuit (Bishop, 1932; Lakatos et al., 2008; Lakatos et al., 2005; Mulholland, Goodman, & Boudrot, 1983) and for synchronizing activity across large-scale neural networks (Canolty et al., 2006; Jones & Wilson, 2005). In particular, studies have shown that higher-frequency rhythms (e.g. > 10 Hz) play a significant role in enhancing stimulus signals within the locus of attention (Fries et al., 2001; Taylor, Mandon, Freiwald, & Kreiter, 2005; Womelsdorf & Fries, 2006) and suppressing potentially-distracting sensory inputs (Kelly, Foxe, Newman, & Edelman, 2010; Thut et al., 2006; Worden, Foxe, Wang, & Simpson, 2000). Conversely, slower rhythms (e.g. 1-7 Hz) are believed to be important in coupling neural activity across different sensory areas (Canolty et al., 2006; Jones & Wilson, 2005) as well as controlling the excitability states of neural ensembles in local circuits (Lakatos, Chen, O'Connell, Mills, & Schroeder, 2007; Lakatos et al., 2005). Further, a number of studies have shown that activity within different frequency bands is not completely divorced from each other, but rather inherently coupled, setting the cortex in a stable and effective state for sensory processing (Canolty & Knight, 2010).

Traditionally, to study visual sensory/perceptual impairments in patients with schizophrenia, researchers have relied on several neurophysiological methods such as event-related potentials (ERP) and hemodynamic responses, which provide exquisite temporal and spatial resolution of purported visual sensory/perceptual mechanisms, respectively. The findings obtained using these techniques have contributed greatly to our understanding of the underlying pathological visual neural mechanisms that give rise to a number of visual perceptual impairments now considered to be a core pathology in schizophrenia (see Javitt, 2009 for a review). For instance, steady-state visual evoked potential (ssVEP) and ERP studies have demonstrated that patients with schizophrenia exhibit dysfunction in sub- and cortical processing of visual sensory information that heavily rely on cell bodies within the magnocellular pathway (Butler et al., 2007; Butler, Zemon et al., 2005; Foxe et al., 2001; Kim et al., 2005). In support of this, functional magnetic resonance imaging (fMRI) studies have shown that schizophrenia patients have significantly less activation to magnocellular-biased sensory stimuli (Martinez et al., 2008), while diffusion tensor imaging (DTI) findings indicate that patients have reduced white matter integrity in optic radiations that was found to be associated with their M-biased visual perceptual deficits (Butler et al., 2005).

However, while much has been understood with the use of these techniques, the large-scale sensory dysfunction in schizophrenia patients has prompted researchers to employ other analytical tools to address these local and cross-cortical impairments through a different platform (i.e. time-frequency analysis) (see for e.g. (Friston, 1999; Phillips & Silverstein, 2003; Uhlhaas & Singer, 2010)). Activity in the frequency and time-frequency domains has begun to be investigated in schizophrenia to ascertain whether visual sensory/perceptual brain regions exhibit specific forms of neural oscillatory dysfunction. Until recently, oscillatory analyses of EEG in patients have mainly focused on the differences in frequency spectra elicited during resting-state conditions (see Boutros et al., 2008; Boutros & Arfken, 2007). These studies have revealed that patients specifically exhibit increased activity in delta (1-3 Hz), theta (4-7 Hz) and beta-band (15-29 Hz) power, and substantial reductions in activity within the alpha-band (8-14 Hz) (Knott, Labelle, Jones, & Mahoney, 2001; Omori et al., 1995; Sponheim et al., 1994).

More recently, researchers have begun to evaluate event and task-related oscillatory activity in schizophrenia patients to further understand their underlying impaired physiology associated with visual perception deficits. Most research in this area has focused on the gamma frequency band (> 30 Hz) which is thought to play a major role in visual perception and visual feature binding, coordinating activity in both striate and extrastriate cortices (Gray et al., 1989; Singer & Gray, 1995). Along these lines, coordinated rhythmic activity within this band has been shown to help with object recognition processes (Yuval-Greenberg & Deouell, 2007) including the processing of a coherent percept ('gestalt') (Keil et al., 1999). Further, patients with schizophrenia have been found to exhibit an abnormal pattern in this power spectrum, either in the form of a supra (Basar-Eroglu et al., 2007; Flynn et al., 2008; Norra et al., 2004) or sub (for e.g. Cho, Konecky, & Carter, 2006; Gallinat et al., 2004; Herrmann & Demiralp, 2005; Schnitzler & Gross, 2005; Spencer et al., 2003; Spencer et al., 2004) power modulation. These findings have been consistently replicated in a number of different visual perceptual paradigms (e.g. visual backward masking, visual oddball, illusory contour, and emotional-face perception) in both un-medicated and medicated patients, suggesting that atypical gamma-band oscillations might potentially symbolize a significant "biomarker" tool for characterizing individuals that might be affected with this disorder (Spencer, 2008; Spencer et al., 2003; Spencer et al., 2004; Spencer et al., 2008; Symond et al., 2005; Uhlhaas et al., 2006; Williams, Whitford, Nagy et al., 2009; Wynn et al., 2005).

Slower oscillatory rhythms (< 30 Hz) have received much less attention in the schizophrenia event-related visual perception literature. However, activity in these lower frequency bands is highly active and selective during processing of a wide range of sensory tasks, and thus is important to investigate within the patient population. For instance, delta-band rhythms have been implicated in salience detection of visual stimuli (see Knyazev, 2007; Steriade, 1997), and more recently, they have been shown to be fundamental for regulating high-and-low excitability states in local sensory areas during active (Lakatos et al., 2008) and sleep states (Battaglia et al., 2004). Further, only two previously conducted studies investigated delta-band activity during active visual tasks in patients. Patients in both studies exhibited reduced evoked delta-power suggesting patients had decreased sensitivity to stimulus saliency (Bates et al., 2009; Ergen et al., 2008). Conversely, findings were mixed in regard to induced delta-power. Patients in the visual oddball study demonstrated unaffected induced-power, while patients in the go/no-go task demonstrated lowered induced-activity.

Moreover, several studies have shown that theta rhythmical activity is critical for facilitating the encoding of new memories (Buzsaki, 2005; Rutishauser, Ross, Mamelak, & Schuman, 2010; Sederberg, Kahana, Howard, Donner, & Madsen, 2003), and for retrieving information from the so-called working-memory space (Axmacher et al., 2010; Kahana, Seelig, & Madsen, 2001; Lisman, 2010; Raghavachari et al., 2001). In addition, a recent study showed that attention modulates theta-band coherence in primary auditory and visual cortices, suggesting that theta oscillations may play a universal role in sensory perception regardless of sensory modality (Lakatos et al., 2009).

Finally, a number of studies show that oscillatory activity in the alpha range is linked to general states of mental alertness and/or arousal (Klimesch et al., 1998). It is also heavily implicated in processes which are involved in the suppression and enhancement (‘gating’) of sensory stimuli within striate and extrastriate cortices (Bastiaansen, Bocker, Brunia, de Munck, & Spekreijse, 2001; Foxe et al., 1998; Gomez-Ramirez et al., 2007; Kelly et al., 2008; Kelly, Lalor, Finucane, McDarby, & Reilly, 2005; Kelly et al., 2006; Sauseng et al., 2006; Thut et al., 2006; Worden et al., 2000). Further, it has repeatedly been shown that upon viewing a visual stimulus, healthy controls demonstrate alpha desynchronization (a reduction in alpha activity as compared to baseline activity) starting ~200 ms post-stimulus onset (for e.g. Pfurtscheller, Neuper, & Mohl, 1994). Researchers have recently proposed that this activity is a type of sensory gating mechanism, and reflects the active release of inhibition of the sensory area in order to process incoming information. Importantly, studies have demonstrated that greater relative decrease in alpha-power leads to lower reaction time and/or higher sensitivity measures (Kelly, Gomez-Ramirez, & Foxe, 2009; Thut et al., 2006). In schizophrenia, event-related alpha activity has mostly been studied within the auditory realm, with patients exhibiting reduced relative decreases in alpha-power in response to auditory stimuli, implying possible sensory gating issues underlying perceptual impairment in the patient population (Higashima et al., 2007; Hong, Summerfelt et al., 2008; Koh et al., 2010).

In this study we aim to characterize between-group differences in lower-frequency oscillatory activity and its topographical distribution in response to non-target visual stimuli during a passive visual task. First, we will inspect activity in the FFT-spectrum and assess differences in the putative underlying generators in each of the oscillatory bands of interest (i.e. delta, theta and alpha). Secondly, we examine the 'tonic' and moment-to-moment 'phasic' (as described in Gomez-Ramirez, Kelly, Montesi, & Foxe, 2009) power trajectories of these oscillatory rhythms in relation to stimulus processing. Briefly, the term 'tonic' is taken to describe the baseline level of activity that is not immediately related to particular events (i.e. pre-stimulus activity). 'Phasic' oscillations refers to changes in activity over much shorter timeframes (e.g. on the order of 100–1,000 ms) that occur in response to specific stimuli or cognitive processes. Particular focus is given to the relationship between pre and post-stimulus processing, so-called desynchronization and synchronization effects in the alpha-band, as they have been thought to reflect neural correlates of sensory activation and deactivation, respectively (Neuper, Wortz, & Pfurtscheller, 2006; Pfurtscheller & Neuper, 2006 for a review).

3. Methods

Participants

Participants were 24 patients (22 male) meeting Diagnostic and Statistical Manual of Mental Disorder (Fourth Edition) (DSM-IV) criteria for schizophrenia (n= 20) or schizoaffective disorder (n=4) and 23 healthy volunteers (16 male). Patients were recruited from inpatient (n=13) and outpatient (n=11) facilities associated with the Nathan Kline Institute for Psychiatric Research. Diagnoses were obtained using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1997) and all available clinical information. Controls were recruited through the Volunteer Recruitment Pool at the Nathan Kline Institute. Healthy volunteers with a history of SCID-defined Axis I psychiatric disorder were excluded. Patients and controls were excluded if they had any neurological or ophthalmologic disorders that might affect performance or met criteria for alcohol or substance dependence within the last 6 months or abuse within the last month. All participants provided informed consent according to the Declaration of Helsinki. This study was approved by the Nathan Kline Institute for Psychiatric Research/Rockland Psychiatric Center and Rockland County Department of Mental Health, and by City College of the City University of New York Institutional Review Boards.

Clinical and demographic information are included in Table 1. The patient and control groups did not differ significantly in age ($t_{45} = 1.1$, $p = 0.28$), or parental socioeconomic status ($t_{37} = -0.5$, $p = 0.6$). All patients were receiving antipsychotic medication at the time of testing. Chlorpromazine equivalents were calculated using conversion factors described previously (Hyman SE, 1995; Jibson & Tandon, 1998; Peuskens & Link, 1997). All participants had 20/32 or better corrected visual acuity on the Logarithmic Visual Acuity Chart (Precision Vision, LaSalle, IL).

Stimuli

Visual stimuli consisted of face-pictures from the Ekman and Friesen stimulus database (Ekman & Friesen, 1976) and a picture of a flower, which served as the target stimulus. The face stimuli were different facial gestures expressing fearful, happy, sad, or neutral emotions from 11 different individuals. An oval mask was placed around the facial image in order to exclude extraneous information, such as hair. Only the gray levels within the oval aperture were considered in computing contrast. Root- mean-square (RMS) contrast is frequently reported for complex images such as faces (Ojanpaa & Nasanen, 2003) and it was set at 2%, 8% and 57%. Stimuli were presented on the central portion of a Phillips CRT monitor located 114 cm from the participants. Major and minor axes of the images subtended 5 x 7 degrees of visual angle. Mean luminance was held constant for each contrast condition, and for the background screen. The flower stimulus was enclosed in the same sized oval and had the same overall mean luminance as the facial images.

Procedure

All face stimuli were randomly intermixed and presented 90% of the time. On the remaining 10% of trials, the flower picture was presented and participants were required to press a button as quickly as possible. No overt response was required for the facial images. Stimuli were presented for 500 milliseconds with an inter-stimulus-interval (ISI) that was uniformly jittered from 900 ms to 1100 ms. A total of 120 trials were presented in a block. Blocks were ~3 minutes long and all participants completed 30 blocks. The primary interest of this study was to examine the neural oscillatory responses of patients in response to a salient visual stimulus. To this end, we only analyzed activity associated with the high-contrast stimuli (collapsed across emotional condition). We reasoned that this approach would maximize the signal to noise ratio in the EEG data of each participant, and thus increase the likelihood of observing a significant difference between groups.

Data acquisition and processing

High-density continuous EEG was acquired from 64 surface electrode sites arranged geodesically, using the BioSemi Active II system (BioSemi, Amsterdam, The Netherlands). Data were digitized online at 512 Hz, and recorded relative to a common-reference during acquisition (see Leavitt, Molholm, Ritter, Shpaner, & Foxe, 2007 for a detailed description of the Biosemi referencing system).

Analysis of the data was made by in-house analysis scripts in Matlab (Natick, Massachusetts). EEG data associated to the facial stimuli were analyzed only. Data were bandpass filtered (.05-110 Hz) using a standard Butterworth filter, and downsampled to 256 Hz. EEG epochs were derived from -400 to 800 ms relative to the onset of the facial stimulus. A baseline measure defined as -100 to 0 ms was applied to each individual epoch before the wavelet or FFT transformations were made. Noisy trials were spline-interpolated if the average (across all time points) was 2 standard deviations greater than the average of the 3 most-neighboring electrodes. Trials with blinks and large eye-movements, defined as continuous deviations of at least ± 10 μV for more than twenty-five milliseconds on both eye channels relative to a ten millisecond baseline period were rejected offline. An artifact rejection criterion of ±125 microvolts was used at all other electrode sites to exclude periods of high EMG and other noise-transients.

Data analysis in the frequency domain

To examine delta, theta and alpha dominant oscillatory frequency components, we conducted a fast fourier transform (FFT) on each individual raw epoch. Given the time-window and sampling rate, the FFT spectrum ranged from 0 – 128 Hz in steps of .83 Hz (see Figure 1). This procedure provides an index of ‘induced’ activity (i.e. stimulus-locked and nonstimulus-locked), averaged across time, for each frequency component.

Instantaneous amplitude was characterized on a single trial level using a Morlet wavelet decomposition method adapted from the fieldtrip MATLAB toolbox (see http://www.ru.nl/fcdonders/fieldtrip/). Similar to the FFT, this procedure also provides a measure of 'induced' activity but unfolded in time (see Lakatos et al., 2007). For each accepted epoch, the wavelet decomposition was computed from 2 to 100 Hz, in steps of 2 Hz.

Statistical Analysis

FFT-data: We assessed between-group differences in amplitude in the peaks of delta (~2 Hz), theta (~7 Hz) and alpha (10Hz) activity. These peaks were chosen based on the maximum amplitude value displayed in the group average FFT-spectra. Peaks were extracted from different electrodes, based on the scalp-voltage distribution for each frequency. A mixed-model analysis of variance (ANOVA) was conducted for each frequency with Group (patient, control) as the between-subjects factor, and hemisphere (right, left) as the within-subjects factor. For analysis in the delta-band and theta bands, electrodes C5 (left hemisphere) and C6 (right hemisphere) were used. For analysis in the alpha-band, the mean of electrodes O1 and PO7 (left hemisphere), and O2 and PO8 (right hemisphere) were used. Post-hoc planned comparison t-tests were conducted when necessary.

Wavelet-data: To evaluate between-group differences in the instantaneous activity, we analyzed activity from the wavelet-transformed dataset. We tested for between-group differences in the pre-stimulus (i.e. tonic activity) and post-stimulus phase (i.e. phasic-activity) of the visual stimulus. In addition, we tested for between-group differences in the ratio between these two time-periods, the so-called event-related synchronization (ERS) or event-related desynchronization (ERD) effect. The ERS and ERD were computed by subtracting the post-stimulus activity from the pre-stimulus period, and dividing this number by the pre-stimulus activity. To illustrate these values in percent-terms (%), the number obtained from the division was multiplied by 100. With this calculation, ERSs are expressed as negative values, while ERDs are expressed as positive values. Pre-stimulus baseline activity was defined from -300 to -100 ms. The post-stimulus window was computed by averaging activity that encompassed two cycles of each frequency-band tested[1]. The amplitude values for each frequency band were extracted from the same electrodes as in the FFT-analysis. For the delta band (2-3 Hz, average 2.5 Hz), the post-stimulus interval was from 0-800 ms, for the theta-band (4- 7 Hz, average 5.5 Hz) it was from 0-500 ms, and for the alpha-band (8 – 14 Hz, 11 Hz) it was from 200 to 400 ms. A separate mixed-model ANOVA was conducted for each time-period (i.e. pre and post-stimulus) and the ratio between them (i.e. ERS/ERD). The ANOVA had a between-subjects factor of Group (patient, control) and a within-subjects factor of hemisphere (left, right). Post-hoc planned comparison t-tests were conducted when necessary.

Topographical Analysis

Scalp topographic maps were derived to illustrate the distribution of the oscillatory signals on the whole-head. These topographic maps represent interpolated voltage distributions derived from the 64 channel EEG data, and are displayed on the 3-D reconstruction of a rendered scalp surface. To assess differences in the FFT topographical distributions, we performed topographical analysis of variance (TANOVA) on each

---

[1] We could not perform this procedure on the pre-stimulus/baseline activity due to the small window of the pre-stimulus epoch (-400- 0 ms).

frequency component for each group. To achieve this, the data were first transformed into the current domain (source current density), after which the global dissimilarity (GD) measure on each FFT-frequency component across all electrodes was computed. The GD is an index of configuration differences between two scalp distributions. To measure effects independent of amplitude modulations, the data were normalized with respect to the global field power in each group (see Strik, Fallgatter, Brandeis, & Pascual-Marqui, 1998 for a description of the method). To assess statistical significance, we computed a two-tailed independent-sample t-test across groups (controls vs. patient) for each frequency component below 15 Hz. The combination of the scalp distributions and the TANOVA allows us to investigate changes in the electrical field, which are indicative of changes in the underlying generator configuration.

4. Results

Effects in the frequency domain

Fourier transforms were computed on the single-trial level to evaluate dominant oscillatory-components in the induced activity in both groups. The left-side panels of Figure 1 illustrate the FFT activity in frontal (Figure 1a) and posterior (Figure 1b) electrodes for controls and patients, while the right-side panels depict the FFT-difference waveforms between groups. The data revealed multiple peaks in the FFT-spectrum in both frontal and posterior sites. Specifically, over frontal cortices, we observed a sharp peak in the theta-band activity (7.5 Hz) of patients, but not of controls. Further, the FFT profile of controls revealed a somewhat smeared peak activation over the lower alpha-range (~ 8 – 11 Hz), which was virtually absent in patients. Finally, the FFT-spectra in the frontal electrodes show that patients have enhanced activity in the lower-frequencies

(< 8 Hz), whereas they demonstrate reduced activations in the higher bands (> 8 Hz, see right-side panel Figure 1a).

The FFT profile in the posterior electrodes revealed a robust alpha-peak component (10 Hz) in the healthy controls but not in the patients. However, the data showed that patients had a peak activation in the theta-band (7.5 Hz), while controls did not. Similar to the frontal activations, the FFT profiles in the posterior electrodes show that patients have enhanced activity in lower frequencies (4 – 7 Hz), but reduced amplitude in the alpha and beta ranges (8 – ~25 Hz). Interestingly, this pattern was reversed in the upper bands (> 25 Hz) with patients again, showing greater activity compared to controls. In what follows, we describe the findings derived from the statistical testing of each FFT frequency component of interest (delta, theta, alpha).

We computed separate mixed-model ANOVAs with the between-subjects factor of Group (patient vs. controls) and within-subjects factor of hemisphere (left vs. right) for the delta (~ 2 Hz), theta (~7 Hz) and alpha (10 Hz) activity. The ANOVA computed on the delta-band activity revealed a trend towards significance, where patients displayed greater activity compared to controls ($F_{1,45} = 3.3$, $p = .076$; see Figure 2a). Similarly, the ANOVA computed on the theta-band activity revealed a trend towards significance for patients having greater overall amplitude versus controls ($F_{1,45} = 3.97$, $p = .052$; see Figure 2B). The ANOVA on the theta-band also revealed a main effect of hemisphere ($F_{1,45} = 4.98$, $p = .031$), whereby activity in the right hemisphere was greater compared to the left hemisphere. Finally, the ANOVA computed on the alpha-band activity revealed a significant main effect of Group ($F_{1,45} = 5.7$, $p = .02$) as well as a Group x Hemisphere interaction ($F_{1,45} = 8.1$, $p = .007$). Follow-up independent sample t-tests showed that controls had a significantly larger overall amplitude in the right hemisphere versus patients ($t_{45} = -2.7$, $p = .011$) (Figure 1B-right, 2C), while a trend towards significance was found within the left hemisphere ($t_{45} = -2$, $p = .052$). No other significant effects were found.

Topographic distribution of frequency activity

We computed separate topographical analysis of variance (TANOVA) to test for between-group differences in the underlying generators of each frequency component. Figure 3 shows the scalp topography maps, and their difference, in the delta (Figure 3a), theta (Figure 3b) and alpha range (Figure 3c). Figure 3d displays the TANOVA results for all frequency components up to 14 Hz. The data revealed a significant effect in the theta ($t_{45} = -2.65$, $p < 0.05$) and alpha components ($t_{45} = 2.09$, $p < 0.05$). Importantly, the topographical distributions of the groups, and their difference (see Figure 3b & 3c), indicate that these TANOVA results represent a true difference in neural generators across groups. Briefly, it can be observed from the scalp topographies in the theta-band (Figure 3b) that both groups displayed similar bilateral peaks in the frontal/midline structures of the scalp. Most importantly however, the difference between the patients and controls scalp distributions showed a robust and narrowed-peak activation in central-posterior scalp areas[2]. On the other hand, the topographic maps in the alpha-band revealed a slightly lateralized posterior distribution for healthy controls, which was virtually nonexistent in patients (see Figure 3c). Accordingly, the difference-topography revealed a similar distribution to that of the healthy controls, suggesting that the alpha-

---

[2] This peak was not apparent in the individual group's topography due to the increased amplitude of the bilateral peaks in the mid-frontal areas

band TANOVA difference is due to the existence of the lateralized distribution in the controls and not in patients.

Effects in the time-frequency domain

Delta-Band Activity: Delta-band waveform trajectories are plotted in Figure 4A for controls and patients from -400 ms to 800 ms. As demonstrated by the ANOVAs, patients showed significantly greater activity during the pre-stimulus ($F_{1,45} = 12.7$, $p = .001$), and post-stimulus ($F_{1,45} = 12.9$, $p = .001$) intervals (see Figure 5a left and right panels). However, the ANOVA computed on the ratio between the pre and post-stimulus intervals, revealed no between-group ($F_{1,45} = 0.22$, $p = .64$) nor hemispheric difference ($F_{1,45} = 0.68$, $p = .4$) in the delta-band ERS. As can be seen in Figure 6a, there was a ~30% increase in delta-band induced activity post-stimulus onset, relative to the baseline of each respective group.

Theta-Band Activity: Theta-band waveform trajectories are plotted in figure 4B for controls and patients from -400- 800 ms. The ANOVAs on the pre and post-stimulus intervals revealed a trends towards significance in both periods ($F_{1,45} = 3.3$, $p = .076$; $F_{1,45} = 3.26$, $p = .078$, respectively; see Figure 5b left and right panels). These trends were driven by patients having greater induced theta-band activity versus controls in both periods. Moreover, the ANOVA computed on the ratio between the pre and post-stimulus intervals, revealed no between-group ($F_{1,45} = 0.2$, $p = .66$) nor hemispheric differences ($F_{1,45} = 0.15$, $p = .70$) in theta-band activity. Figure 6b shows very little change in post-stimulus induced theta activity relative to baseline in both groups.

Alpha-Band Activity: Alpha-band waveform trajectories are plotted in figure 4C for controls and patients from -400- 800ms. The ANOVA conducted on the pre-stimulus interval revealed no main effect of Group ($F_{1,45} = 2.4$, $p = .13$), while there was a trend towards significance in Hemisphere ($F_{1,45} = 3.7$, $p = .06$; see Figure 5c left panel). In addition, the ANOVA revealed Group x Hemisphere interaction ($F_{1,45} = 5.9$, $p = .02$). Follow-up independent sample t-tests showed that this interaction was driven by a larger alpha-band value in the right versus left hemisphere of controls ($t_{22} = 2.5$, $p = .022$; see Figure 5c left panel). The ANOVA computed on the post-stimulus interval did not reveal a main effect of Group ($F_{1,45} = .12$, $p = .73$) nor Hemisphere ($F_{1,45} = .04$, $p = .85$). However, the ANOVA revealed an interaction effect of Group x Hemisphere ($F_{1,45} = 9$, $p = .004$). Follow-up paired-sample t-tests revealed that this interaction effect was driven by patients having greater between-hemisphere difference in alpha amplitude compared to controls ($t_{23} = -2.7$, $p = .013$; see Figure 5c right panel). Lastly, the ANOVA computed on the ERD revealed a main effect of Group ($F_{1,45} = 7.1$, $p = .01$), whereby controls revealed a greater ERD compared to patients (see Figure 6c).

Correlations

All patients were taking antipsychotic medication at the time of testing, but medication was not correlated with any dependent measure ($p>.09$). In addition, we found that alpha desynchronization significantly correlated with increased GAF (global assessment of functioning) scores ($r = .52$, $p = .02$).

5. Discussion

The present study examined the spatial-temporal oscillatory dynamics in schizophrenia patients, compared to healthy individuals, during processing of complex visual stimuli. We evaluated activity in the FFT-spectrum and assessed differences in the putative underlying generators of the delta, theta and alpha oscillatory frequencies.

Further, we examined activity in the pre and post-stimulus intervals, and the ratio between them (so-called ERS and/or ERD), and investigated whether there were significant relationships between these measures and clinical ratings in patients. The FFT-data revealed distinct activations in the alpha band in posterior electrodes between groups, whereby controls had greater power compared to patients. The data also revealed a trend towards significance in the theta-band over anterior electrodes, driven by patients exhibiting greater activation compared to controls. Moreover, the topographical analysis showed significantly different distributions in both bands, suggesting that patients and controls may have a distinct set of generators giving rise to these neural oscillatory rhythms. The analyses conducted on the instantaneous delta-band activity revealed that patients have significantly greater power during the pre and post-stimulus intervals, but the modulating-ratio between them (i.e. the ERS) was similar across groups. Finally, the data revealed that patients had a substantially reduced alpha-ERD compared to controls, thus highlighting their impairment in cortical gating mechanisms during processing of visual sensory inputs.

Delta-band differences between populations

The findings revealed that patients had significantly greater delta-band activity during the pre and post-stimulus intervals compared to healthy controls. Further, while we observed that both groups displayed an ERS effect (~30%), the difference in this measure was not found to be significant between them. Indeed, higher delta-band power in patients has been previously observed during resting states and cognitive-type tasks that do not involve active processing of sensory stimuli (e.g. Fehr et al., 2003; Knott et al., 2001; Sponheim et al., 1994). Our data replicate and further extend these findings by revealing their existence during an active visual sensory processing. Yet, given the prevalence of this effect in so many different behavioral contexts, one has to speculate about the specificity of this rhythm in indexing a particular cortical dysfunction in the schizophrenia population. While this still remains a possibility, it is also quite possible that this delta-band effect may be a by-product of general increased activations (not necessarily in-phase) within and across cortical areas. However, this interpretation should be treated with caution as more rigorous testing in this band is clearly needed.

Theta-band differences between populations

The FFT-profiles in the anterior cortices revealed a strong peak in theta-band activity in patients but not in controls. This peak activity was found to be trending towards significance (p-value = .052), and slighted lateralized towards the right hemisphere. Moreover, the data revealed significant differences in the topographical distributions in the theta-band, whereby patients displayed an additional voltage distribution over central-posterior sites in addition to the bilateral voltage peaks over midline/frontal scalp areas (see Figure 3b). This topographical difference is important because it suggests that patients engage a different set of neural populations, compared to controls, to give rise to theta-band oscillatory activity. However, what this difference signifies for sensory perception and/or cognitive processing in patients needs to be further clarified.

Theta-band oscillations have been regularly studied in the field. They are highly implicated in encoding new information as well as retrieving information from working-memory space (see Lisman 2010 for a review). Our results found a trend towards significance in the pre and post-stimulus intervals, whereby patients displayed greater activity than controls. Yet, we observed that neither patients nor controls exhibited an ERD/ERS, suggesting that theta-band mechanisms may not have been selectively engaged during stimulus processing in our task. It is plausible that similar to the findings in the delta-band, our measure of theta-band activity might represent a general (i.e. non-specific) effect of ongoing activations in the patient population.

In contrast to our findings, a previous study reported reduced theta-band activation in patients compared to controls during a visual event-related paradigm (see Bates et al 2009). This mixed result could be explained by a difference in the data analysis technique used by Bates and colleagues (2009) versus ours. Specifically, Bates and colleagues (2009) characterized 'induced' activity by wavelet-transforming each single trial, averaging them out and then subtracting the evoked-wavelet data (i.e. wavelet transformation of the ERP waveform) from it. This subtraction procedure should be looked at critically as it makes very strong assumptions on what is considered 'evoked' (i.e. phase-locked) and 'induced' (not-strictly phase-locked) activity. In fact, this procedure becomes highly controversial in the case where the inter-stimulus-interval (ISI) is not adequately randomized, or when examining activity in the lower frequencies, where phase-jitters influence oscillatory activity minimally (see Jensen & Colgin 2007). Thus, it is quite possible that lower-frequency activity that is not-strictly phase locked to the sensory stimulus will still survive the averaging process of the ERP, and thus be present in the evoked wavelet transformed data. To this end, we contend that it is best to always characterize 'induced' activity as that derived from single-trial analysis, which of course also contains the so-called 'evoked' activity.

Alpha-band activity and its implication for gain control

The FFT-profiles in the posterior cortices revealed a strong peak in the alpha band activity in controls but not in patients. The activity within this band was found to be significantly greater in controls and lateralized towards the right hemisphere. Furthermore, and similar to the findings in the theta-band, the data revealed significant differences in the topographical distributions in this frequency band. This topographical difference was mainly driven by the greater distribution of alpha-power over posterior cortices, which was virtually absent in patients (see Figure 3c). This lateralized alpha topography map, which we and others term as 'phasic' alpha, has been observed in many different tasks and it is believed to index a specific mode of sensory processing related to suppression and/or enhancement of sensory inputs (see Gomez-Ramirez et al 2009). In contrast to the 'tonic' alpha activity, which is sustained over long-periods of time and has a topographical distribution over central parieto-occipital cortices, this phasic alpha-activity (which encompasses the ERD effect) refers to modulations over much shorter timeframes (e.g. < 1000 ms) and it occurs in response to specific sensory stimuli that need to be further processed or suppressed. That being said, it is quite remarkable that patients do not exhibit the typical alpha-band topographical distribution and have significantly reduced ERD activity compared to controls. Clearly, these findings have significant implications in the sensory processing deficits in schizophrenia patients, which we describe below.

Studies in healthy controls have repeatedly demonstrated ERD in response to visual stimuli, which is maximal over extrastriate sites around 200-300 ms (Neuper et al., 2006; Pfurtscheller & Neuper, 2006; Pfurtscheller et al., 1994; Thut et al., 2006). This ERD effect following visual stimulation is thought to reflect the release of neural inhibition, resulting in cortical activation allowing visual areas to process incoming stimuli (Klimesch, Sauseng, & Hanslmayr, 2007). In this way, researchers have suggested that alpha-band activity is a sensory gating mechanism, helping rout information throughout the sensory processing stream via active cortical inhibition and dis-inhibition of relevant neural regions (Jensen & Mazaheri, 2010). Further, underlying mechanisms that modulate alpha activity are thought to originate from the exchange between glutamatergic excitatory and GABAergic inhibitory signals (Jones, Pinto, Kaper, & Kopell, 2000; Lorincz, Kekesi, Juhasz, Crunelli, & Hughes, 2009; Mann & Paulsen, 2007).

Similarly, visual alpha desynchronization appears to be an example of gain control. Regarding the visual domain, ‘gain control’ refers to a mechanism that allows visual pathways to adapt and optimize their responses in different contextual situations by either amplifying or attenuating neuronal signals which in turn affect the integrity of sensory registration (Butler et al., 2008). Indeed, patients with schizophrenia have repeatedly demonstrated gain control deficits in behavioral center-surround experiments (see Dakin, Carlin, & Hemsley, 2005), and in magnocellular-biased steady-state and transient visual evoked potential contrast response functions (see Butler, Zemon et al., 2005). Gain control mechanisms underlying magnocellular pathway responses and alpha-band activity in general are both thought to be mediated by the interplay of excitatory glutamate neurotransmitters/N-methyl d-aspartate (NMDA) receptors (Daw et al., 1993; Fox et al., 1990; Kwon et al., 1992), and inhibitory GABAergic interneurons (Lisman et al., 2008). Taken together, the lack of alpha desynchronization at extrastriate electrode sites in patients appears to be another example of dysfunctional gain control mechanisms that contributes to abnormal visual perceptual.

Alpha-band activity and its relation to global patient functioning

In the current study, increased GAF (global assessment of function) scores in patients, indicative of higher functioning, were significantly correlated with increased alpha desynchronization (a trend was seen in the left hemisphere). This is the first study to explore the association between visual alpha-desynchronization and clinical ratings. It is consistent with previous data that have shown gain control function is important in predicting functional outcome (Butler, Zemon et al., 2005; Schechter et al., 2005), implicating its potential importance for remediation strategies and targeted drug therapies. No other measure was correlated with symptoms or clinical ratings.

Limitations & Conclusions

A limitation of this study was that all patients were chronically ill and receiving medication. However, visual processing deficits have been found in both medicated and unmedicated patient populations (Braff and Sacuzzo, 1982; Harvey et al., 1990; Butler et al., 1996; Cadenhead et al., 1997; Butler et al., 2002) and first-degree relatives (Green et al., 1997; Chen et al., 1999; Keri et al., 2004). Further, studies have shown that frequency characteristics of the EEG in patients are similar between first-episode and chronic, medicated patients, suggesting that long-term treatment and illness duration have no overall differential effects on these potential trait markers (Fenton, Fenwick, Dollimore, Dunn, & Hirsch, 1980; Gattaz, Mayer, Ziegler, Platz, & Gasser, 1992; Sponheim et al., 1994).With regard to medication, there were no correlations found between the chlorpromazine equivalents and any dependent measure ($p>.09$).

In conclusion, induced delta activity was seen to be abnormally larger in patients versus controls during pre- and post-stimulus intervals. Conversely, patients exhibited comparable delta-band ERS to controls. This suggests that the impairment in patients is based on elevated ongoing activity, possibly reflective of general cognitive decline, or a general failure in overall cortical suppression in the patient population. Further, patients exhibited a trend towards theta-band activity being greater versus controls, and topographic distribution of this rhythm was significantly altered, suggestive of theta-cortical generator abnormalities. Lastly, patients exhibited a significant deficit in visual alpha-desynchronization. Accordingly, patients showed a significantly altered topographic distribution of their alpha-band activity, suggesting impaired neural generation of these rhythms that may result in abnormal instantaneous activity also seen in the current study. Indeed, the current finding provides another example of gain control deficits in a novel way in patients with schizophrenia that may ultimately contribute to low-level visual processing dysfunction.

6. References

Andreasen, N. C. (1984). *The scale for the assessment of negative symptoms (SANS)*. Iowa City: The University of Iowa.

Axmacher, N., Henseler, M. M., Jensen, O., Weinreich, I., Elger, C. E., & Fell, J. (2010). Cross-frequency coupling supports multi-item working memory in the human hippocampus. *Proc Natl Acad Sci U S A, 107*(7), 3228-3233.

Basar-Eroglu, C., Brand, A., Hildebrandt, H., Karolina Kedzior, K., Mathes, B., & Schmiedt, C. (2007). Working memory related gamma oscillations in schizophrenia patients. *Int J Psychophysiol, 64*(1), 39-45.

Bastiaansen, M. C., Bocker, K. B., Brunia, C. H., de Munck, J. C., & Spekreijse, H. (2001). Event-related desynchronization during anticipatory attention for an upcoming stimulus: a comparative EEG/MEG study. *Clin Neurophysiol, 112*(2), 393-403.

Bates, A. T., Kiehl, K. A., Laurens, K. R., & Liddle, P. F. (2009). Low-frequency EEG oscillations associated with information processing in schizophrenia. *Schizophr Res, 115*(2-3), 222-230.

Battaglia, F. P., Sutherland, G. R., & McNaughton, B. L. (2004). Hippocampal sharp wave bursts coincide with neocortical "up-state" transitions. *Learn Mem, 11*(6), 697-704.

Bishop, G. (1932). Cyclical changes in excitability of the optic pathways of the rabbit. *American Journal of Physiology, 103*, 213-224.

Boutros, N. N., Arfken, C., Galderisi, S., Warrick, J., Pratt, G., & Iacono, W. (2008). The status of spectral EEG abnormality as a diagnostic test for schizophrenia. *Schizophr Res, 99*(1-3), 225-237.

Boutros, N. N., & Arfken, C. L. (2007). A four-step approach for developing diagnostic tests in psychiatry. *Clin EEG Neurosci, 38*(2), 62-65.

Butler, P. D., Martinez, A., Foxe, J. J., Kim, D., Zemon, V., Silipo, G., et al. (2007). Subcortical visual dysfunction in schizophrenia drives secondary cortical impairments. *Brain, 130*, 417-430.

Butler, P. D., Zemon, V., Schechter, I., Saperstein, A. M., Hoptman, M. J., Lim, K. O., et al. (2005). Early-stage visual processing and cortical amplification deficits in schizophrenia. *Arch Gen Psychiatry, 62*(5), 495-504.

Buzsaki, G. (2005). Theta rhythm of navigation: link between path integration and landmark navigation, episodic and semantic memory. *Hippocampus, 15*(7), 827-840.

Buzsaki, G. (2006). *Rhythms of the Brain*. USA: Oxford University Press.

Canolty, R. T., Edwards, E., Dalal, S. S., Soltani, M., Nagarajan, S. S., Kirsch, H. E., et al. (2006). High gamma power is phase-locked to theta oscillations in human neocortex. *Science, 313*(5793), 1626-1628.

Canolty, R. T., & Knight, R. T. (2010). The functional role of cross-frequency coupling. *Trends Cogn Sci, 14*(11), 506-515.

Cho, R. Y., Konecky, R. O., & Carter, C. S. (2006). Impairments in frontal cortical gamma synchrony and cognitive control in schizophrenia. *Proc Natl Acad Sci U S A, 103*(52), 19878-19883.

Dakin, S., Carlin, P., & Hemsley, D. (2005). Weak suppression of visual context in chronic schizophrenia. *Curr Biol, 15*(20), R822-824.

Daw, N. W., Stein, P. S. G., & Fox, K. (1993). The role of NMDA receptors in information processing. *Ann Rev Neurosci, 16*, 207-222.

Ekman, P., & Friesen, W. V. (1976). *Pictures of facial affect*. Palo Alto: Consulting Psychologists Press.

Ergen, M., Marbach, S., Brand, A., Basar-Eroglu, C., & Demiralp, T. (2008). P3 and delta band responses in visual oddball paradigm in schizophrenia. *Neurosci Lett, 440*(3), 304-308.

Fehr, T., Kissler, J., Wienbruch, C., Moratti, S., Elbert, T., Watzl, H., et al. (2003). Source distribution of neuromagnetic slow-wave activity in schizophrenic patients--effects of activation. *Schizophr Res, 63*(1-2), 63-71.

Fenton, G. W., Fenwick, P. B., Dollimore, J., Dunn, T. L., & Hirsch, S. R. (1980). EEG spectral analysis in schizophrenia. *Br J Psychiatry, 136*, 445-455.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (1997). *Structured Clinical Interview for DSM-IV Axis I Disorders- Patient Edition*. New York: New York State Psychiatric Institute.

Flynn, G., Alexander, D., Harris, A., Whitford, T., Wong, W., Galletly, C., et al. (2008). Increased absolute magnitude of gamma synchrony in first-episode psychosis. *Schizophr Res, 105*(1-3), 262-271.

Fox, K., Sato, H., & Daw, N. (1990). The effect of varying stimulus intensity on NMDA-receptor activity in cat visual cortex. *J Neurophysiol, 64*(5), 1413-1428.

Foxe, J. J., Doniger, G. M., & Javitt, D. C. (2001). Early visual processing deficits in schizophrenia: impaired PI generation revealed by high-density electrical mapping. *NeuroReport, 12*(17).

Foxe, J. J., Simpson, G. V., & Ahlfors, S. P. (1998). Parieto-occipital approximately 10 Hz activity reflects anticipatory state of visual attention mechanisms. *Neuroreport, 9*(17), 3929-3933.

Fries, P., Reynolds, J. H., Rorie, A. E., & Desimone, R. (2001). Modulation of oscillatory neuronal synchronization by selective visual attention. *Science, 291*(5508), 1560-1563.

Friston, K. J. (1999). Schizophrenia and the disconnection hypothesis. *Acta Psychiatr Scand Suppl, 395*, 68-79.

Gallinat, J., Winterer, G., Herrmann, C. S., & Senkowski, D. (2004). Reduced oscillatory gamma-band responses in unmedicated schizophrenic patients indicate impaired frontal network processing. *Clin Neurophysiol, 115*(8), 1863-1874.

Gattaz, W. F., Mayer, S., Ziegler, P., Platz, M., & Gasser, T. (1992). Hypofrontality on topographic EEG in schizophrenia. Correlations with neuropsychological and psychopathological parameters. *Eur Arch Psychiatry Clin Neurosci, 241*(6), 328-332.

Gomez-Ramirez, M., Higgins, B. A., Rycroft, J. A., Owen, G. N., Mahoney, J., Shpaner, M., et al. (2007). The deployment of intersensory selective attention: a high-density electrical mapping study of the effects of theanine. *Clin Neuropharmacol, 30*(1), 25-38.

Gomez-Ramirez, M., Kelly, S. P., Montesi, J. L., & Foxe, J. J. (2009). The effects of L-theanine on alpha-band oscillatory brain activity during a visuo-spatial attention task. *Brain Topogr, 22*(1), 44-51.

Gray, C. M., Konig, P., Engel, A. K., & Singer, W. (1989). Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties. *Nature, 338*(6213), 334-337.

Herrmann, C. S., & Demiralp, T. (2005). Human EEG gamma oscillations in neuropsychiatric disorders. *Clin Neurophysiol, 116*(12), 2719-2733.

Higashima, M., Tsukada, T., Nagasawa, T., Oka, T., Okamoto, T., Okamoto, Y., et al. (2007). Reduction in event-related alpha attenuation during performance of an auditory oddball task in schizophrenia. *Int J Psychophysiol, 65*(2), 95-102.

Hollingshead, A. (1975). Four Factor Index of Social Status. Yale University Department of Sociology.

Hong, L. E., Summerfelt, A., Mitchell, B. D., McMahon, R. P., Wonodi, I., Buchanan, R. W., et al. (2008). Sensory gating endophenotype based on its neural oscillatory pattern and heritability estimate. *Arch Gen Psychiatry, 65*(9), 1008-1016.

Hyman SE, A. G., Rosenbaum JF (Ed.). (1995). *Handbook of*

Psychiatric Drug Therapy. Boston: Little, Brown and Company.

Javitt, D. C. (2009). When doors of perception close: bottom-up models of disrupted cognition in schizophrenia. *Annu Rev Clin Psychol, 5*, 249-275.

Jensen, O., & Mazaheri, A. (2010). Shaping functional architecture by oscillatory alpha activity: gating by inhibition. *Front Hum Neurosci, 4*, 186.

Jibson, M. D., & Tandon, R. (1998). New atypical antipsychotic medications. *J Psychiatr Res, 32*(3-4), 215-228.

Jones, M. W., & Wilson, M. A. (2005). Theta rhythms coordinate hippocampal-prefrontal interactions in a spatial memory task. *PLoS Biol, 3*(12), e402.

Jones, S. R., Pinto, D. J., Kaper, T. J., & Kopell, N. (2000). Alpha-frequency rhythms desynchronize over long cortical distances: a modeling study. *J Comput Neurosci, 9*(3), 271-291.

Kahana, M. J., Seelig, D., & Madsen, J. R. (2001). Theta returns. *Curr Opin Neurobiol, 11*(6), 739-744.

Keil, A., Muller, M. M., Ray, W. J., Gruber, T., & Elbert, T. (1999). Human gamma band activity and perception of a gestalt. *J Neurosci, 19*(16), 7152-7161.

Kelly, S. P., Foxe, J. J., Newman, G., & Edelman, J. A. (2010). Prepare for conflict: EEG correlates of the anticipation of target competition during overt and covert shifts of visual attention. *Eur J Neurosci, 31*(9), 1690-1700.

Kelly, S. P., Gomez-Ramirez, M., & Foxe, J. J. (2009). The strength of anticipatory spatial biasing predicts target discrimination at attended locations: a high-density EEG study. *Eur J Neurosci, 30*(11), 2224-2234.

Kelly, S. P., Gomez-Ramirez, M., Montesi, J. L., & Foxe, J. J. (2008). L-theanine and caffeine in combination affect human cognition as evidenced by oscillatory alpha-band activity and attention task performance. *J Nutr, 138*(8), 1572S-1577S.

Kelly, S. P., Lalor, E. C., Finucane, C., McDarby, G., & Reilly, R. B. (2005). Visual spatial attention control in an independent brain-computer interface. *IEEE Trans Biomed Eng, 52*(9), 1588-1596.

Kelly, S. P., Lalor, E. C., Reilly, R. B., & Foxe, J. J. (2006). Increases in alpha oscillatory power reflect an active retinotopic mechanism for distracter suppression during sustained visuospatial attention. *J Neurophysiol, 95*(6), 3844-3851.

Kim, D., Zemon, V., Saperstein, A., Butler, P. D., & Javitt, D. C. (2005). Dysfunction of early-stage visual processing in schizophrenia: harmonic analysis. *Schizophr Res, 76*(1), 55-65.

Klimesch, W., Doppelmayr, M., Russegger, H., Pachinger, T., & Schwaiger, J. (1998). Induced alpha band power changes in the human EEG and attention. *Neurosci Lett, 244*(2), 73-76.

Klimesch, W., Sauseng, P., & Hanslmayr, S. (2007). EEG alpha oscillations: the inhibition-timing hypothesis. *Brain Res Rev, 53*(1), 63-88.

Knott, V., Labelle, A., Jones, B., & Mahoney, C. (2001). Quantitative EEG in schizophrenia and in response to acute and chronic clozapine treatment. *Schizophr Res, 50*(1-2), 41-53.

Knyazev, G. G. (2007). Motivation, emotion, and their inhibitory control mirrored in brain oscillations. *Neurosci Biobehav Rev, 31*(3), 377-395.

Koh, Y., Shin, K. S., Kim, J. S., Choi, J. S., Kang, D. H., Jang, J. H., et al. (2010). An MEG study of alpha modulation in patients with schizophrenia and in subjects at high risk of developing psychosis. *Schizophr Res*.

Kwon, Y. H., Nelson, S. B., Toth, L. J., & Sur, M. (1992). Effect of stimulus contrast and size on NMDA receptor activity in cat lateral geniculate nucleus. *J Neurophysiol, 68*(1), 182-196.

Lakatos, P., Chen, C. M., O'Connell, M. N., Mills, A., & Schroeder, C. E. (2007). Neuronal oscillations and multisensory interaction in primary auditory cortex. *Neuron, 53*(2), 279-292.

Lakatos, P., Karmos, G., Mehta, A. D., Ulbert, I., & Schroeder, C. E. (2008). Entrainment of neuronal oscillations as a mechanism of attentional selection. *Science, 320*(5827), 110-113.

Lakatos, P., O'Connell, M. N., Barczak, A., Mills, A., Javitt, D. C., & Schroeder, C. E. (2009). The leading sense: supramodal control of neurophysiological context by attention. *Neuron, 64*(3), 419-430.

Lakatos, P., Shah, A. S., Knuth, K. H., Ulbert, I., Karmos, G., & Schroeder, C. E. (2005). An oscillatory hierarchy controlling neuronal excitability and stimulus processing in the auditory cortex. *J Neurophysiol, 94*(3), 1904-1911.

Leavitt, V. M., Molholm, S., Ritter, W., Shpaner, M., & Foxe, J. J. (2007). Auditory processing in schizophrenia during the middle latency period (10-50 ms): high-density electrical mapping and source analysis reveal subcortical antecendents to early cortical deficits. *J Psychiatr Neurosci, 32*(5), 339-353.

Lisman, J. (2010). Working memory: the importance of theta and gamma oscillations. *Curr Biol, 20*(11), R490-492.

Lisman, J. E., Coyle, J. T., Green, R. W., Javitt, D. C., Benes, F. M., Heckers, S., et al. (2008). Circuit-based framework for understanding neurotransmitter and risk gene interactions in schizophrenia. *Trends Neurosci, 31*(5), 234-242.

Lorincz, M. L., Kekesi, K. A., Juhasz, G., Crunelli, V., & Hughes, S. W. (2009). Temporal framing of thalamic relay-mode firing by phasic inhibition during the alpha rhythm. *Neuron, 63*(5), 683-696.

Mann, E. O., & Paulsen, O. (2007). Role of GABAergic inhibition in hippocampal network oscillations. *Trends Neurosci, 30*(7), 343-349.

Martinez, A., Hillyard, S. A., Dias, E. C., Hagler, D. J., Butler, P. D., Guilfoyle, D. N., et al. (2008). Magnocellular pathway impairment in schizophrenia: evidence from fMRI. *J Neuroscience, 28*(30), 7492-7500.

Mulholland, T., Goodman, D., & Boudrot, R. (1983). Attention and regulation of EEG alpha-attenuation responses. *Biofeedback Self Regul, 8*(4), 585-600.

Neuper, C., Wortz, M., & Pfurtscheller, G. (2006). ERD/ERS patterns reflecting sensorimotor activation and deactivation. *Prog Brain Res, 159*, 211-222.

Norra, C., Waberski, T. D., Kawohl, W., Kunert, H. J., Hock, D., Gobbele, R., et al. (2004). High-frequency somatosensory thalamocortical oscillations and psychopathology in schizophrenia. *Neuropsychobiology, 49*(2), 71-80.

Ojanpaa, H., & Nasanen, R. (2003). Utilisation of spatial frequency information in face search. *Vision Res, 43*(24), 2505-2515.

Omori, M., Koshino, Y., Murata, T., Murata, I., Nishio, M., Sakamoto, K., et al. (1995). Quantitative EEG in never-treated schizophrenic patients. *Biol Psychiatry, 38*(5), 305-309.

Overall, J. E., & Gorham, D. R. (1962). The brief psychiatric rating scale. *Psychological Reports, 10*, 799-812.

Peuskens, J., & Link, C. G. (1997). A comparison of quetiapine and chlorpromazine in the treatment of schizophrenia. *Acta Psychiatr Scand, 96*(4), 265-273.

Pfurtscheller, G., & Neuper, C. (2006). Future prospects of ERD/ERS in the context of brain-computer interface (BCI) developments. *Prog Brain Res, 159*, 433-437.

Pfurtscheller, G., Neuper, C., & Mohl, W. (1994). Event-related desynchronization (ERD) during visual processing. *Int J Psychophysiol, 16*(2-3), 147-153.

Phillips, W. A., & Silverstein, S. M. (2003). Convergence of biological and psychological perspectives on cognitive coordination in schizophrenia. *Behavioral and Brain Sciences, 26*, 65-138.

Raghavachari, S., Kahana, M. J., Rizzuto, D. S., Caplan, J. B., Kirschen, M. P., Bourgeois, B., et al. (2001). Gating of human theta oscillations by a working memory task. *J Neurosci, 21*(9), 3175-3183.

Rutishauser, U., Ross, I. B., Mamelak, A. N., & Schuman, E. M. (2010). Human memory strength is predicted by theta-frequency phase-locking of single neurons. *Nature, 464*(7290), 903-907.

Sauseng, P., Klimesch, W., Freunberger, R., Pecherstorfer, T., Hanslmayr, S., & Doppelmayr, M. (2006). Relevance of EEG alpha and theta oscillations during task switching. *Exp Brain Res, 170*(3), 295-301.

Schechter, I., Butler, P. D., Zemon, V. M., Revheim, N., Saperstein, A. M., Jalbrzikowski, M., et al. (2005). Impairments in generation of early-stage transient visual evoked potentials to magno- and parvocellular-selective stimuli in schizophrenia. *Clin Neurophysiol, 116*(9), 2204-2215.

Schnitzler, A., & Gross, J. (2005). Normal and pathological oscillatory communication in the brain. *Nat Rev Neurosci, 6*(4), 285-296.

Sederberg, P. B., Kahana, M. J., Howard, M. W., Donner, E. J., & Madsen, J. R. (2003). Theta and gamma oscillations during encoding predict subsequent recall. *J Neurosci, 23*(34), 10809-10814.

Singer, W., & Gray, C. M. (1995). Visual feature integration and the temporal correlation hypothesis. *Annu Rev Neurosci, 18*, 555-586.

Spencer, K. M. (2008). Visual gamma oscillations in schizophrenia: implications for understanding neural circuitry abnormalities. *Clin EEG Neurosci, 39*(2), 65-68.

Spencer, K. M., Nestor, P. G., Niznikiewicz, M. A., Salisbury, D. F., Shenton, M. E., & McCarley, R. W. (2003). Abnormal neural synchrony in schizophrenia. *J Neurosci, 23*(19), 7407-7411.

Spencer, K. M., Nestor, P. G., Perlmutter, R., Niznikiewicz, M. A., Klump, M. C., Frumin, M., et al. (2004). Neural synchrony indexes disordered perception and cognition in schizophrenia. *Proc Natl Acad Sci U S A, 101*(49), 17288-17293.

Spencer, K. M., Niznikiewicz, M. A., Shenton, M. E., & McCarley, R. W. (2008). Sensory-evoked gamma oscillations in chronic schizophrenia. *Biol Psychiatry, 63*(8), 744-747.

Sponheim, S. R., Clementz, B. A., Iacono, W. G., & Beiser, M. (1994). Resting EEG in first-episode and chronic schizophrenia. *Psychophysiology, 31*(1), 37-43.

Steriade, M. (1997). Synchronized activities of coupled oscillators in the cerebral cortex and thalamus at different levels of vigilance. *Cereb Cortex, 7*(6), 583-604.

Strik, W. K., Fallgatter, A. J., Brandeis, D., & Pascual-Marqui, R. D. (1998). Three-dimensional tomography of event-related potentials during response inhibition: evidence for phasic frontal lobe activation. *Electroencephalogr Clin Neurophysiol, 108*(4), 406-413.

Symond, M. P., Harris, A. W., Gordon, E., & Williams, L. M. (2005). "Gamma synchrony" in first-episode schizophrenia: a disorder of temporal connectivity? *Am J Psychiatry, 162*(3), 459-465.

Taylor, K., Mandon, S., Freiwald, W. A., & Kreiter, A. K. (2005). Coherent oscillatory activity in monkey area v4 predicts successful allocation of attention. *Cereb Cortex, 15*(9), 1424-1437.

Thut, G., Nietzel, A., Brandt, S. A., & Pascual-Leone, A. (2006). Alpha-band electroencephalographic activity over occipital cortex indexes visuospatial attention bias and predicts visual target detection. *J Neurosci, 26*(37), 9494-9502.

Uhlhaas, P. J., Linden, D. E., Singer, W., Haenschel, C., Lindner, M., Maurer, K., et al. (2006). Dysfunctional long-range coordination of neural activity during Gestalt perception in schizophrenia. *J Neurosci, 26*(31), 8168-8175.

Uhlhaas, P. J., & Singer, W. (2010). Abnormal neural oscillations and synchrony in schizophrenia. *Nat Rev Neurosci, 11*(2), 100-113.

Williams, L. M., Whitford, T. J., Nagy, M., Flynn, G., Harris, A. W., Silverstein, S. M., et al. (2009). Emotion-elicited gamma synchrony in patients with first-episode schizophrenia: a neural correlate of social cognition outcomes. *J Psychiatry Neurosci, 34*(4), 303-313.

Womelsdorf, T., & Fries, P. (2006). Neuronal coherence during selective attentional processing and sensory-motor integration. *J Physiol Paris, 100*(4), 182-193.

Worden, M. S., Foxe, J. J., Wang, N., & Simpson, G. V. (2000). Anticipatory biasing of visuospatial attention indexed by retinotopically specific alpha-band electroencephalography increases over occipital cortex. *J Neurosci, 20*(6), RC63.

Wynn, J. K., Light, G. A., Breitmeyer, B., Nuechterlein, K. H., & Green, M. F. (2005). Event-related gamma activity in schizophrenia patients during a visual backward-masking task. *Am J Psychiatry, 162*(12), 2330-2336.

Yuval-Greenberg, S., & Deouell, L. Y. (2007). What you see is not (always) what you hear: induced gamma band responses reflect cross-modal interactions in familiar object recognition. *J Neurosci, 27*(5), 1090-1096.

9. Tables

Table 1

Demographic and Clinical Characteristics of Healthy Controls and Patients with Schizophrenia

Characteristic	**Controls (n=23)**	**Patients (n=24)**
Age	36.3± 15	40.4 ± 11.2
Gender (M/F)	16/7	22/2
Chlorpromazine daily equivalent, mg		1117 ± 579.7
Antipsychotics		
Atypical		19
Typical		
Both		5
Parental socioeconomic status	41.7 ± 17.7 (n=22)	38.9 ± 15.1 (n=17)
BPRS total score		38.1 ± 6.8 (n =21)
SANS total score (including global Scores)		36.8 ± 13.3 (n =21)
Duration of illness (years)		14 ± 9.2 (n=24)

Note: Values are mean ± SD. Numbers of subjects per group are noted when there is missing data. Socioeconomic status was measured by the 4-factor Hollingshead Scale (Hollingshead, 1975). M, male; F, female; BPRS, Brief Psychiatric Rating Scale (Overall & Gorham, 1962); SANS, Schedule for Assessment of Negative Symptoms (Andreasen, 1984).

7. Figure Legends

Figure 1: Left: Frequency spectra for controls and patients with schizophrenia. Right: Difference waveforms, with controls subtracted from patients. Red: Controls. Blue: Patients. A) Electrode C6 was plotted as an example of delta and theta activity. As can be seen in the difference waveform, patients demonstrated higher amplitudes in the low-frequency bands, with the largest difference within the high-theta range. B) The average of electrodes O2 and PO8 was plotted as an example of alpha activity. As can be seen in the difference waveform, controls exhibited a much larger alpha, with their peak occurring at 10 Hz.

Figure 2: Bar graphs were plotted for the peak amplitudes found within each frequency band of the FFT for controls and patients. Left and right hemispheres are shown. Red: Controls. Blue: Patients. *: significant ($p<.05$). A) There was a trend seen for overall delta-band amplitude in patients being greater than controls ($p = .076$). B) There was a trend seen for overall theta amplitude in patients being greater than controls ($p = .052$). C) There was a trend seen for left-hemispheric alpha-band amplitude for controls being greater than that seen for patients ($p = .052$). Right-hemispheric alpha-band amplitude for controls was significantly greater than that seen for patients.

Figure 3: Top A-C: Frequency topographic maps for delta, theta, and alpha-bands for controls and patients with schizophrenia. Bottom A-C: Difference topographic maps representing controls subtracted from patients for delta, theta, and alpha bands. D) Results from the topographic analysis of variance. There was a significant between-group difference in topographic distribution of frequency amplitudes for the theta (~7 Hz) and

alpha (10 Hz) frequency bands (p = .01, p = .04, respectively). This is illustrated in the difference topographies.

Figure 4: Waveform trajectories for each frequency band of interest over time for left and right hemispheres. Red: Controls. Blue: Patients. A) Delta waveform trajectories for left (C5) and right (C6) hemispheres. Patients demonstrate an increase in delta-band activity over the whole epoch. B) Theta waveform trajectories for left (C5) and right (C6) hemispheres. Patients demonstrate an increase in theta-band activity over the whole epoch. C) Alpha waveform trajectories for left (O1, PO7) and right (O2, PO8) hemispheres. Controls demonstrate increased pre-stimulus alpha, and larger attenuation of activity from 200-400 ms versus controls.

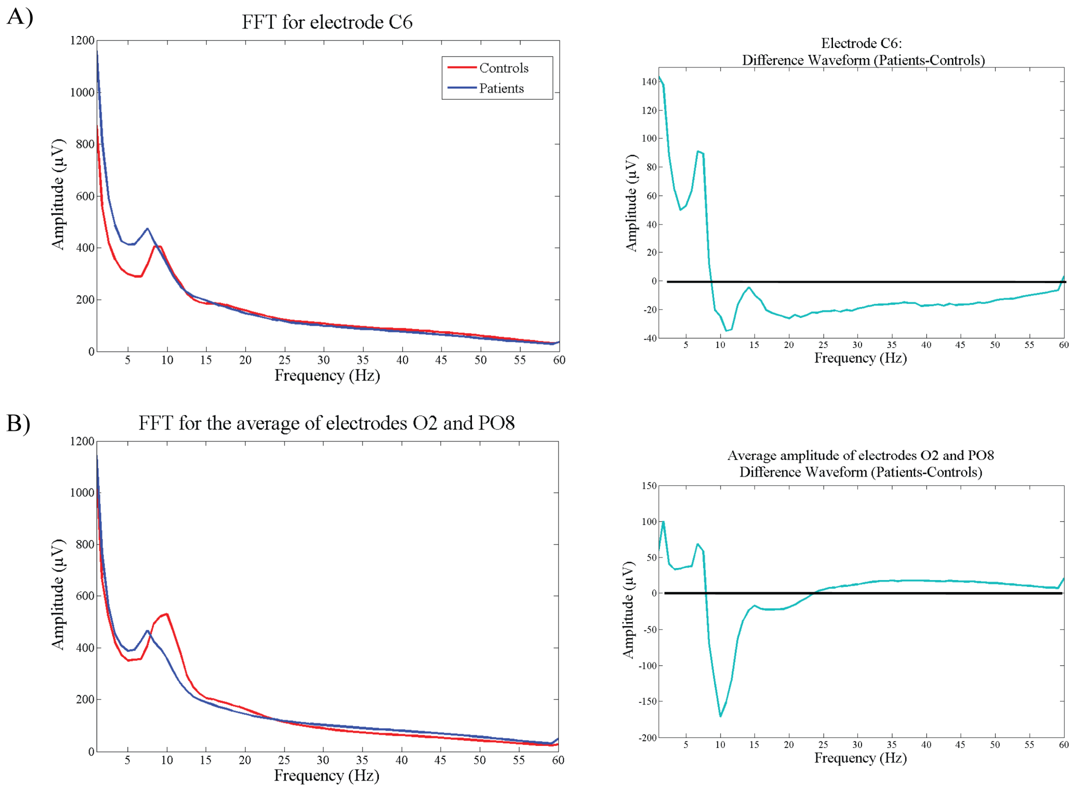
Figure 5: Average amplitudes during the pre-stimulus time period (-300--100 ms) and during the post-stimulus time period. Red: Controls. Blue: Patients. **: significant (p<.01). A) Average delta-band activity for patients was significantly greater than controls in both pre-stimulus and post-stimulus (0-800 ms) time periods. B) There was a trend towards significance for average theta-band activity being greater in patients versus controls in pre-stimulus and post-stimulus (0-500 ms) time periods for both hemispheres. C) There was a trend towards significance for the right hemisphere alpha-band activity being greater for controls versus patients during the pre-stimulus time period.

Figure 6: Synchronization and desynchronization values (in percentage) for each frequency band, reflecting the amount of increase or decrease in activity from the respective baseline of each group. Red: Controls. Blue: Patients. * = significant (p = <.05). A) Both groups exhibited similar increases in delta-band activity or ‘synchronization,’ post-stimulus onset. B) The change in theta-band activity from

baseline was less affected by stimulus onset. C) Patients exhibited a significantly reduced alpha desynchronization, meaning that their alpha-band activity was decreased to a much lesser extent as compared to controls post-stimulus onset across hemispheres.

8. Figures

<u>Figure 1:</u>
Frequency Spectra for Patients and Controls


A)

FFT for electrode C6

Electrode C6:
Difference Waveform (Patients-Controls)

B)

FFT for the average of electrodes O2 and PO8

Average amplitude of electrodes O2 and PO8
Difference Waveform (Patients-Controls)

Figure 2:
Peak amplitudes for each frequency band from frequency spectra

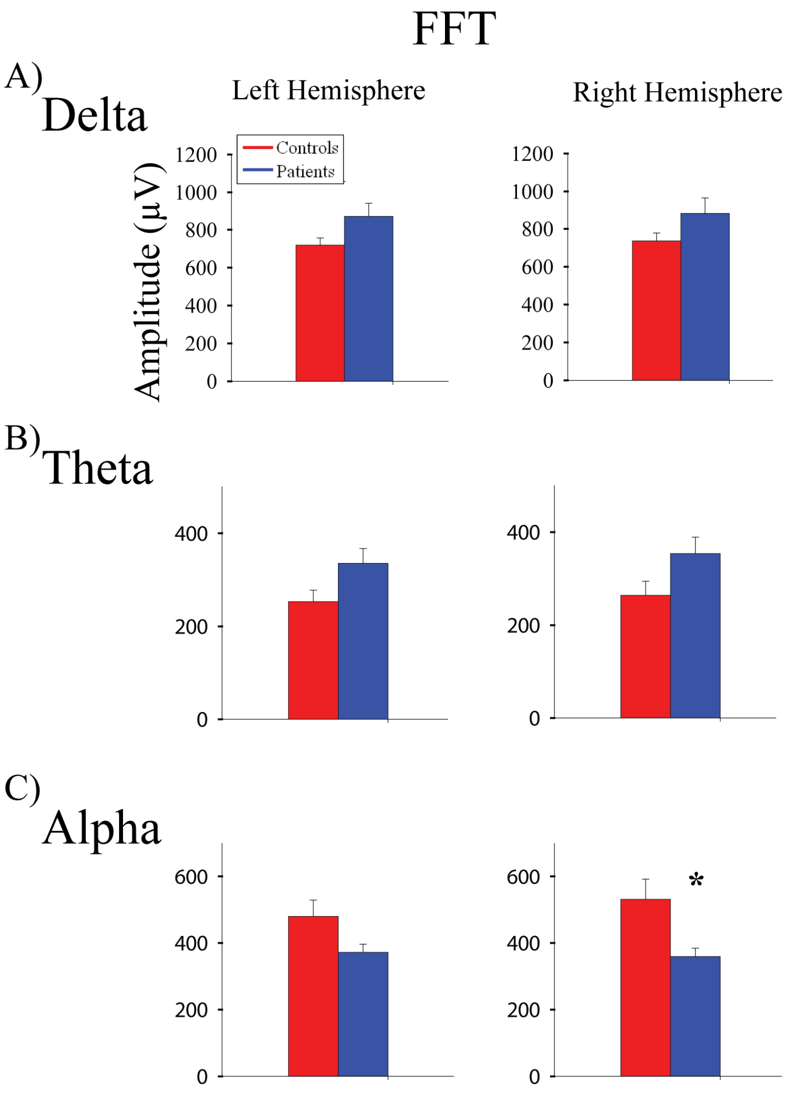


Figure 3:
Frequency topographic maps and TANOVA

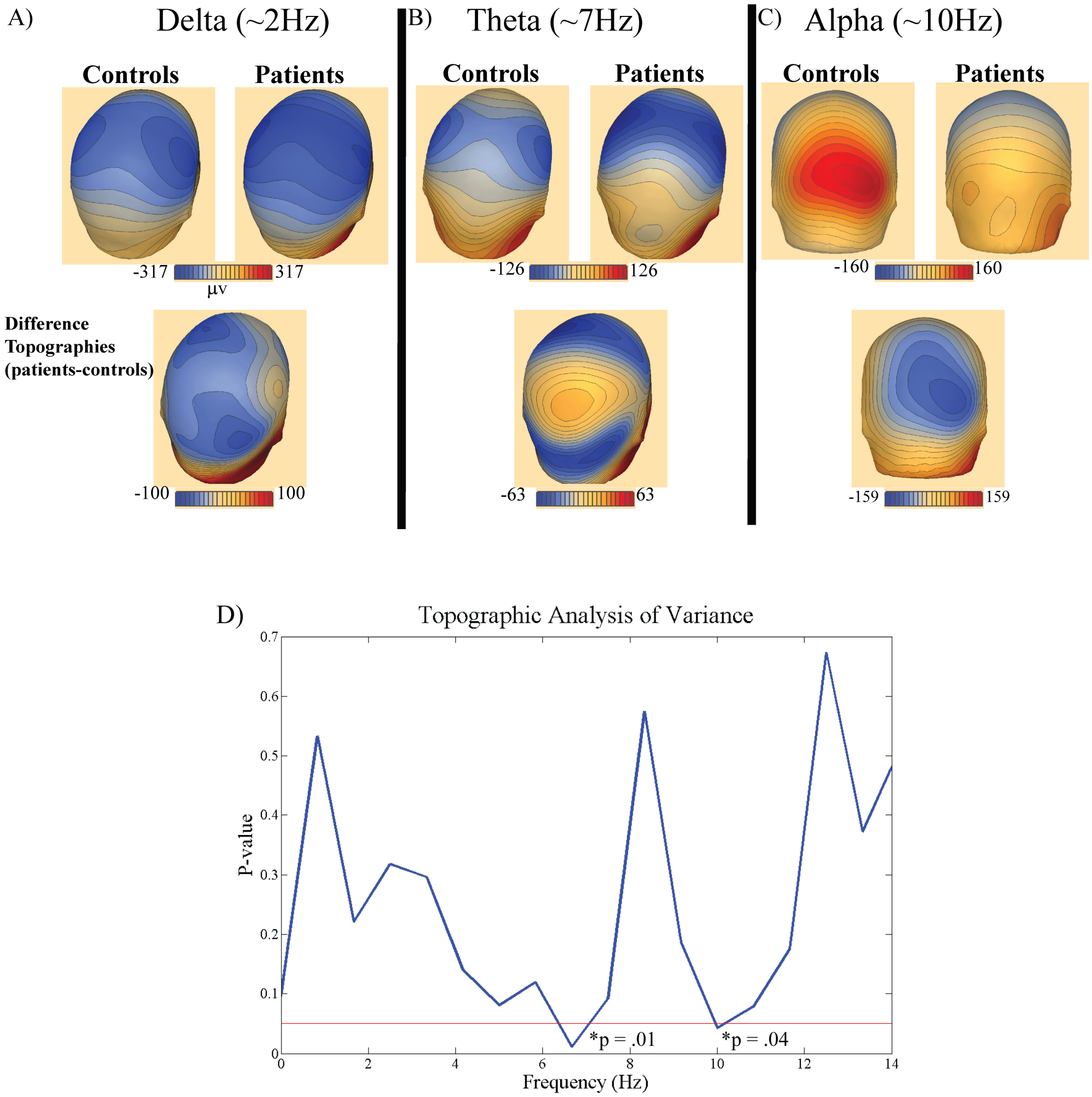
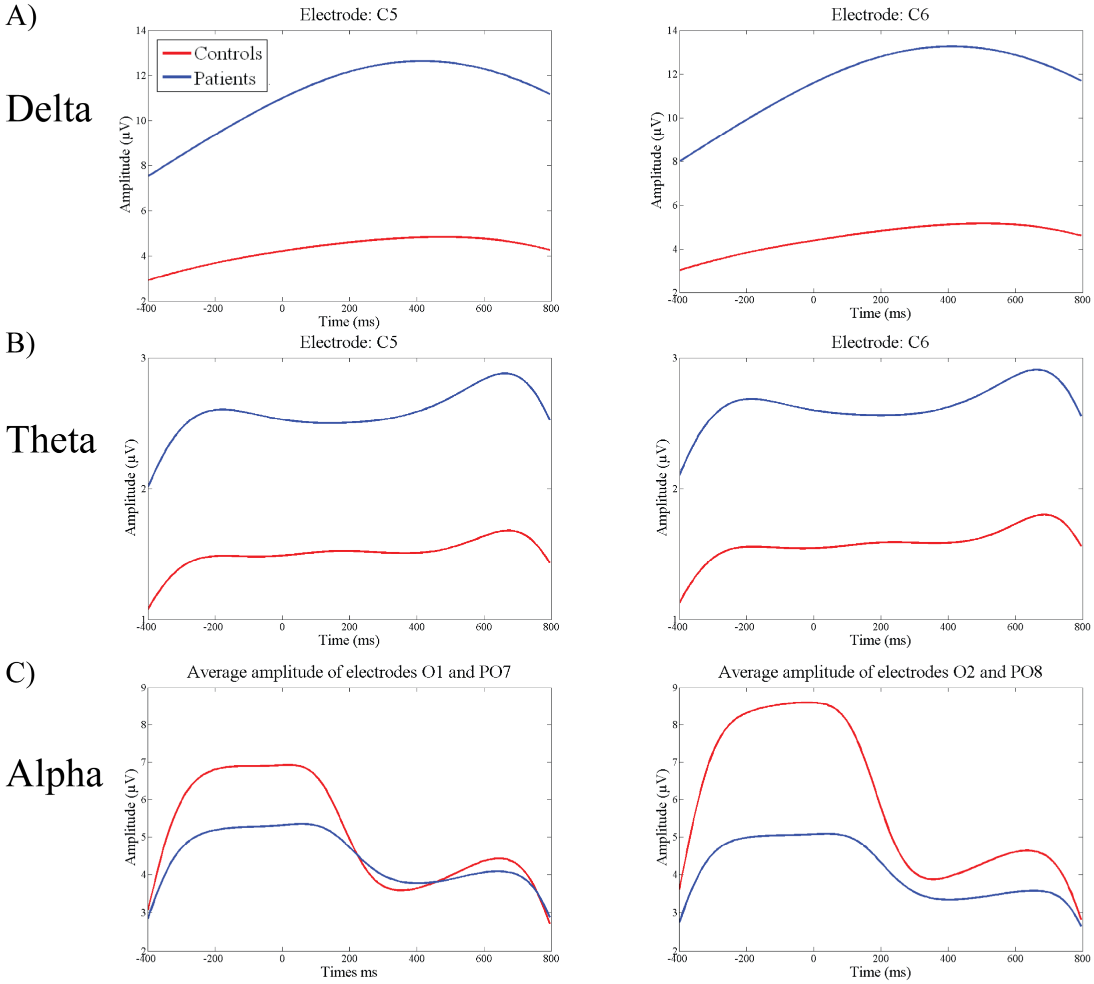


Figure 4:
Waveform trajectories for delta, theta and alpha bands



<u>Figure 5:</u>
Pre-stimulus and post-stimulus amplitudes

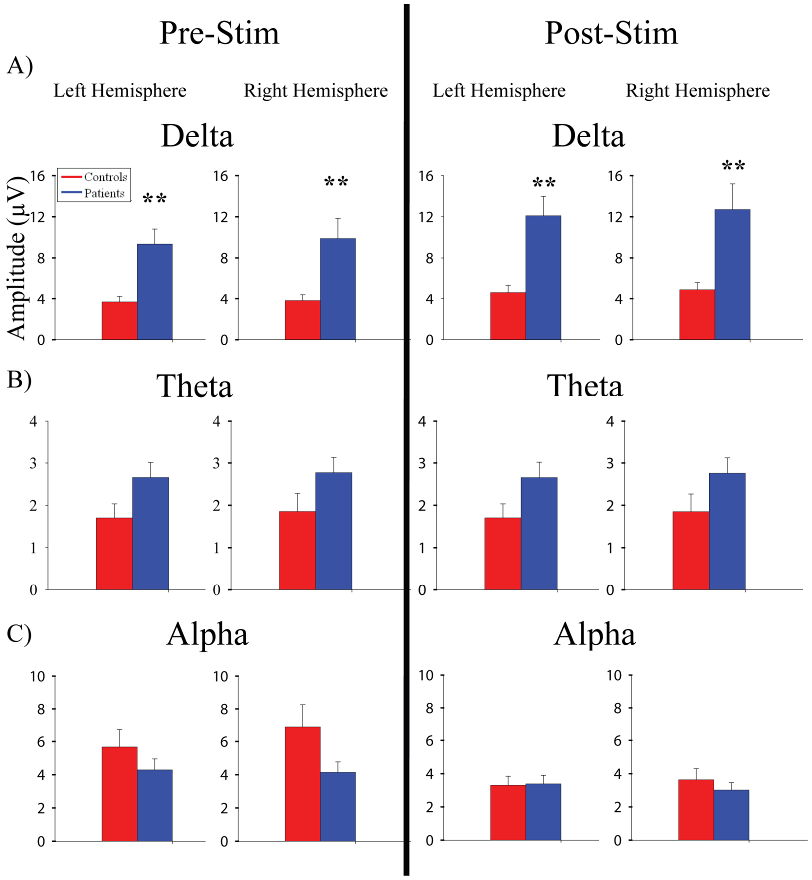
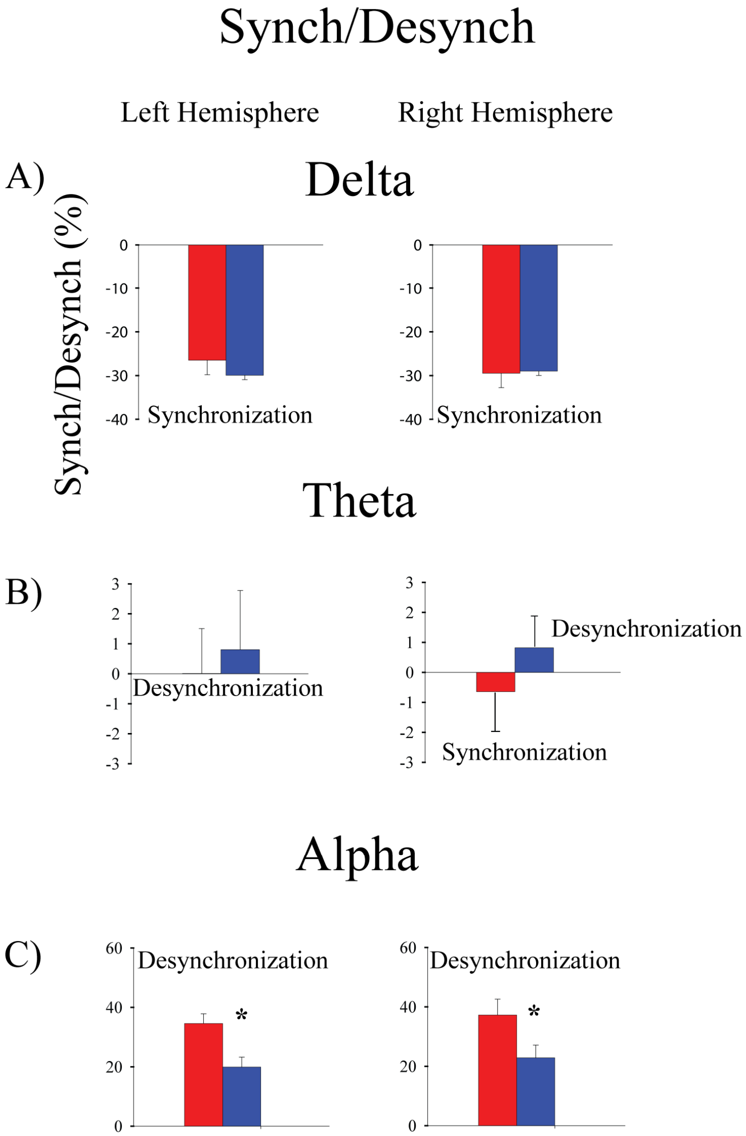


Figure 6:
Synchronization and desynchronization effects



CHAPTER 5

Discussion

This dissertation first set out to further clarify and provide evidence that patients with schizophrenia have a preferential magnocellular visual pathway deficit via a contrast threshold paradigm with altered luminance levels (Experiment 1). Furthermore, it attempted to provide evidence that emotion recognition deficits were not based on inherent limbic dysfunction, but rather were secondary problems to general visual processing impairments. To this end, we used ERP analysis to investigate abnormal M/dorsal stream influences on affect-related perceptual processing (Experiment 2). Lastly, Experiment 3 evaluated potential abnormal oscillatory mechanisms underlying visual perceptual processing deficits with a focus on lower-frequency band oscillatory activity.

Experiment 1 implemented a typical contrast threshold paradigm using five different levels of luminance and two stimulus durations[3]. Luminance was utilized to facilitate the biasing of processing towards the M-pathway, as scotopic vision is thought to be predominantly driven by M-pathway neurons (Benedek et al., 2003; Hawken & Parker, 1984; Hicks et al., 1983; Purpura et al., 1988). To our knowledge, no other experiment has utilized both scotopic luminance and SF manipulation to isolate the M-pathway and investigate its integrity in patients with schizophrenia.

Firstly, robust M-stream deficits were found at the LSFs during scotopic luminance conditions for both stimulus durations, with patients needing higher contrasts to resolve the stimuli versus controls. This finding is in line with previous studies that have shown enhanced M-stream impairment during a number of paradigms utilizing SF and temporal

---

[3] 32 ms and 500 ms conditions were conducted in separate sittings as to avoid ceiling and floor effects in contrast thresholds.

frequency manipulations (Butler et al., 2002; Butler et al., 1996; Schechter et al., 2003; Slaghuis, 2004; Slaghuis & Bakker, 1995; Slaghuis & Bishop, 2001). Secondly, within the current study, the shape of the contrast response functions in both groups at scotopic levels (for both 32 ms and 500 ms) reflected M-stream characteristics as has been recorded previously in both animal physiological and human psychophysical studies (Figure 1B, Figure 3A-B) (Benedek et al., 2003; Daitch & Green, 1969; Hofmann et al., 1990; Kelly, 1972; Patel, 1966). Therefore, we were fairly confident that the influence of the P-system was minimized during scotopic luminance conditions.

Experiment 1 also investigated between-group differences in threshold at higher luminance levels. Patients maintained similar deficits as P-information was introduced from mesopic to photopic conditions for both stimulus durations and each SF (Figures 2 & 4), implying they were able to utilize P-biased information effectively to improve performance. This suggests that their P-pathway function was relatively preserved, and the deficits maintained at higher luminance levels were due to M-pathway impairment. Indeed, while P-pathway influences were minimized during the scotopic condition, the M-pathway continued to respond as P-information was introduced at higher luminance levels. Therefore, deficits at higher luminance levels were to be expected as the M-pathway maintained a high-level of response during these conditions.

Further, both patients and controls improved performance similarly as stimulus duration was increased from 32 ms to 500 ms. Our results are in-line with previous duration threshold studies that show patients have the ability to employ increased stimulus length to improve performance (Braff & Saccuzzo, 1985; Butler, Tambini et al., 2008; Cattapan-Ludewig et al., 2005; Saccuzzo & Braff, 1981; Schwartz et al., 1992;

Slaghuis & Bakker, 1995; Weiner et al., 1990). In general, patients may be able to take advantage of longer stimulus durations because they are able to employ a relatively preserved P-pathway to assist in processing the visual stimulus.

In conclusion, Experiment 1 revealed that, similar to previous studies, patients with schizophrenia exhibit low-level visual processing deficits as reflected by significant M-stream impairment while P-pathway functions were relatively preserved (Butler, 2007; Butler et al., 2004; Butler, Zemon et al., 2005; Gutherie et al., 2006; Keri et al., 2002; Keri & Janka, 2004; Kim et al., 2005; Martinez et al., 2008; Schechter et al., 2005; Slaghuis, 1998; Slaghuis & Bishop, 2001). Visual dysfunction in the M-stream at the sub-cortical level necessarily has negative consequences and implications for higher-order, more complex visual processing. This brings us to Experiment 2, which evaluated low-level visual pathway impairment and its contribution to later emotion recognition and emotion perceptual processing dysfunction in patients with schizophrenia.

Experiment 2 manipulated the contrast of emotional faces in separate behavioral and ERP paradigms in order to first evaluate visual pathway integrity in patients with schizophrenia and second, to investigate how visual pathway dysfunction in patients (particularly in the M/dorsal stream) contributes to their emotion perception and recognition deficits.

Overall, patients displayed a significant emotion recognition deficit for each emotion at each contrast. In addition, controls performed well during the low-contrast condition suggesting M-biased information was sufficient for emotion perception. This finding is in-line with previous data that have shown configural and course (LSFs) information, both properties mediated by the M-pathway, are vital for emotion identification (Adolphs et al., 2005; Calder et al., 2000; Morris et al., 2002; Schyns & Oliva, 1999). To investigate these findings neurophysiologically, dorsal (P1) and ventral (N170) pathway integrity and contributions of these pathways to later affect-related processes (P250) and behavior were evaluated.

P1 amplitudes were significantly reduced for each contrast and emotion. Reduced P1 activity has similarly been demonstrated in some (Caharel et al., 2007; Campanella et al., 2006; Obayashi et al., 2009) but not all (Herrmann et al., 2004; Johnston et al., 2005; Turetsky et al., 2007; Wynn et al., 2008) face-emotion studies. Further, the P1 contrast response curves reflected prototypical M-functions in controls, and patients demonstrated blunted slopes and lowered saturation of response as previously demonstrated in behavioral (Butler et al., 2009), ERP (Butler et al., 2007), and ssVEP paradigms (Butler et al., 2001; Butler, Zemon et al., 2005). The present results are the first to extend these findings to more complex emotion-based stimuli. Taken together, data from these studies suggest that abnormal gain control mechanisms mediating M-pathway function may underlie abnormal contrast response functions of patients in response to simple and complex stimuli. These results further implicate the M-pathway as a precursor to emotion recognition deficits in schizophrenia.

Further, in the M-biased condition, the P1 amplitude differentiated among emotion in controls while it did not in patients. This is in-line with previous studies that found P1 amplitudes varied by emotion via quick stimulus presentation times and LSFs which are all characteristics processed by the M-stream (Pourtois et al., 2005; Turetsky et al., 2007; Vuilleumier et al., 2003; Winston et al., 2003). Thus, sensory characteristics mediated by the M-pathway may underlie emotion differentiation at this early stage of processing. Difficulty in the accurate extraction of M-pathway information may ultimately result in atypical P1 modulation to emotion in patients. This may be most pronounced in response to the low contrast manipulation that emphasizes the M-pathway in the present study. Indeed, the P1 can be modulated both by direct M-stream input into the dorsal stream (Butler et al., 2007) and by fast M-stream input via tecto-pulvinar projections to the amygdala which then feedback to extrastriate visual areas (Aggleton et al., 1980; Amaral et al., 2003; Cowey & Stoerig, 1991; Morris et al., 2001; Morris et al., 1998, 1999; Vuilleumier et al., 2003; Winston et al., 2003). This study however, cannot determine through which pathway (if not both), processing breaks down in schizophrenia when viewing face emotion stimuli.

N170 contrast response functions showed a linear relationship in patients and controls, similar to P-pathway functions. Indeed, the N170 is thought to have a generator in the ventral stream (e.g., fusiform gyrus) (Herrmann et al., 2005; Shibata et al., 2002) which is known to receive P-stream inputs (Schroeder et al., 1998). In addition, similar to Streit et al. (2001), Wynn et al (2008) and Butler et al., (2007), we did not find an N170 deficit in amplitude when comparing patients to controls (but see (Caharel et al., 2007; Campanella et al., 2006; Johnston et al., 2005; Lee, Gosselin et al., 2010; Turetsky et al., 2007)). The majority of studies looking at non-face stimuli also show normal N1 amplitudes in schizophrenia (Doniger et al., 2002; Foxe et al., 2001; Sehatpour et al., 2010). The intact N170 to face emotion stimuli in the present study, like the N1 to non-face stimuli, may reflect preserved initial P-stream input to the ventral stream (e.g. fusiform gyrus) in schizophrenia.

Further, similar to previous results in controls, the N170 was influenced by emotion (at all contrasts) (Batty & Taylor, 2003; Blau et al., 2007; Caharel et al., 2007; Caharel et al., 2005; Campanella et al., 2006; Campanella et al., 2002; Williams et al., 2006), supporting a role for the N170 in affect modulation rather than simply in structural encoding of facial features. However, differential emotion response profiles were elicited in patients versus controls, as has previously been demonstrated (Lynn & Salisbury, 2008; Turetsky et al., 2007). The aberrant pattern of N170 modulation in patients could be due to impaired M-stream input to both, ventral stream areas via dorsal stream crossover (as is thought to underlie object processing deficits in schizophrenia, see Sehatpour et al., 2010), and the amygdala which heavily projects to and influences fusiform gyrus, a possible generator of the N170 component (Fukuda et al., 1987; Iwai et al., 1987; Iwai et al., 1990; Spiegler & Mishkin, 1981).

The affect-related P250 discriminated among emotions in both groups in all conditions, even at low-contrasts, supporting previous data indicating that emotion discrimination is in-part reliant on M-mediated information (Calder et al., 2000; Schyns & Oliva, 1999). The underlying neural mechanisms of the P250 have not been thoroughly addressed in the emotion processing literature. Recent data suggest that in addition to possible rapid discrimination of emotions at the level of P1, projections from ventral visual areas feedback onto extrastriate cortices at later time-points in the visual processing pathway in order to assist in the differentiation of emotions (Freese & Amaral, 2005; Sabatinelli et al., 2009; Vuilleumier et al., 2004). The P250 may represent this recursive visual cortical processing that enhances saliency of emotional stimuli (Sabatinelli et al., 2009). However, the P250 amplitude was shown to be reduced in patients at each contrast and for each emotion. The deficit seen in patients at low-contrast and the significant relationship between P1 and P250 components, which was absent between N170 and P250 components, supports the hypothesis that early sensory deficits involving the M/dorsal pathway contribute to later emotion processing dysfunction.

Lastly, across groups, the dorsal P1 predicted behavior at low-contrasts and the P250 predicted performance at the lowest contrast[4]. Alternatively, the N170 was only associated with behavioral performance in patients. This suggested the emotion recognition network heavily depended on M-pathway input to the dorsal stream (P1) while the network in patients additionally relied on ventral stream activity (N170). Relationships between ERP components and behavior in the present study highlight the importance of processing at an early stage (i.e., the P1) in the ability to identify emotion.

In conclusion, the finding of impaired P1 amplitude in schizophrenia to face emotion stimuli and its relationship to later P250 amplitudes and poor behavioral performance provides evidence that deficits in emotion recognition in schizophrenia occur at an early stage of visual processing. Further, the P1 contrast response functions showed M-pathway characteristics and the initial steep slope and plateau of response was impaired in patients. This pattern of response suggests that the reduced P1 amplitude is at least in-part due to M-dysfunction in schizophrenia. Further, a normal N170 suggests that P-pathway input to the ventral stream is preserved in patients. Therefore, impaired low-level dorsal stream activity, along with a significant relationship between the P1 and P250 amplitudes and P1 and behavioral performance suggest M/dorsal stream

---

[4] Relationships between P1 and behavioral performance during the 57% contrast condition may not have been found due to ceiling effects during emotion recognition in controls.

involvement in emotion perception deficits and indicate the importance of early deficits for later emotion processing ability.

Experiment 3 examined the spatial-temporal oscillatory dynamics in schizophrenia patients, compared to healthy individuals, during processing of complex visual stimuli. Visual perceptual dysfunction is considered a core pathology in schizophrenia and has most notably been documented as impairments in behavioral and visually-evoked potential paradigms. We evaluated delta, theta and alpha activity in patients with schizophrenia as these have not been fully explored during visual perceptual paradigms within the schizophrenia literature, but have been found to be important for proper perception.

We evaluated activity in the FFT-spectrum and assessed differences in the putative underlying generators of the delta, theta and alpha oscillatory frequencies. Further, we examined activity in the pre and post-stimulus intervals, and the ratio between them (so-called ERS and/or ERD), and investigated whether there were significant relationships between these measures and clinical ratings in patients.

The findings revealed that patients had significantly greater delta-band activity during the pre and post-stimulus intervals compared to healthy controls. Further, while we observed that both groups displayed an ERS effect (~30%), the difference in this measure was not found to be significant between them. Indeed, higher delta-band power in patients has been previously observed during resting states and cognitive-type tasks that do not involve active processing of sensory stimuli (e.g. Fehr et al., 2003; Knott et al., 2001; Sponheim et al., 1994). Our data replicate and further extend these findings by revealing their existence during an active visual sensory processing. It is possible that this delta-band effect may be a by-product of general increased activations (not necessarily in-phase) within and across cortical areas.

The FFT-profiles in the anterior cortices revealed a strong peak in theta-band activity in patients but not in controls. This peak activity was found to be trending towards significance (p-value = .052), and slighted lateralized towards the right hemisphere. Moreover, the data revealed significant differences in the topographical distributions in the theta-band, whereby patients displayed an additional voltage distribution over central-posterior sites in addition to the bilateral voltage peaks over midline/frontal scalp areas (see Figure 3b). This topographical difference is important because it suggests that patients engage a different set of neural populations, compared to controls, to give rise to theta-band oscillatory activity.

Our results found a trend towards significance in the pre and post-stimulus intervals, whereby patients displayed greater theta-band activity than controls. Yet, we observed that neither patients nor controls exhibited an ERD/ERS, suggesting that theta-band mechanisms may not have been selectively engaged during stimulus processing in our task. It is plausible that similar to the findings in the delta-band, our measure of theta-band activity might represent a general (i.e. non-specific) effect of ongoing activations in the patient population.

The FFT-profiles in the posterior cortices revealed a strong peak in the alpha band activity in controls but not in patients. The activity within this band was found to be significantly greater in controls and lateralized towards the right hemisphere. Furthermore, and similar to the findings in the theta-band, the data revealed significant differences in the topographical distributions in this frequency band. This topographical difference was mainly driven by the greater distribution of alpha-power over posterior cortices, which was virtually absent in patients. This lateralized alpha topography map, which we and others term as ‘phasic’ alpha, has been observed in many different tasks and it is believed to index a specific mode of sensory processing related to suppression and/or enhancement of sensory inputs (see Gomez-Ramirez et al 2009). Phasic alpha-activity (which encompasses the ERD effect) refers to modulations over much shorter timeframes (e.g. < 1000 ms) and it occurs in response to specific sensory stimuli that need to be further processed or suppressed. Indeed, patients do not exhibit the typical alpha-band topographical distribution and have significantly reduced ERD activity compared to controls. Clearly, these findings have significant implications in the sensory processing deficits in schizophrenia patients, which we describe below.

Studies in healthy controls have repeatedly demonstrated ERD in response to visual stimuli, which is maximal over extrastriate sites around 200-300 ms (Neuper et al., 2006; Pfurtscheller & Neuper, 2006; Pfurtscheller et al., 1994; Thut et al., 2006). This ERD effect following visual stimulation is thought to reflect the release of neural inhibition, resulting in cortical activation allowing visual areas to process incoming stimuli (Klimesch et al., 2007). In this way, researchers have suggested that alpha-band activity is a sensory gating mechanism, helping rout information throughout the sensory processing stream via active cortical inhibition and dis-inhibition of relevant neural regions (Jensen & Mazaheri, 2010). Accordingly, visual alpha desynchronization appears to be an example of gain control. Indeed, patients with schizophrenia have repeatedly demonstrated gain control deficits in behavioral center-surround experiments (see Dakin et al., 2005), and in magocellular-biased steady-state and transient visual evoked potential contrast response functions (see Butler, Zemon et al., 2005). Gain control mechanisms underlying magnocellular pathway responses and alpha-band activity in general are both thought to be mediated by the interplay of excitatory glutamate neurotransmitters/N-methyl d-aspartate (NMDA) receptors (Daw et al., 1993; Fox et al., 1990; Kwon et al., 1992), and inhibitory GABAergic interneurons (Lisman et al., 2008). Taken together, the lack of alpha desynchronization at extrastriate electrode sites in patients appears to be another example of dysfunctional gain control mechanisms that contributes to abnormal visual perceptual.

In conclusion, induced delta activity was seen to be abnormally larger in patients versus controls during pre- and post-stimulus intervals. Conversely, patients exhibited comparable delta-band ERS to controls. This suggests that the impairment in patients is based on elevated ongoing activity, possibly reflective of general cognitive decline, or a general failure in overall cortical suppression in the patient population. Further, patients exhibited a trend towards theta-band activity being greater versus controls, and topographic distribution of this rhythm was significantly altered, suggestive of theta-cortical generator abnormalities. Lastly, patients exhibited a significant deficit in visual alpha-desynchronization. Accordingly, patients showed a significantly altered topographic distribution of their alpha-band activity, suggesting impaired neural generation of these rhythms that may result in their abnormal instantaneous activity. The current finding provides another example of gain control deficits in patients with schizophrenia that may ultimately contribute to low-level visual processing dysfunction.

Conclusion

The current findings within this dissertation add to the growing literature regarding visual perceptual deficits in schizophrenia, and their relation to higher-order cognitive deficits. While the bulk of previous schizophrenia literature focused on cognitive dysfunction being a consequence of only executive-level neural functions such as attention and working memory, the bottom-up model for cognitive dysfunction cannot be ignored. This dissertation demonstrated that there are indeed lower-level deficits at the very beginning stages of visual processing, as indicated by magnocellular pathway dysfunction. Deficits were not localized to sub-cortical streams however, but extended to cortical visual areas, with impairments seen in the time, frequency and time-frequency domains. Both the stunted contrast response functions seen in patients for the P1 component, and the attenuated alpha desynchronization at the same electrode locations support previous evidence that patients with schizophrenia have visual gain control impairments, which ultimately contribute to abnormal visual perception. Further, results from Experiment 2 showed that dorsal-stream impairments (i.e. reduced gain control ability) had negative implications for higher-level more complex processes like emotion recognition, providing evidence that higher-order dysfunction is based on abnormal lower-level perceptual processes.

Neural mechanisms involving glutamatergic (NMDA receptor mediated) excitatory neurons and GABAergic inhibitory interneurons are not only thought to underlie low-level M-pathway dysfunction that leads to abnormal contrast threshold performance and P1 responses, but they are implicated in abnormal oscillatory activity that was exhibited in patients in Experiment 3. Taken together, altered neurotransmission involving these cell-types may be at the heart of low-level perceptual and higher-order cognitive deficits at several levels throughout the neural processing stream within the schizophrenia population. Future medications targeting these neurotransmitters and their receptor complexes may help ameliorate the more elusive perceptual and cognitive symptomatology.

APPENDIX
(Figures for introduction and discussion chapters)

Figure 1: Schematic diagram of the primate visual system. Magnocellular (M) system is shown in red. Parvocellular (P) system is shown in blue. Yellow: Dorsal stream ("where" system). Green: Ventral stream ("what" system)

Figure 2: Examples of spatial frequency gratings processed by different visual pathways. Left: Low-spatial frequency (LSF) grating against a controlled luminance background. LSFs are processed by the magnocellular pathway. Right: High-spatial frequency (HSF) grating against a controlled luminance background. HSFs are processed by the parvocellular pathway

Figure 3: Left panel shows high spatial frequency information, center panel is intact, and right panel shows low spatial frequency information (Bar, 2003).

Figure 4: (A) Contrast response functions recorded in Macaque monkey retinal ganglion cells (Kaplan and Shapley, 1986). The initial gain of the M cells is the straight line derived from the M-cell curve. The initial gain is a steep slope in response to increases in low-contrast stimuli. At higher contrasts, the response of the M cell plateaus. The gain of the P cells is the line fitted to the P-cell function. (B) NMDA antagonists produce shallower gain at low contrast and a lower response plateau (Kwon et al., 1992). (C, D) Human responses to M- and P- biased (Butler et al., 2005) stimuli that mirror responses recorded in animal physiological studies. Black squares represent healthy controls and open circles represent patients with schizophrenia.

Figure 5: From Butler et al., (2005). Example of a contrast sensitivity/threshold response curve. The contrast needed to accurately detect the spatial frequency grating is evaluated and then plotted. Spatial frequency (from low to high) is plotted along the x-axis, and contrast sensitivity and/or threshold is plotted the dependent measure and plotted on the

y-axis. LSFs are thought to bias processing towards the M-pathway and HSFs are thought to bias processing towards the P-pathway.

Figure 6: From Butler et al. (2007). Group-averaged voltage waveforms for controls (n = 16) and patients (n = 18) in response to low spatial frequency (1 c/deg) (left) and high spatial frequency (5 c/deg) (right) gratings. Controls exhibited a P1 over dorsal occipital sites in both LSF (left) and HSF (right) conditions. Patients however, demonstrated an abnormal P1 in response to the LSF stimuli, while their P1 in response to HSF stimuli remained intact. This indicated that dorsal stream dysfunction found in patients with schizophrenia was an input problem from the magnocellular stream.

<u>Figure 1:</u>
Schematic of the visual system

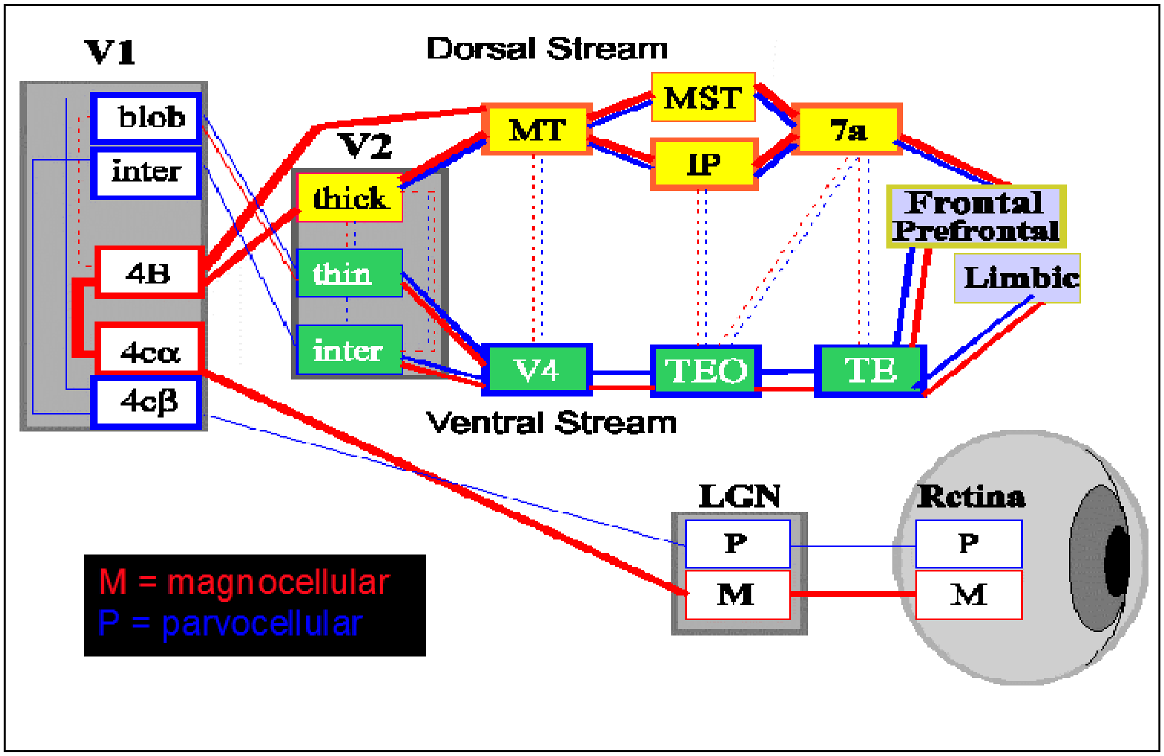


Figure 2:
Examples of spatial frequency

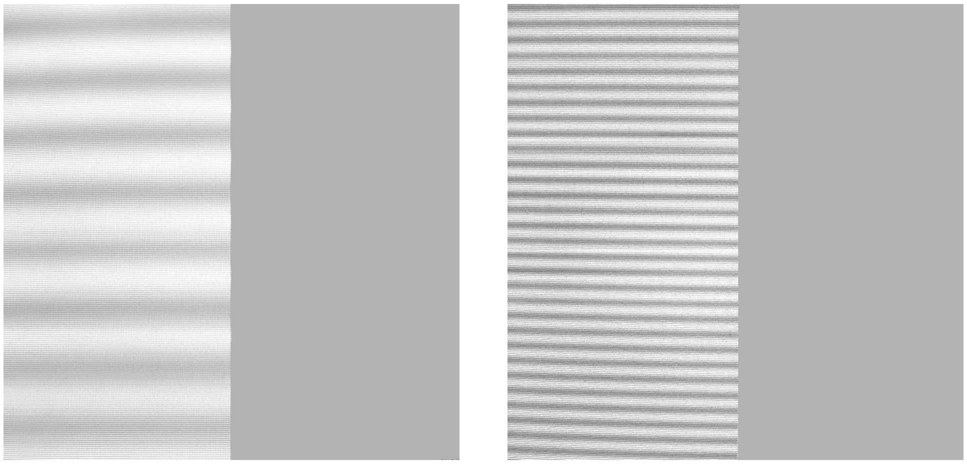


Figure 3:
Examples of spatial frequency filtering

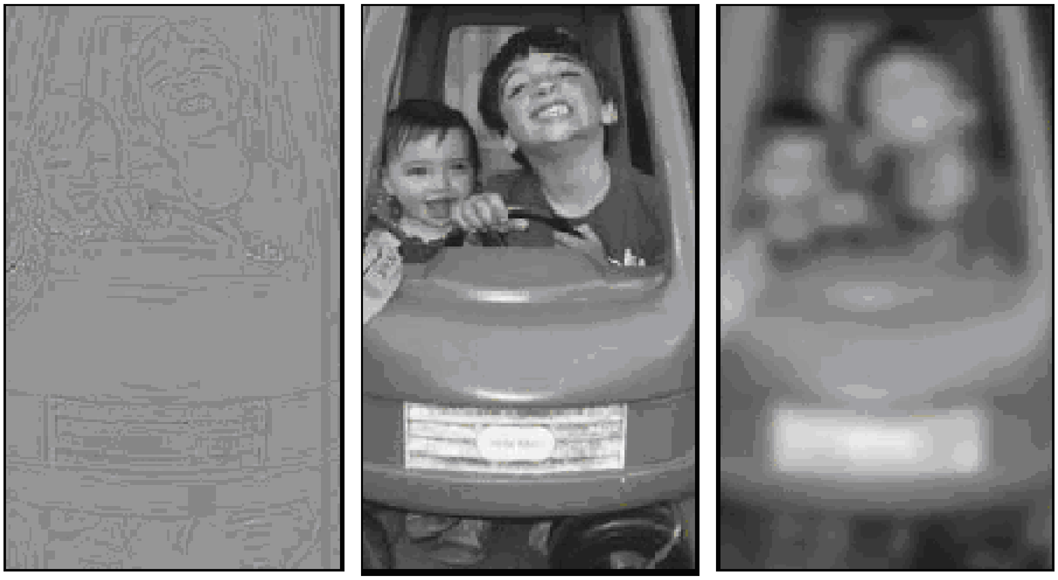


Figure 4:
Contrast response functions

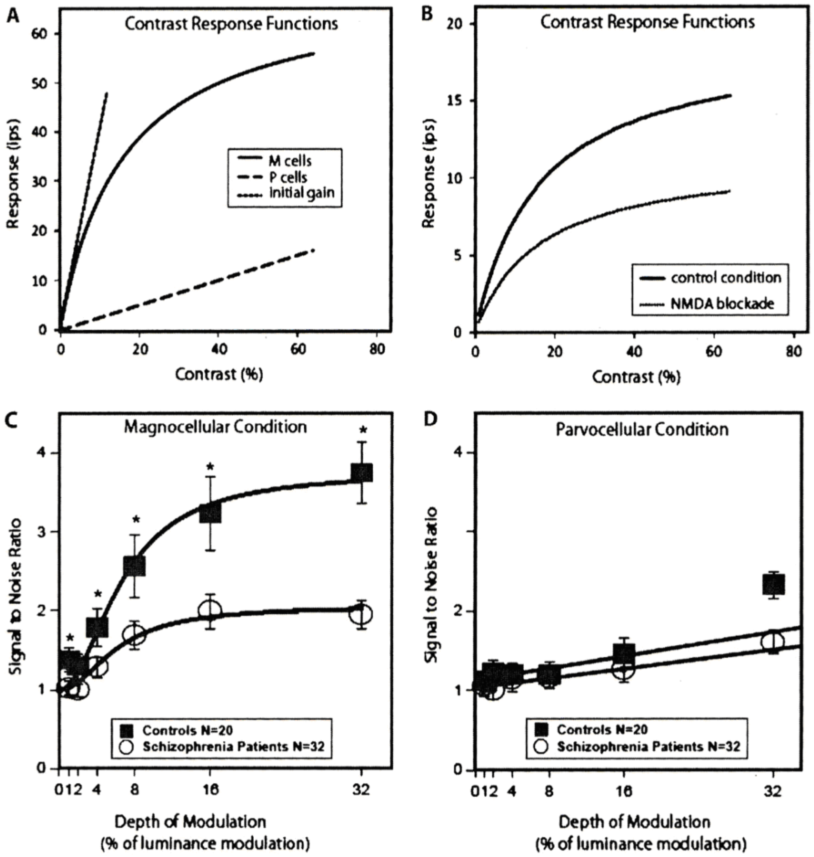


Figure 5:
Contrast sensitivity/threshold curves

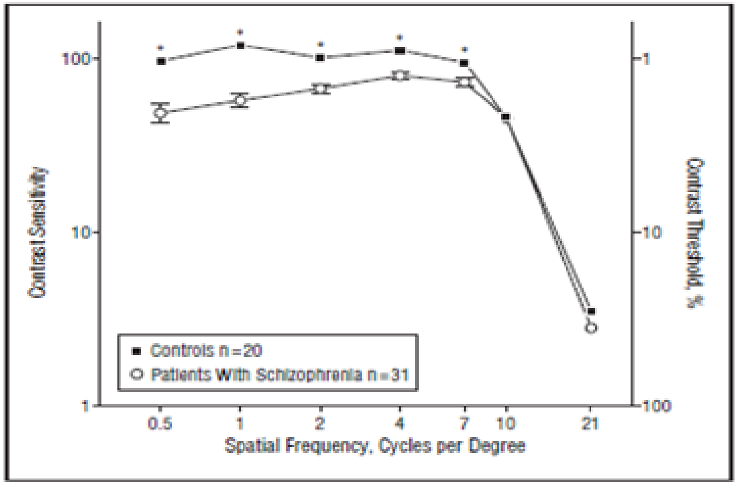
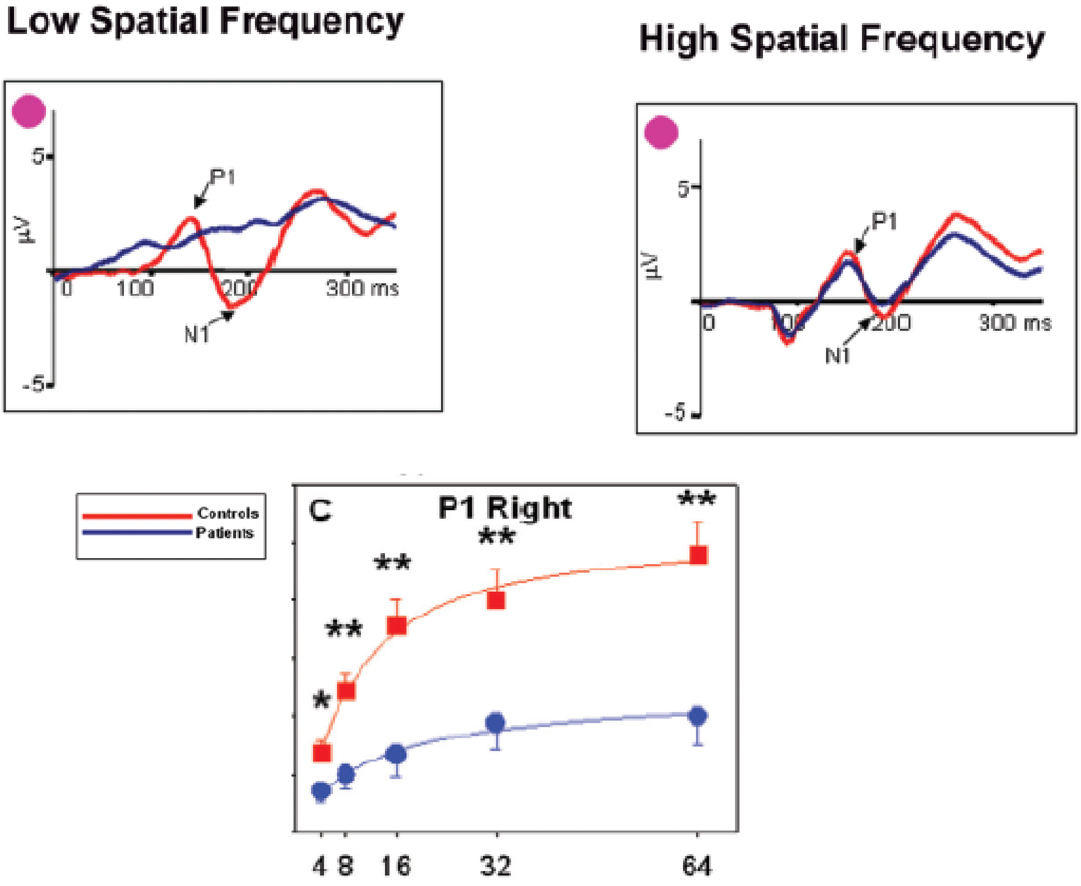


Figure 6:
Cortical responses to M- versus P-biased stimuli



BIBLIOGRAPHY

CHAPTER 1 (Introduction) and CHAPTER 5 (Discussion)

Abd-El-Barr, M. M., Pennesi, M. E., Saszik, S. M., Barrow, A. J., Lem, J., Bramblett, D. E., et al. (2009). Genetic dissection of rod and cone pathways in the dark-adapted mouse retina. *J Neurophysiol, 102*(3), 1945-1955.

Addington, J., & Addington, D. (1998). Facial affect recognition and information processing in schizophrenia and bipolar disorder. *Schizophr Res, 32*(3), 171-181.

Adolphs, R. (2002). Recognizing emotion from facial expressions: psychological and neurological mechanisms. *Behav Cogn Neurosci Rev, 1*(1), 21-62.

Adolphs, R., Tranel, D., & Buchanan, T. W. (2005). Amygdala damage impairs emotional memory for gist but not details of complex stimuli. *Nat Neurosci, 8*(4), 512-518.

Aggleton, J. P., Burton, M. J., & Passingham, R. E. (1980). Cortical and subcortical afferents to the amygdala of the rhesus monkey (Macaca mulatta). *Brain Res, 190*(2), 347-368.

Aghevli, M. A., Blanchard, J. J., & Horan, W. P. (2003). The expression and experience of emotion in schizophrenia: a study of social interactions. *Psychiatry Res, 119*(3), 261-270.

Alegre, M., de Gurtubay, I. G., Labarga, A., Iriarte, J., Malanda, A., & Artieda, J. (2004). Alpha and beta oscillatory activity during a sequence of two movements. *Clin Neurophysiol, 115*(1), 124-130.

Allison, T., Puce, A., Spencer, D., & McCarthy, G. (1999). Electrophysiological studies of human face perception I: potentials generated in occipitotemporal cortex by face and non-face stimuli. *Cerebral Cortex, 9*, 415-430.

Alorda, C., Serrano-Pedraza, I., Campos-Bueno, J. J., Sierra-Vazquez, V., & Montoya, P. (2007). Low spatial frequency filtering modulates early brain processing of affective complex pictures. *Neuropsychologia, 45*(14), 3223-3233.

Amaral, D. G., Behniea, H., & Kelly, J. L. (2003). Topographic organization of projections from the amygdala to the visual cortex in the macaque monkey. *Neuroscience, 118*(4), 1099-1120.

Anderson, A. K., Christoff, K., Panitz, D., De Rosa, E., & Gabrieli, J. D. (2003). Neural correlates of the automatic processing of threat facial signals. *J Neurosci, 23*(13), 5627-5633.

Ashley, V., Vuilleumier, P., & Swick, D. (2004). Time course and specificity of event-related potentials to emotional expressions. *Neuroreport, 15*(1), 211-216.

Atallah, B. V., & Scanziani, M. (2009). Instantaneous modulation of gamma oscillation frequency by balancing excitation with inhibition. *Neuron, 62*(4), 566-577.

Balconi, M., & Pozzoli, U. (2003). Face-selective processing and the effect of pleasant and unpleasant emotional expressions on ERP correlates. *Int J Psychophysiol, 49*(1), 67-74.

Bar, M., Kassam, K. S., Ghuman, A. S., Boshyan, J., Schmid, A. M., Dale, A. M., et al. (2006). Top-down facilitation of visual recognition. *Proc Natl Acad Sci U S A, 103*(2), 449-454.

Bar, M., Neta, M., & Linz, H. (2006). Very first impressions. *Emotion, 6*(2), 269-278.

Basar-Eroglu, C., Brand, A., Hildebrandt, H., Karolina Kedzior, K., Mathes, B., & Schmiedt, C. (2007). Working memory related gamma oscillations in schizophrenia patients. *Int J Psychophysiol, 64*(1), 39-45.

Basar-Eroglu, C., Schmiedt-Fehr, C., Marbach, S., Brand, A., & Mathes, B. (2008). Altered oscillatory alpha and theta networks in schizophrenia. *Brain Res, 1235*, 143-152.

Basar, E., & Schurmann, M. (1994). Functional aspects of evoked alpha and theta responses in humans and cats. Occipital recordings in "cross modality" experiments. *Biol Cybern, 72*(2), 175-183.

Bassi, C. J., & Lehmkuhle, S. (1990). Clinical implications of parallel visual pathways. *J Am Optom Assoc, 61*(2), 98-110.

Bates, A. T., Kiehl, K. A., Laurens, K. R., & Liddle, P. F. (2009). Low-frequency EEG oscillations associated with information processing in schizophrenia. *Schizophr Res, 115*(2-3), 222-230.

Battaglia, F. P., Sutherland, G. R., & McNaughton, B. L. (2004). Hippocampal sharp wave bursts coincide with neocortical "up-state" transitions. *Learn Mem, 11*(6), 697-704.

Batty, M., & Taylor, M. J. (2003). Early processing of the six basic facial emotional expressions. *Brain Res Cogn Brain Res, 17*(3), 613-620.

Benedek, G., Benedek, K., Keri, S., & Janaky, M. (2003). The scotopic low-frequency spatial contrast sensitivity develops in children between the ages of 5 and 14 years. *Neurosci Lett, 345*(3), 161-164.

Bentin, S., & Deouell, L. Y. (2000). Structural encoding and identification in face processing: erp evidence for separate mechanisms. *Cogn Neuropsychol, 17*(1), 35-55.

Bentin, S., Mouchetant-Rostaing, Y., Giard, M. H., Echallier, J. F., & Pernier, J. (1999). ERP manifestations of processing printed words at different psycholinguistic levels: time course and scalp distribution. *Journal of Cognitive Neuroscience, 11*, 235-260.

Berenbaum, H., & Oltmanns, T. F. (1992). Emotional experience and expression in schizophrenia and depression. *J Abnorm Psychol, 101*(1), 37-44.

Berlin, I., Givry-Steiner, L., Lecrubier, Y., & Puech, A. J. (1998). Measures of anhedonia and hedonic responses to sucrose in depressive and schizophrenic patients in comparison with healthy subjects. *Eur Psychiatry, 13*(6), 303-309.

Blau, V. C., Maurer, U., Tottenham, N., & McCandliss, B. D. (2007). The face-specific N170 component is modulated by emotional facial expression. *Behav Brain Funct, 3*, 7.

Bleuler, E. (1950). *Dementia praecox of the group of schizophrenias*. New York: International Universities Press.

Braff, D. L. (1981). Impaired speed of information processing in nonmedicated schizotypal patients. *Schizophr Bull, 7*(3), 499-508.

Braff, D. L., & Saccuzzo, D. P. (1985). The time course of information-processing deficits in schizophrenia. *Am J Psychiatry, 142*(2), 170-174.

Breitmeyer, B., & Ganz, L. (1976). Implications of sustained and transient channels for theories of visual pattern masking, saccadic suppression and information processing. *Psychological Review, 83*, 1-36.

Breitmeyer, B. G., & Williams, M. C. (1990). Effects of isoluminant-background color on metacontrast and stroboscopic motion: interactions between sustained (P) and transient (M) channels. *Vision Res, 30*(7), 1069-1075.

Brenner, C. A., Lysaker, P. H., Wilt, M. A., & O'Donnell, B. F. (2002). Visual processing and neuropsychological function in schizophrenia and schizoaffective disorder. *Psychiatry Res, 111*(2-3), 125-136.

Bruder, G., Kayser, J., Tenke, C., Rabinowicz, E., Friedman, M., Amador, X., et al. (1998). The time course of visuospatial processing deficits in schizophrenia: an event-related brain potential study. *J Abnorm Psychol, 107*(3), 399-411.

Burbridge, J. A., & Barch, D. M. (2007). Anhedonia and the experience of emotion in individuals with schizophrenia. *J Abnorm Psychol, 116*(1), 30-42.

Busch, N. A., Debener, S., Kranczioch, C., Engel, A. K., & Herrmann, C. S. (2004). Size matters: effects of stimulus size, duration and eccentricity on the visual gamma-band response. *Clin Neurophysiol, 115*(8), 1810-1820.

Butler, P. D. (2007). Visual processing and emotion perception in schizophrenia. *ACNP abstract*.

Butler, P. D., Abeles, I. Y., Weiskopf, N. G., Tambini, A., Jalbrzikowski, M., Legatt, M. E., et al. (2009). Sensory contributions to impaired emotion processing in schizophrenia. *Schizophr Bull, 35*(6), 1095-1107.

Butler, P. D., DeSanti, L. A., Maddox, J., Harkavy-Friedman, J. M., Amador, X. F., Goetz, R. R., et al. (2002). Visual backward-masking deficits in schizophrenia: relationship to visual pathway function and symptomatology. *Schizophr Res, 59*(2-3), 199-209.

Butler, P. D., Harkavy-Friedman, J. M., Amador, X. F., & Gorman, J. M. (1996). Backward masking in schizophrenia: relationship to medication status, neuropsychological functioning, and dopamine metabolism. *Biol Psychiatry, 40*(4), 295-298.

Butler, P. D., Kim, D., Foxe, J. J., Piesco, J. R., Hoptman, M. J., Lim, K. O., et al. (2004). Decreased signal amplification in schizophrenia: evidence from visual studies. *Society for Neuroscience Abstracts*, Program No. 348.341.

Butler, P. D., Martinez, A., Foxe, J. J., Kim, D., Zemon, V., Silipo, G., et al. (2007). Subcortical visual dysfunction in schizophrenia drives secondary cortical impairments. *Brain, 130*, 417-430.

Butler, P. D., Schechter, I., Zemon, V., Schwartz, S. G., Greenstein, V. C., Gordon, J., et al. (2001). Dysfunction of early stage visual processing in schizophrenia. *Am J Psychiatry, 158*(7), 1126-1133.

Butler, P. D., Silverstein, S. M., & Dakin, S. C. (2008). Visual perception and its impairment in schizophrenia. *Biol Psychiatry, 64*(1), 40-47.

Butler, P. D., Tambini, A., Yovel, G., Jalbrzikowski, M., Ziwich, R., Silipo, G., et al. (2008). What's in a face? Effects of stimulus duration and inversion on face processing in schizophrenia. *Schizophr Res*.

Butler, P. D., Zemon, V., Schechter, I., Saperstein, A. M., Hoptman, M. J., Lim, K. O., et al. (2005). Early-stage visual processing and cortical amplification deficits in schizophrenia. *Arch Gen Psychiatry, 62*(5), 495-504.

Buzsaki, G., & Draguhn, A. (2004). Neuronal oscillations in cortical networks. *Science, 304*(5679), 1926-1929.

Cadenhead, K. S., Serper, Y., & Braff, D. L. (1998). Transient versus sustained visual channels in the visual backward masking deficits of schizophrenia patients. *Biol Psychiatry, 43*(2), 132-138.

Caharel, S., Bernard, C., Thibaut, F., Haouzir, S., Di Maggio-Clozel, C., Allio, G., et al. (2007). The effects of familiarity and emotional expression on face processing examined by ERPs in patients with schizophrenia. *Schizophr Res, 95*(1-3), 186-196.

Caharel, S., Courtay, N., Bernard, C., Lalonde, R., & Rebai, M. (2005). Familiarity and emotional expression influence an early stage of face processing: an electrophysiological study. *Brain Cogn, 59*(1), 96-100.

Calder, A. J., Rowland, D., Young, A. W., Nimmo-Smith, I., Keane, J., & Perrett, D. I. (2000). Caricaturing facial expressions. *Cognition, 76*(2), 105-146.

Campanella, S., Montedoro, C., Streel, E., Verbanck, P., & Rosier, V. (2006). Early visual components (P100, N170) are disrupted in chronic schizophrenic patients: an event-related potentials study. *Neurophysiol Clin, 36*(2), 71-78.

Campanella, S., Quinet, P., Bruyer, R., Crommelinck, M., & Guerit, J. M. (2002). Categorical perception of happiness and fear facial expressions: an ERP study. *J Cogn Neurosci, 14*(2), 210-227.

Carretie, L., Martin-Loeches, M., Hinojosa, J. A., & Mercado, F. (2001). Emotion and attention interaction studied through event-related potentials. *J Cogn Neurosci, 13*(8), 1109-1128.

Carretie, L., Mercado, F., Tapia, M., & Hinojosa, J. A. (2001). Emotion, attention, and the 'negativity bias', studied through event-related potentials. *Int J Psychophysiol, 41*(1), 75-85.

Castner, S. A., Williams, G. V., & Goldman-Rakic, P. S. (2000). Reversal of antipsychotic-induced working memory deficits by short-term dopamine D1 receptor stimulation. *Science, 287*(5460), 2020-2022.

Cattapan-Ludewig, K., Hilti, C. C., Ludewig, S., Vollenweider, F. X., & Feldon, J. (2005). Rapid visual information processing in schizophrenic patients: the impact of cognitive load and duration of stimulus presentation. A pilot study. *Neuropsychobiology, 52*(3), 130-134.

Chen, Y., Nakayama, K., Levy, D., Matthysse, S., & Holzman, P. (2003). Processing of global, but not local, motion direction is deficient in schizophrenia. *Schizophr Res, 61*(2-3), 215-227.

Colgin, L. L., Denninger, T., Fyhn, M., Hafting, T., Bonnevie, T., Jensen, O., et al. (2009). Frequency of gamma oscillations routes flow of information in the hippocampus. *Nature, 462*(7271), 353-357.

Cowey, A., & Stoerig, P. (1991). The neurobiology of blindsight. *Trends Neurosci, 14*(4), 140-145.

Daitch, J. M., & Green, D. G. (1969). Contrast sensitivity of the human peripheral retina. *Vision Res, 9*(8), 947-952.

Dakin, S., Carlin, P., & Hemsley, D. (2005). Weak suppression of visual context in chronic schizophrenia. *Curr Biol, 15*(20), R822-824.

Das, P., Kemp, A. H., Flynn, G., Harris, A. W., Liddell, B. J., Whitford, T. J., et al. (2007). Functional disconnections in the direct and indirect amygdala pathways for fear processing in schizophrenia. *Schizophr Res, 90*(1-3), 284-294.

Davis, K. L., Kahn, R. S., Ko, G., & Davidson, M. (1991). Dopamine in schizophrenia: a review and reconceptualization. *Am J Psychiatry, 148*(11), 1474-1486.

Daw, N. W., Stein, P. S. G., & Fox, K. (1993). The role of NMDA receptors in information processing. *Ann Rev Neurosci, 16*, 207-222.

Delay, J., Deniker, P., & Ropert, R. (1956a). [Four years of experience with chlorpromazine in therapy of psychoses]. *Presse Med, 64*(22), 493-496.

Delay, J., Deniker, P., & Ropert, R. (1956b). [Study of 300 case histories of psychotic patients treated with chlorpromazine in closed wards since 1952]. *Encephale, 45*(4), 528-535.

Derrington, A. M., & Lennie, P. (1984). Spatial and temporal contrast sensitivities of neurones in lateral geniculate nucleus of macaque. *J Physiol, 357*, 219-240.

Doege, K., Kumar, M., Bates, A. T., Das, D., Boks, M. P., & Liddle, P. F. (2010). Time and frequency domain event-related electrical activity associated with response control in schizophrenia. *Clin Neurophysiol, 121*(10), 1760-1771.

Doniger, G. M., Foxe, J. J., Murrary, M. M., Higgins, B. A., & Javitt, D. C. (2002). Impaired visual object recogntion and dorsal/ventral stream interaction in schizophrenia. *Arch Gen Psychiatry, 59*, 1011-1020.

Doniger, G. M., Foxe, J. J., Murray, M. M., Higgins, B. A., Snodgrass, J. G., Schroeder, C. E., et al. (2000). Activation timecourse of ventral visual stream object-recognition areas: high density electrical mapping of perceptual closure processes. *J Cogn Neurosci, 12*(4), 615-621.

Dorph-Petersen, K. A., Pierri, J. N., Perel, J. M., Sun, Z., Sampson, A. R., & Lewis, D. A. (2005). The influence of chronic exposure to antipsychotic medications on brain size before and after tissue fixation: a comparison of haloperidol and olanzapine in macaque monkeys. *Neuropsychopharmacology, 30*(9), 1649-1661.

Dragoi, G., & Buzsaki, G. (2006). Temporal encoding of place sequences by hippocampal cell assemblies. *Neuron, 50*(1), 145-157.

Edwards, J., Jackson, H. J., & Pattison, P. E. (2002). Emotion recognition via facial expression and affective prosody in schizophrenia: a methodological review. *Clin Psychol Rev, 22*, 789-832.

Eger, E., Jedynak, A., Iwaki, T., & Skrandies, W. (2003). Rapid extraction of emotional expression: evidence from evoked potential fields during brief presentation of face stimuli. *Neuropsychologia, 41*(7), 808-817.

Eimer, M., & Holmes, A. (2002). An ERP study on the time course of emotional face processing. *Neuroreport, 13*(4), 427-431.

Ergen, M., Marbach, S., Brand, A., Basar-Eroglu, C., & Demiralp, T. (2008). P3 and delta band responses in visual oddball paradigm in schizophrenia. *Neurosci Lett, 440*(3), 304-308.

Fehr, T., Kissler, J., Wienbruch, C., Moratti, S., Elbert, T., Watzl, H., et al. (2003). Source distribution of neuromagnetic slow-wave activity in schizophrenic patients--effects of activation. *Schizophr Res, 63*(1-2), 63-71.

Feinberg, T. E., Rifkin, A., Schaffer, C., & Walker, E. (1986). Facial discrimination and emotional recognition in schizophrenia and affective disorders. *Arch Gen Psychiatry, 43*(3), 276-279.

Ferman, T. J., Primeau, M., Delis, D., & Jampala, C. V. (1999). Global-local processing in schizophrenia: hemispheric asymmetry and symptom-specific interference. *J Int Neuropsychol Soc, 5*(5), 442-451.

Fernandez-Bouzas, A., Harmony, T., Bosch, J., Aubert, E., Fernandez, T., Valdes, P., et al. (1999). Sources of abnormal EEG activity in the presence of brain lesions. *Clin Electroencephalogr, 30*(2), 46-52.

Fox, K., Sato, H., & Daw, N. (1990). The effect of varying stimulus intensity on NMDA-receptor activity in cat visual cortex. *J Neurophysiol, 64*(5), 1413-1428.

Foxe, J. J., Doniger, G. M., & Javitt, D. C. (2001). Early visual processing deficits in schizophrenia: impaired PI generation revealed by high-density electrical mapping. *NeuroReport, 12*(17).

Foxe, J. J., Murray, M. M., & Javitt, D. C. (2005). Filling-in in Schizophrenia: a High-density Electrical Mapping and Source-analysis Investigation of Illusory Contour Processing. *Cereb Cortex, 15*(12), 1914-1927.

Foxe, J. J., Simpson, G. V., & Ahlfors, S. P. (1998). Parieto-occipital approximately 10 Hz activity reflects anticipatory state of visual attention mechanisms. *Neuroreport, 9*(17), 3929-3933.

Freese, J. L., & Amaral, D. G. (2005). The organization of projections from the amygdala to visual cortical areas TE and V1 in the macaque monkey. *J Comp Neurol, 486*(4), 295-317.

Fries, P., Reynolds, J. H., Rorie, A. E., & Desimone, R. (2001). Modulation of oscillatory neuronal synchronization by selective visual attention. *Science, 291*(5508), 1560-1563.

Friston, K. J. (1999). Schizophrenia and the disconnection hypothesis. *Acta Psychiatr Scand Suppl, 395*, 68-79.

Frith, C. D., Stevens, M., Johnstone, E. C., Owens, D. G., & Crow, T. J. (1983). Integration of schematic faces and other complex objects in schizophrenia. *J Nerv Ment Dis, 171*(1), 34-39.

Fukuda, M., Ono, T., & Nakamura, K. (1987). Functional relations among inferotemporal cortex, amygdala, and lateral hypothalamus in monkey operant feeding behavior. *J Neurophysiol, 57*(4), 1060-1077.

Gallinat, J., Winterer, G., Herrmann, C. S., & Senkowski, D. (2004). Reduced oscillatory gamma-band responses in unmedicated schizophrenic patients indicate impaired frontal network processing. *Clin Neurophysiol, 115*(8), 1863-1874.

Gilmore, P. C., & Brenner, R. P. (1981). Correlation of EEG, computerized tomography, and clinical findings. Study of 100 patients with focal delta activity. *Arch Neurol, 38*(6), 371-372.

Goff, D. C., & Coyle, J. T. (2001). The emerging role of glutamate in the pathophysiology and treatment of schizophrenia. *Am J Psychiatry, 158*(9), 1367-1377.

Goff, D. C., Hill, M., & Barch, D. (2010). The treatment of cognitive impairment in schizophrenia. *Pharmacol Biochem Behav*.

Goffaux, V., Gauthier, I., & Rossion, B. (2003). Spatial scale contribution to early visual differences between face and object processing. *Brain Res Cogn Brain Res, 16*(3), 416-424.

Goffaux, V., Hault, B., Michel, C., Vuong, Q. C., & Rossion, B. (2005). The respective role of low and high spatial frequencies in supporting configural and featural processing of faces. *Perception, 34*(1), 77-86.

Goffaux, V., & Rossion, B. (2006). Faces are "spatial"--holistic face perception is supported by low spatial frequencies. *J Exp Psychol Hum Percept Perform, 32*(4), 1023-1039.

Gold, J. M., Goldberg, R. W., McNary, S. W., Dixon, L. B., & Lehman, A. F. (2002). Cognitive correlates of job tenure among patients with severe mental illness. *Am J Psychiatry, 159*(8), 1395-1402.

Gomez-Ramirez, M., Higgins, B. A., Rycroft, J. A., Owen, G. N., Mahoney, J., Shpaner, M., et al. (2007). The deployment of intersensory selective attention: a high-density electrical mapping study of the effects of theanine. *Clin Neuropharmacol, 30*(1), 25-38.

Goodarzi, M. A., Wykes, T., & Hemsley, D. R. (2000). Cerebral lateralization of global-local processing in people with schizotypy. *Schizophr Res, 45*(1-2), 115-121.

Gosselin, F., & Schyns, P. G. (2001). Bubbles: a technique to reveal the use of information in recognition tasks. *Vision Res, 41*(17), 2261-2271.

Gray, C. M., Konig, P., Engel, A. K., & Singer, W. (1989). Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties. *Nature, 338*(6213), 334-337.

Green, M. F., Nuechterlein, K. H., & Mintz, J. (1994). Backward masking in schizophrenia and mania. II. Specifying the visual channels. *Arch Gen Psychiatry, 51*(12), 945-951.

Guntekin, B., & Basar, E. (2010). Event-related beta oscillations are affected by emotional eliciting stimuli. *Neurosci Lett, 483*(3), 173-178.

Gur, R. E., Loughead, J., Kohler, C. G., Elliott, M. A., Lesko, K., Ruparel, K., et al. (2007). Limbic activation associated with misidentification of fearful faces and flat affect in schizophrenia. *Arch Gen Psychiatry, 64*(12), 1356-1366.

Gur, R. E., McGrath, C., Chan, R. M., Schroeder, L., Turner, T., Turetsky, B. I., et al. (2002). An fMRI study of facial emotion processing in patients with schizophrenia. *Am J Psychiatry, 159*(12), 1992-1999.

Gutherie, A. H., McDowell, J. E., & Hammond, B. R., Jr. (2006). Scotopic sensitivity in schizophrenia. *Schizophr Res, 84*(2-3), 378-385.

Habel, U., Chechko, N., Pauly, K., Koch, K., Backes, V., Seiferth, N., et al. (2010). Neural correlates of emotion recognition in schizophrenia. *Schizophr Res, 122*(1-3), 113-123.

Haenschel, C., Bittner, R. A., Waltz, J., Haertling, F., Wibral, M., Singer, W., et al. (2009). Cortical oscillatory activity is critical for working memory as revealed by deficits in early-onset schizophrenia. *J Neurosci, 29*(30), 9481-9489.

Haenschel, C., Waltz, J., Bittner, R. A., Hartling, F., Rotarska-Jagiela, A., Maurer, K., et al. (2004). Intertrial synchronization deficits account for reduced P1 and high-frequency EEG activity in schizophrenia. *Society for Neuroscience Abstracts*, Program No. 348.343.

Hamm, A. O., Weike, A. I., Schupp, H. T., Treig, T., Dressel, A., & Kessler, C. (2003). Affective blindsight: intact fear conditioning to a visual cue in a cortically blind patient. *Brain, 126*(Pt 2), 267-275.

Hancock, P. J., Bruce, V. V., & Burton, A. M. (2000). Recognition of unfamiliar faces. *Trends Cogn Sci, 4*(9), 330-337.

Hassler, R. (Ed.). (1966). *Comparative anatomy of the central visual system in day- and night-active primates*. Stuttgart: Thieme Verlag.

Hawken, M. J., & Parker, A. J. (1984). Contrast sensitivity and orientation selectivity in lamina IV of the striate cortex of Old World monkeys. *Exp Brain Res, 54*(2), 367-372.

Heimberg, C., Gur, R. E., Erwin, R. J., Shtasel, D. L., & Gur, R. C. (1992). Facial emotion discrimination: III. Behavioral findings in schizophrenia. *Psychiatry Res, 42*(3), 253-265.

Herbener, E. S., Rosen, C., Khine, T., & Sweeney, J. A. (2007). Failure of positive but not negative emotional valence to enhance memory in schizophrenia. *J Abnorm Psychol, 116*(1), 43-55.

Herbener, E. S., Song, W., Khine, T. T., & Sweeney, J. A. (2008). What aspects of emotional functioning are impaired in schizophrenia? *Schizophr Res, 98*(1-3), 239-246.

Herrmann, C. S., & Demiralp, T. (2005). Human EEG gamma oscillations in neuropsychiatric disorders. *Clin Neurophysiol, 116*(12), 2719-2733.

Herrmann, M. J., Aranda, D., Ellgring, H., Mueller, T. J., Strik, W. K., Heidrich, A., et al. (2002). Face-specific event-related potential in humans is independent from facial expression. *Int J Psychophysiol, 45*(3), 241-244.

Herrmann, M. J., Ehlis, A. C., Muehlberger, A., & Fallgatter, A. J. (2005). Source localization of early stages of face processing. *Brain Topogr, 18*(2), 77-85.

Herrmann, M. J., Ellgring, H., & Fallgatter, A. J. (2004). Early-Stage face processing dysfunction in patients with schizophrenia. *Am J Psychiatry, 161*(5), 915-917.

Hicks, T. P., Lee, B. B., & Vidyasagar, T. R. (1983). The responses of cells in macaque lateral geniculate nucleus to sinusoidal gratings. *J Physiol, 337*, 183-200.

Hofmann, M. I., Barnes, C. S., & Hallett, P. E. (1990). Detection of briefly flashed sine-gratings in dark-adapted vision. *Vision Res, 30*(10), 1453-1466.

Holmes, A., Winston, J. S., & Eimer, M. (2005). The role of spatial frequency information for ERP components sensitive to faces and emotional facial expression. *Brain Res Cogn Brain Res, 25*(2), 508-520.

Holscher, C., McGlinchey, L., Anwyl, R., & Rowan, M. J. (1997). HFS-induced long-term potentiation and LFS-induced depotentiation in area CA1 of the hippocampus are not good models for learning. *Psychopharmacology (Berl), 130*(2), 174-182.

Holt, D. J., Kunkel, L., Weiss, A. P., Goff, D. C., Wright, C. I., Shin, L. M., et al. (2006). Increased medial temporal lobe activation during the passive viewing of emotional and neutral facial expressions in schizophrenia. *Schizophr Res, 82*(2-3), 153-162.

Hong, L. E., Buchanan, R. W., Thaker, G. K., Shepard, P. D., & Summerfelt, A. (2008). Beta (~16 Hz) frequency neural oscillations mediate auditory sensory gating in humans. *Psychophysiology, 45*(2), 197-204.

Horan, W. P., Green, M. F., Kring, A. M., & Nuechterlein, K. H. (2006). Does anhedonia in schizophrenia reflect faulty memory for subjectively experienced emotions? *J Abnorm Psychol, 115*(3), 496-508.

Horley, K., Gonsalvez, C., Williams, L., Lazzaro, I., Bahramali, H., & Gordon, E. (2001). Event-related potentials to threat-related faces in schizophrenia. *Int J Neurosci, 107*(1-2), 113-130.

Iacono, W. G. (1982). Bilateral electrodermal habituation-dishabituation and resting EEG in remitted schizophrenics. *J Nerv Ment Dis, 170*(2), 91-101.

Iwai, E., Yukie, M., Suyama, H., & Shirakawa, S. (1987). Amygdalar connections with middle and inferior temporal gyri of the monkey. *Neurosci Lett, 83*(1-2), 25-29.

Iwai, E., Yukie, M., Watanabe, J., Hikosaka, K., Suyama, H., & Ishikawa, S. (1990). A role of amygdala in visual perception and cognition in macaque monkeys (Macaca fuscata and Macaca mulatta). *Tohoku J Exp Med, 161 Suppl*, 95-120.

Javitt, D. C. (2004). Glutamate as a therapeutic target in psychiatric disorders. *Mol Psychiatry, 9*(11), 984-997, 979.

Javitt, D. C. (2007). Glutamate and schizophrenia: phencyclidine, N-methyl-D-aspartate receptors, and dopamine-glutamate interactions. *Int Rev Neurobiol, 78*, 69-108.

Javitt, D. C. (2009). When doors of perception close: bottom-up models of disrupted cognition in schizophrenia. *Annu Rev Clin Psychol, 5*, 249-275.

Javitt, D. C., Liederman, E., Cienfuegos, A., & Shelley, A. M. (1999). Panmodal processing imprecision as a basis for dysfunction of transient memory storage systems in schizophrenia. *Schizophr Bull, 25*(4), 763-775.

Javitt, D. C., & Zukin, S. R. (1991). Recent advances in the phencyclidine model of schizophrenia. *Am J Psychiatry, 148*(10), 1301-1308.

Johnston, P. J., Stojanov, W., Devir, H., & Schall, U. (2005). Functional MRI of facial emotion recognition deficits in schizophrenia and their electrophysiological correlates. *Eur J Neurosci, 22*(5), 1221-1232.

Joshua, N., & Rossell, S. (2009). Configural face processing in schizophrenia. *Schizophr Res, 112*(1-3), 99-103.

Kanwisher, N., & Yovel, G. (2006). The fusiform face area: a cortical region specialized for the perception of faces. *Philos Trans R Soc Lond B Biol Sci, 361*(1476), 2109-2128.

Kaplan, E. (1991). The receptive field structure of retinal ganglion cells in cat and monkey. In A. G. Leventhal (Ed.), *Vision and Visual Dysfunction* (pp. 10-40). Boston: CRC Press.

Kaplan, E. (2003). The M,P, and K pathways of the primate visual system. In L. M. Chalupa & J. S. Werner (Eds.), *The Visual Neurosciences* (Vol. 1). Cambridge, Mass: MIT Press.

Kaplan, E., Purpura, K., & Shapley, R. M. (1987). Contrast affects the transmission of visual information through the mammalian lateral geniculate nucleus. *J Physiol, 391*, 267-288.

Kaplan, E., & Shapley, R. (1986). The primate retina contains two types of ganglion cells, with high and low contrast sensitivity. *Proc Natl Acad Sci U S A, 83*, 2755-2757.

Kaplan, E., & Shapley, R. M. (1982). X and Y cells in the lateral geniculate nucleus of macaque monkeys. *J Physiol (Lond), 330*, 125-143.

Keil, A., Muller, M. M., Gruber, T., Wienbruch, C., Stolarova, M., & Elbert, T. (2001). Effects of emotional arousal in the cerebral hemispheres: a study of oscillatory brain activity and event-related potentials. *Clin Neurophysiol, 112*(11), 2057-2068.

Keil, A., Muller, M. M., Ray, W. J., Gruber, T., & Elbert, T. (1999). Human gamma band activity and perception of a gestalt. *J Neurosci, 19*(16), 7152-7161.

Kelly, D. H. (1972). Adaptation effects on spatio-temporal sine-wave thresholds. *Vision Res, 12*(1), 89-101.

Kelly, S. P., Gomez-Ramirez, M., Montesi, J. L., & Foxe, J. J. (2008). L-theanine and caffeine in combination affect human cognition as evidenced by oscillatory alpha-band activity and attention task performance. *J Nutr, 138*(8), 1572S-1577S.

Kelly, S. P., Lalor, E. C., Reilly, R. B., & Foxe, J. J. (2006). Increases in alpha oscillatory power reflect an active retinotopic mechanism for distracter suppression during sustained visuospatial attention. *J Neurophysiol, 95*(6), 3844-3851.

Keri, S., Antal, A., Szekeres, G., Benedek, G., & Janka, Z. (2002). Spatiotemporal visual processing in schizophrenia. *J Neuropsychiatry Clin Neurosci, 14*(2), 190-196.

Keri, S., & Janka, Z. (2004). Critical evaluation of cognitive dysfunctions as endophenotypes of schizophrenia. *Acta Psychiatr Scand, 110*(2), 83-91.

Keri, S., Kelemen, O., Benedek, G., & Janka, Z. (2004). Vernier threshold in patients with schizophrenia and in their unaffected siblings. *Neuropsychology, 18*(3), 537-542.

Keri, S., Kelemen, O., Janka, Z., & Benedek, G. (2005). Visual-perceptual dysfunctions are possible endophenotypes of schizophrenia: evidence from the psychophysical investigation of magnocellular and parvocellular pathways. *Neuropsychology, 19*(5), 649-656.

Keri, S., Kiss, I., Kelemen, O., Benedek, G., & Janka, Z. (2005). Anomalous visual experiences, negative symptoms, perceptual organization and the magnocellular pathway in schizophrenia: a shared construct? *Psychol Med, 35*(10), 1445-1455.

Kerr, S. L., & Neale, J. M. (1993). Emotion perception in schizophrenia: specific deficit or further evidence of generalized poor performance? *J Abnorm Psychol, 102*(2), 312-318.

Kilner, J. M., Baker, S. N., Salenius, S., Hari, R., & Lemon, R. N. (2000). Human cortical muscle coherence is directly related to specific motor parameters. *J Neurosci, 20*(23), 8838-8845.

Kim, D., Wylie, G., Pasternak, R., Butler, P. D., & Javitt, D. C. (2006). Magnocellular contributions to impaired motion processing in schizophrenia. *Schizophr Res, 82*(1), 1-8.

Kim, D., Zemon, V., Saperstein, A., Butler, P. D., & Javitt, D. C. (2005). Dysfunction of early-stage visual processing in schizophrenia: harmonic analysis. *Schizophr Res, 76*(1), 55-65.

Klimesch, W., Doppelmayr, M., Russegger, H., Pachinger, T., & Schwaiger, J. (1998). Induced alpha band power changes in the human EEG and attention. *Neurosci Lett, 244*(2), 73-76.

Klimesch, W., Sauseng, P., & Hanslmayr, S. (2007). EEG alpha oscillations: the inhibition-timing hypothesis. *Brain Res Rev, 53*(1), 63-88.

Knott, V., Labelle, A., Jones, B., & Mahoney, C. (2001). Quantitative EEG in schizophrenia and in response to acute and chronic clozapine treatment. *Schizophr Res, 50*(1-2), 41-53.

Knyazev, G. G. (2007). Motivation, emotion, and their inhibitory control mirrored in brain oscillations. *Neurosci Biobehav Rev, 31*(3), 377-395.

Kohler, C. G., Bilker, W., Hagendoorn, M., Gur, R. E., & Gur, R. C. (2000). Emotion recognition deficit in schizophrenia: association with symptomatology and cognition. *Biol Psychiatry, 48*(2), 127-136.

Kohler, C. G., Turner, T. H., Bilker, W. B., Brensinger, C. M., Siegel, S. J., Kanes, S. J., et al. (2003). Facial emotion recognition in schizophrenia: intensity effects and error pattern. *Am J Psychiatry, 160*(10), 1768-1774.

Kohler, C. G., Walker, J. B., Martin, E. A., Healey, K. M., & Moberg, P. J. (2009). Facial emotion perception in schizophrenia: a meta-analytic review. *Schizophr Bull, 36*(5), 1009-1019.

Kraepelin, E. (1904). *Psychiatrie ein lehrbuch for studierende und arzte*. Liepzig: Verlag von Johann Ambrosius Barth.

Kring, A. M., Kerr, S. L., Smith, D. A., & Neale, J. M. (1993). Flat affect in schizophrenia does not reflect diminished subjective experience of emotion. *J Abnorm Psychol, 102*(4), 507-517.

Kring, A. M., & Neale, J. M. (1996). Do schizophrenic patients show a disjunctive relationship among expressive, experiential, and psychophysiological components of emotion? *J Abnorm Psychol, 105*(2), 249-257.

Krishnan, G. P., Vohs, J. L., Hetrick, W. P., Carroll, C. A., Shekhar, A., Bockbrader, M. A., et al. (2005). Steady state visual evoked potential abnormalities in schizophrenia. *Clin Neurophysiol, 116*(3), 614-624.

Krystal, J. H., Perry, E. B., Jr., Gueorguieva, R., Belger, A., Madonick, S. H., Abi-Dargham, A., et al. (2005). Comparative and interactive human psychopharmacologic effects of ketamine and amphetamine: implications for glutamatergic and dopaminergic model psychoses and cognitive function. *Arch Gen Psychiatry, 62*(9), 985-994.

Kveraga, K., Boshyan, J., & Bar, M. (2007). Magnocellular projections as the trigger of top-down facilitation in recognition. *J Neurosci, 27*(48), 13232-13240.

Kwon, J. S., O'Donnell, B. F., Wallenstein, G. V., Greene, R. W., Hirayasu, Y., Nestor, P. G., et al. (1999). Gamma frequency-range abnormalities to auditory stimulation in schizophrenia. *Arch Gen Psychiatry, 56*(11), 1001-1005.

Kwon, Y. H., Nelson, S. B., Toth, L. J., & Sur, M. (1992). Effect of stimulus contrast and size on NMDA receptor activity in cat lateral geniculate nucleus. *J Neurophysiol, 68*(1), 182-196.

Lakatos, P., Karmos, G., Mehta, A. D., Ulbert, I., & Schroeder, C. E. (2008). Entrainment of neuronal oscillations as a mechanism of attentional selection. *Science, 320*(5827), 110-113.

Laprevote, V., Oliva, A., Delerue, C., Thomas, P., & Boucart, M. (2010). Patients with schizophrenia are biased toward low spatial frequency to decode facial expression at a glance. *Neuropsychologia, 48*(14), 4164-4168.

Larson, J., & Lynch, G. (1988). Role of N-methyl-D-aspartate receptors in the induction of synaptic potentiation by burst stimulation patterned after the hippocampal theta-rhythm. *Brain Res, 441*(1-2), 111-118.

Laycock, R., Crewther, S. G., & Crewther, D. P. (2007). A role for the 'magnocellular advantage' in visual impairments in neurodevelopmental and psychiatric disorders. *Neurosci Biobehav Rev, 31*(3), 363-376.

Leder, H., Candrian, G., Huber, O., & Bruce, V. (2001). Configural features in the context of upright and inverted faces. *Perception, 30*(1), 73-83.

Lee, B. B., Smith, V. C., Pokorny, J., & Kremers, J. (1997). Rod inputs to macaque ganglion cells. *Vision Res, 37*(20), 2813-2828.

Lee, J., Gosselin, F., Wynn, J. K., & Green, M. F. (2010). How Do Schizophrenia Patients Use Visual Information to Decode Facial Emotion? *Schizophr Bull.*

Lee, S. H., Kim, E. Y., Kim, S., & Bae, S. M. (2010). Event-related potential patterns and gender effects underlying facial affect processing in schizophrenia patients. *Neurosci Res, 67*(2), 172-180.

Leung, L. S., & Shen, B. (2007). GABAB receptor blockade enhances theta and gamma rhythms in the hippocampus of behaving rats. *Hippocampus, 17*(4), 281-291.

Lewis, D. A., Campbell, M. J., Foote, S. L., Goldstein, M., & Morrison, J. H. (1987). The distribution of tyrosine hydroxylase-immunoreactive fibers in primate neocortex is widespread but regionally specific. *J Neurosci, 7*(1), 279-290.

Li, H., Chan, R. C., McAlonan, G. M., & Gong, Q. Y. (2009). Facial emotion processing in schizophrenia: a meta-analysis of functional neuroimaging data. *Schizophr Bull, 36*(5), 1029-1039.

Liddell, B. J., Brown, K. J., Kemp, A. H., Barton, M. J., Das, P., Peduto, A., et al. (2005). A direct brainstem-amygdala-cortical 'alarm' system for subliminal signals of fear. *Neuroimage, 24*(1), 235-243.

Lisman, J. E., Coyle, J. T., Green, R. W., Javitt, D. C., Benes, F. M., Heckers, S., et al. (2008). Circuit-based framework for understanding neurotransmitter and risk gene interactions in schizophrenia. *Trends Neurosci, 31*(5), 234-242.

Livingstone, M. S., & Hubel, D. H. (1987). Psychophysical evidence for separate channels for the perception of form, color, movement, and depth. *J Neurosci, 7*(11), 3416-3468.

Lund, J. S. (1973). Organization of neurons in the visual cortex, area 17, of the monkey (Macaca mulatta). *J Comp Neurol, 147*(4), 455-496.

Lynn, S. K., & Salisbury, D. F. (2008). Attenuated modulation of the N170 ERP by facial expressions in schizophrenia. *Clin EEG Neurosci, 39*(2), 108-111.

Marosi, E., Rodriguez, H., Yanez, G., Bernal, J., Rodriguez, M., Fernandez, T., et al. (2001). Broad band spectral measurements of EEG during emotional tasks. *Int J Neurosci, 108*(3-4), 251-279.

Martinez, A., Di Russo, F., Anllo-Vento, L., & Hillyard, S. A. (2001). Electrophysiological analysis of cortical mechanisms of selective attention to high and low spatial frequencies. *Clin Neurophysiol, 112*(11), 1980-1998.

Martinez, A., Hillyard, S. A., Dias, E. C., Hagler, D. J., Butler, P. D., Guilfoyle, D. N., et al. (2008). Magnocellular pathway impairment in schizophrenia: evidence from fMRI. *J Neuroscience, 28*(30), 7492-7500.

McGhie, A. (1964). Disturbances in Selective Attention in Schizophrenia. *Proc R Soc Med, 57*, 419-422.

McGhie, A., & Chapman, J. (1961). Disorders of attention and perception in early schizophrenia. *Br J Med Psychol, 34*, 103-116.

Merigan, W. H., & Maunsell, J. H. R. (1993). How parallel are the primate visual pathways? In W. M. Cowan, E. M. Shooter, C. F. Stevens & R. F. Thompson (Eds.), *Ann Rev Neuroscience* (pp. 369-402). Palo Alto, CA: Annual Reviews, Inc.

Millson, D. S., Haworth, S. J., Rushton, A., Wilkinson, D., Hobson, S., & Harry, J. (1991). The effects of a 5-HT2 receptor antagonist (ICI 169,369) on changes in waking EEG, pupillary responses and state of arousal in human volunteers. *Br J Clin Pharmacol, 32*(4), 447-454.

Minzenberg, M. J., Laird, A. R., Thelen, S., Carter, C. S., & Glahn, D. C. (2009). Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. *Arch Gen Psychiatry, 66*(8), 811-822.

Morris, J. S., deBonis, M., & Dolan, R. J. (2002). Human amygdala responses to fearful eyes. *Neuroimage, 17*(1), 214-222.

Morris, J. S., DeGelder, B., Weiskrantz, L., & Dolan, R. J. (2001). Differential extrageniculostriate and amygdala responses to presentation of emotional faces in a cortically blind field. *Brain, 124*(Pt 6), 1241-1252.

Morris, J. S., Ohman, A., & Dolan, R. J. (1998). Conscious and unconscious emotional learning in the human amygdala. *Nature, 393*(6684), 467-470.

Morris, J. S., Ohman, A., & Dolan, R. J. (1999). A subcortical pathway to the right amygdala mediating "unseen" fear. *Proc Natl Acad Sci U S A, 96*(4), 1680-1685.

Nakashima, T., Kaneko, K., Goto, Y., Abe, T., Mitsudo, T., Ogata, K., et al. (2008). Early ERP components differentially extract facial features: evidence for spatial frequency-and-contrast detectors. *Neurosci Res, 62*(4), 225-235.

Neuper, C., Wortz, M., & Pfurtscheller, G. (2006). ERD/ERS patterns reflecting sensorimotor activation and deactivation. *Prog Brain Res, 159*, 211-222.

Norton, D., McBain, R., Holt, D. J., Ongur, D., & Chen, Y. (2009). Association of impaired facial affect recognition with basic facial and visual processing deficits in schizophrenia. *Biol Psychiatry, 65*(12), 1094-1098.

O'Donnell, B. F., Potts, G. F., Nestor, P. G., Stylianopoulos, K. C., Shenton, M. E., & McCarley, R. W. (2002). Spatial frequency discrimination in schizophrenia. *J Abnorm Psychol, 111*(4), 620-625.

Obayashi, C., Nakashima, T., Onitsuka, T., Maekawa, T., Hirano, Y., Hirano, S., et al. (2009). Decreased spatial frequency sensitivities for processing faces in male patients with chronic schizophrenia. *Clin Neurophysiol, 120*(8), 1525-1533.

Olney, J. W., & Farber, N. B. (1995). Glutamate receptor dysfunction and schizophrenia. *Arch Gen Psychiatry, 52*(12), 998-1007.

Onitsuka, T., Niznikiewicz, M. A., Spencer, K. M., Frumin, M., Kuroki, N., Lucia, L. C., et al. (2006). Functional and structural deficits in brain regions subserving face perception in schizophrenia. *Am J Psychiatry, 163*(3), 455-462.

Pare, D. (2003). Role of the basolateral amygdala in memory consolidation. *Prog Neurobiol, 70*(5), 409-420.

Patel, A. S. (1966). Spatial resolution by the human visual system. The effect of mean retinal illuminance. *J Opt Soc Am, 56*(5), 689-694.

Pavlides, C., Greenstein, Y. J., Grudman, M., & Winson, J. (1988). Long-term potentiation in the dentate gyrus is induced preferentially on the positive phase of theta-rhythm. *Brain Res, 439*(1-2), 383-387.

Pfurtscheller, G. (1992). Event-related synchronization (ERS): an electrophysiological correlate of cortical areas at rest. *Electroencephalogr Clin Neurophysiol, 83*(1), 62-69.

Pfurtscheller, G., & Neuper, C. (2006). Future prospects of ERD/ERS in the context of brain-computer interface (BCI) developments. *Prog Brain Res, 159*, 433-437.

Pfurtscheller, G., Neuper, C., & Mohl, W. (1994). Event-related desynchronization (ERD) during visual processing. *Int J Psychophysiol, 16*(2-3), 147-153.

Phillips, W. A., & Silverstein, S. M. (2003). Convergence of biological and psychological perspectives on cognitive coordination in schizophrenia. *Behavioral and Brain Sciences, 26*, 65-138.

Pizzagalli, D., Regard, M., & Lehmann, D. (1999). Rapid emotional face processing in the human right and left brain hemispheres: an ERP study. *Neuroreport, 10*(13), 2691-2698.

Pizzagalli, D. A., Lehmann, D., Hendrick, A. M., Regard, M., Pascual-Marqui, R. D., & Davidson, R. J. (2002). Affective judgments of faces modulate early activity (approximately 160 ms) within the fusiform gyri. *Neuroimage, 16*(3 Pt 1), 663-677.

Pourtois, G., Dan, E. S., Grandjean, D., Sander, D., & Vuilleumier, P. (2005). Enhanced extrastriate visual response to bandpass spatial frequency filtered fearful faces: time course and topographic evoked-potentials mapping. *Hum Brain Mapp, 26*(1), 65-79.

Purpura, K., Kaplan, E., & Shapley, R. M. (1988). Background light and the contrast gain of primate P and M retinal ganglion cells. *Proc Natl Acad Sci U S A, 85*(12), 4534-4537.

Purpura, K., Tranchina, D., Kaplan, E., & Shapley, R. M. (1990). Light adaptation in the primate retina: analysis of changes in gain and dynamics of monkey retinal ganglion cells. *Vis Neurosci, 4*(1), 75-93.

Quintana, J., Wong, T., Ortiz-Portillo, E., Marder, S. R., & Mazziotta, J. C. (2003). Right lateral fusiform gyrus dysfunction during facial information processing in schizophrenia. *Biol Psychiatry, 53*(12), 1099-1112.

Raghavachari, S., Lisman, J. E., Tully, M., Madsen, J. R., Bromfield, E. B., & Kahana, M. J. (2006). Theta oscillations in human cortex during a working-memory task: evidence for local generators. *J Neurophysiol, 95*(3), 1630-1638.

Ramos-Loyo, J., Gonzalez-Garrido, A. A., Amezcua, C., & Guevara, M. A. (2004). Relationship between resting alpha activity and the ERPs obtained during a highly demanding selective attention task. *Int J Psychophysiol, 54*(3), 251-262.

Ramos-Loyo, J., Gonzalez-Garrido, A. A., Sanchez-Loyo, L. M., Medina, V., & Basar-Eroglu, C. (2009). Event-related potentials and event-related oscillations during identity and facial emotional processing in schizophrenia. *Int J Psychophysiol, 71*(1), 84-90.

Reichenberg, A., & Harvey, P. D. (2007). Neuropsychological impairments in schizophrenia: Integration of performance-based and brain imaging findings. *Psychol Bull, 133*(5), 833-858.

Rizzuto, D. S., Madsen, J. R., Bromfield, E. B., Schulze-Bonhage, A., Seelig, D., Aschenbrenner-Scheibe, R., et al. (2003). Reset of human neocortical oscillations during a working memory task. *Proc Natl Acad Sci U S A, 100*(13), 7931-7936.

Rossion, B., Delvenne, J. F., Debatisse, D., Goffaux, V., Bruyer, R., Crommelinck, M., et al. (1999). Spatio-temporal localization of the face inversion effect: an event-related potentials study. *Biol Psychol, 50*(3), 173-189.

Sabatinelli, D., Lang, P. J., Bradley, M. M., Costa, V. D., & Keil, A. (2009). The timing of emotional discrimination in human amygdala and ventral visual cortex. *J Neurosci, 29*(47), 14864-14868.

Saccuzzo, D. P., & Braff, D. L. (1981). Early information processing deficit in schizophrenia. New findings using schizophrenic subgroups and manic control subjects. *Arch Gen Psychiatry, 38*(2), 175-179.

Saccuzzo, D. P., & Braff, D. L. (1986). Information-processing abnormalities: trait- and state-dependent components. *Schizophr Bull, 12*(3), 447-459.

Saccuzzo, D. P., & Schubert, D. L. (1981). Backward masking as a measure of slow processing in schizophrenia spectrum disorders. *J Abnorm Psychol, 90*(4), 305-312.

Salem, J. E., Kring, A. M., & Kerr, S. L. (1996). More evidence for generalized poor performance in facial emotion perception in schizophrenia. *J Abnorm Psychol, 105*(3), 480-483.

Sauseng, P., Klimesch, W., Freunberger, R., Pecherstorfer, T., Hanslmayr, S., & Doppelmayr, M. (2006). Relevance of EEG alpha and theta oscillations during task switching. *Exp Brain Res, 170*(3), 295-301.

Savage, G. L., & Banks, M. S. (1992). Scotopic visual efficiency: constraints by optics, receptor properties, and rod pooling. *Vision Res, 32*(4), 645-656.

Schechter, I., Butler, P. D., Silipo, G., Zemon, V., & Javitt, D. C. (2003). Magnocellular and parvocellular contributions to backward masking dysfunction in schizophrenia. *Schizophrenia Research, 64*, 91-101.

Schechter, I., Butler, P. D., Zemon, V. M., Revheim, N., Saperstein, A. M., Jalbrzikowski, M., et al. (2005). Impairments in generation of early-stage transient visual evoked potentials to magno- and parvocellular-selective stimuli in schizophrenia. *Clin Neurophysiol, 116*(9), 2204-2215.

Schiller, P. H., Malpeli, J. G., & Schein, S. J. (1979). Composition of geniculostriate input ot superior colliculus of the rhesus monkey. *J Neurophysiol, 42*(4), 1124-1133.

Schmiedt, C., Brand, A., Hildebrandt, H., & Basar-Eroglu, C. (2005). Event-related theta oscillations during working memory tasks in patients with schizophrenia and healthy controls. *Brain Res Cogn Brain Res, 25*(3), 936-947.

Schneider, F., Gur, R. C., Koch, K., Backes, V., Amunts, K., Shah, N. J., et al. (2006). Impairment in the specificity of emotion processing in schizophrenia. *Am J Psychiatry, 163*(3), 442-447.

Schnitzler, A., & Gross, J. (2005). Normal and pathological oscillatory communication in the brain. *Nat Rev Neurosci, 6*(4), 285-296.

Schroeder, C. E., Mehta, A. D., & Givre, S. J. (1998). A spatiotemporal profile of visual system activation revealed by current source density analysis in the awake macaque. *Cereb Cortex, 8*(7), 575-592.

Schutter, D. J., de Haan, E. H., & van Honk, J. (2004). Functionally dissociated aspects in anterior and posterior electrocortical processing of facial threat. *Int J Psychophysiol, 53*(1), 29-36.

Schwartz, B. D., Evans, W. J., Sautter, F., Pena, J. M., & Winstead, D. K. (1992). Deficits in initial feature registration of schizophrenics and substance abusers. *Schizophr Res, 7*(3), 217-224.

Schyns, P. G., Bonnar, L., & Gosselin, F. (2002). Show me the features! Understanding recognition from the use of visual information. *Psychol Sci, 13*(5), 402-409.

Schyns, P. G., & Oliva, A. (1999). Dr. Angry and Mr. Smile: when categorization flexibly modifies the perception of faces in rapid visual presentations. *Cognition, 69*(3), 243-265.

Sehatpour, P., Dias, E. C., Butler, P. D., Revheim, N., Guilfoyle, D. N., Foxe, J. J., et al. (2010). Impaired visual object processing across an occipital-frontal-hippocampal brain network in schizophrenia: an integrated neuroimaging study. *Arch Gen Psychiatry, 67*(8), 772-782.

Sehatpour, P., Molholm, S., Javitt, D. C., & Foxe, J. J. (2006). Spatiotemporal dynamics of human object recognition processing: an integrated high-density electrical mapping and functional imaging study of "closure" processes. *Neuroimage, 29*(2), 605-618.

Sehatpour, P., Molholm, S., Schwartz, T. H., Mahoney, J. R., Mehta, A. D., Javitt, D. C., et al. (2008). A human intracranial study of long-range oscillatory coherence across a frontal-occipital-hippocampal brain network during visual object processing. *Proc Natl Acad Sci U S A, 105*(11), 4399-4404.

Sergent, J. (1984). An investigation into component and configural processes underlying face perception. *Br J Psychol, 75 (Pt 2)*, 221-242.

Sergi, M. J., & Green, M. F. (2003). Social perception and early visual processing in schizophrenia. *Schizophr Res, 59*(2-3), 233-241.

Sergi, M. J., Rassovsky, Y., Nuechterlein, K. H., & Green, M. F. (2006). Social perception as a mediator of the influence of early visual processing on functional status in schizophrenia. *Am J Psychiatry, 163*(3), 448-454.

Shapley, R. M., & Victor, J. D. (1978). The effect of contrast on the transfer properties of cat retinal ganglion cells. *J Physiol, 285*, 275-298.

Shapley, R. M., & Victor, J. D. (1981). How the contrast gain control modifies the frequency responses of cat retinal ganglion cells. *J Physiol, 318*, 161-179.

Shibata, T., Nishijo, H., Tamura, R., Miyamoto, K., Eifuku, S., Endo, S., et al. (2002). Generators of visual evoked potentials for faces and eyes in the human brain as determined by dipole localization. *Brain Topogr, 15*(1), 51-63.

Shin, Y. W., Na, M. H., Ha, T. H., Kang, D. H., Yoo, S. Y., & Kwon, J. S. (2008). Dysfunction in configural face processing in patients with schizophrenia. *Schizophr Bull, 34*(3), 538-543.

Siegel, M., Warden, M. R., & Miller, E. K. (2009). Phase-dependent neuronal coding of objects in short-term memory. *Proc Natl Acad Sci U S A, 106*(50), 21341-21346.

Silva, L. R., Amitai, Y., & Connors, B. W. (1991). Intrinsic oscillations of neocortex generated by layer 5 pyramidal neurons. *Science, 251*(4992), 432-435.

Singer, W., & Gray, C. M. (1995). Visual feature integration and the temporal correlation hypothesis. *Annu Rev Neurosci, 18*, 555-586.

Slaghuis, W. L. (1998). Contrast sensitivity for stationary and drifting spatial frequency gratings in positive- and negative-symptom schizophrenia. *J Abnorm Psychol, 107*(1), 49-62.

Slaghuis, W. L. (2004). Spatio-temporal luminance contrast sensitivity and visual backward masking in schizophrenia. *Exp Brain Res, 156*(2), 196-211.

Slaghuis, W. L., & Bakker, V. J. (1995). Forward and backward visual masking of contour by light in positive- and negative-symptom schizophrenia. *J Abnorm Psychol, 104*(1), 41-54.

Slaghuis, W. L., & Bishop, A. M. (2001). Luminance flicker sensitivity in positive- and negative-symptom schizophrenia. *Exp Brain Res, 138*(1), 88-99.

Slaghuis, W. L., & Thompson, A. K. (2003). The effect of peripheral visual motion on focal contrast sensitivity in positive- and negative-symptom schizophrenia. *Neuropsychologia, 41*(8), 968-980.

Spencer, K. M. (2008). Visual gamma oscillations in schizophrenia: implications for understanding neural circuitry abnormalities. *Clin EEG Neurosci, 39*(2), 65-68.

Spencer, K. M., Nestor, P. G., Niznikiewicz, M. A., Salisbury, D. F., Shenton, M. E., & McCarley, R. W. (2003). Abnormal neural synchrony in schizophrenia. *J Neurosci, 23*(19), 7407-7411.

Spencer, K. M., Nestor, P. G., Perlmutter, R., Niznikiewicz, M. A., Klump, M. C., Frumin, M., et al. (2004). Neural synchrony indexes disordered perception and cognition in schizophrenia. *Proc Natl Acad Sci U S A, 101*(49), 17288-17293.

Spencer, K. M., Niznikiewicz, M. A., Shenton, M. E., & McCarley, R. W. (2008). Sensory-evoked gamma oscillations in chronic schizophrenia. *Biol Psychiatry, 63*(8), 744-747.

Spiegler, B. J., & Mishkin, M. (1981). Evidence for the sequential participation of inferior temporal cortex and amygdala in the acquisition of stimulus-reward associations. *Behav Brain Res, 3*(3), 303-317.

Sponheim, S. R., Clementz, B. A., Iacono, W. G., & Beiser, M. (1994). Resting EEG in first-episode and chronic schizophrenia. *Psychophysiology, 31*(1), 37-43.

Steriade, M. (1997). Synchronized activities of coupled oscillators in the cerebral cortex and thalamus at different levels of vigilance. *Cereb Cortex, 7*(6), 583-604.

Steriade, M., Gloor, P., Llinas, R. R., Lopes de Silva, F. H., & Mesulam, M. M. (1990). Report of IFCN Committee on Basic Mechanisms. Basic mechanisms of cerebral rhythmic activities. *Electroencephalogr Clin Neurophysiol, 76*(6), 481-508.

Streit, M., Ioannides, A. A., Liu, L., Wolwer, W., Dammers, J., Gross, J., et al. (1999). Neurophysiological correlates of the recognition of facial expressions of emotion as revealed by magnetoencephalography. *Brain Res Cogn Brain Res, 7*(4), 481-491.

Streit, M., Wolwer, W., Brinkmeyer, J., Ihl, R., & Gaebel, W. (2001). EEG-correlates of facial affect recognition and categorisation of blurred faces in schizophrenic patients and healthy volunteers. *Schizophr Res, 49*(1-2), 145-155.

Symond, M. P., Harris, A. W., Gordon, E., & Williams, L. M. (2005). "Gamma synchrony" in first-episode schizophrenia: a disorder of temporal connectivity? *Am J Psychiatry, 162*(3), 459-465.

Takahashi, H., Koeda, M., Oda, K., Matsuda, T., Matsushima, E., Matsuura, M., et al. (2004). An fMRI study of differential neural response to affective pictures in schizophrenia. *Neuroimage, 22*(3), 1247-1254.

Tallon-Baudry, C., Bertrand, O., Delpuech, C., & Pernier, J. (1996). Stimulus specificity of phase-locked and non-phase-locked 40 Hz visual responses in human. *J Neurosci, 16*(13), 4240-4249.

Taylor, S. F., Phan, K. L., Britton, J. C., & Liberzon, I. (2005). Neural response to emotional salience in schizophrenia. *Neuropsychopharmacology, 30*(5), 984-995.

Thut, G., Nietzel, A., Brandt, S. A., & Pascual-Leone, A. (2006). Alpha-band electroencephalographic activity over occipital cortex indexes visuospatial attention bias and predicts visual target detection. *J Neurosci, 26*(37), 9494-9502.

Tootell, R. B., Silverman, M. S., Hamilton, S. L., Switkes, E., & De Valois, R. L. (1988). Functional anatomy of macaque striate cortex. V. Spatial frequency. *J Neurosci, 8*(5), 1610-1624.

Traub, R. D., Bibbig, A., LeBeau, F. E., Buhl, E. H., & Whittington, M. A. (2004). Cellular mechanisms of neuronal population oscillations in the hippocampus in vitro. *Annu Rev Neurosci, 27*, 247-278.

Tsai, G., & Coyle, J. T. (2002). Glutamatergic mechanisms in schizophrenia. *Annu Rev Pharmacol Toxicol, 42*, 165-179.

Tsujimoto, T., Shimazu, H., & Isomura, Y. (2006). Direct recording of theta oscillations in primate prefrontal and anterior cingulate cortices. *J Neurophysiol, 95*(5), 2987-3000.

Turetsky, B. I., Kohler, C. G., Indersmitten, T., Bhati, M. T., Charbonnier, D., & Gur, R. C. (2007). Facial emotion recognition in schizophrenia: when and why does it go awry? *Schizophr Res, 94*(1-3), 253-263.

Uhlhaas, P. J., Haenschel, C., Nikolic, D., & Singer, W. (2008). The role of oscillations and synchrony in cortical networks and their putative relevance for the pathophysiology of schizophrenia. *Schizophr Bull, 34*(5), 927-943.

Uhlhaas, P. J., Linden, D. E., Singer, W., Haenschel, C., Lindner, M., Maurer, K., et al. (2006). Dysfunctional long-range coordination of neural activity during Gestalt perception in schizophrenia. *J Neurosci, 26*(31), 8168-8175.

Uhlhaas, P. J., & Singer, W. (2006). Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. *Neuron, 52,* 155-168.

Uhlhaas, P. J., & Singer, W. (2010). Abnormal neural oscillations and synchrony in schizophrenia. *Nat Rev Neurosci, 11*(2), 100-113.

van der Stelt, O., Frye, J., Lieberman, J. A., & Belger, A. (2004). Impaired P3 generation reflects high-level and progressive neurocognitive dysfunction in schizophrenia. *Arch Gen Psychiatry, 61*(3), 237-248.

Vidyasagar, T. R. (1999). A neuronal model of attentional spotlight: parietal guiding the temporal. *Brain Res Brain Res Rev, 30*(1), 66-76.

Vinogradova, O. S. (1995). Expression, control, and probable functional significance of the neuronal theta-rhythm. *Prog Neurobiol, 45*(6), 523-583.

Vlamings, P. H., Goffaux, V., & Kemner, C. (2009). Is the early modulation of brain activity by fearful facial expressions primarily mediated by coarse low spatial frequency information? *J Vis, 9*(5), 12 11-13.

von Stein, A., Chiang, C., & Konig, P. (2000). Top-down processing mediated by interareal synchronization. *Proc Natl Acad Sci U S A, 97*(26), 14748-14753.

Vuilleumier, P., Armony, J. L., Driver, J., & Dolan, R. J. (2003). Distinct spatial frequency sensitivities for processing faces and emotional expressions. *Nat Neurosci, 6*(6), 624-631.

Vuilleumier, P., Richardson, M. P., Armony, J. L., Driver, J., & Dolan, R. J. (2004). Distant influences of amygdala lesion on visual cortical activation during emotional face processing. *Nat Neurosci, 7*(11), 1271-1278.

Walther, S., Federspiel, A., Horn, H., Bianchi, P., Wiest, R., Wirth, M., et al. (2009). Encoding deficit during face processing within the right fusiform face area in schizophrenia. *Psychiatry Res, 172*(3), 184-191.

Weiner, R. U., Opler, L. A., Kay, S. R., Merriam, A. E., & Papouchis, N. (1990). Visual information processing in positive, mixed, and negative schizophrenic syndromes. *J Nerv Ment Dis, 178*(10), 616-626.

Whalen, P. J., Kagan, J., Cook, R. G., Davis, F. C., Kim, H., Polis, S., et al. (2004). Human amygdala responsivity to masked fearful eye whites. *Science, 306*(5704), 2061.

White, J. A., Banks, M. I., Pearce, R. A., & Kopell, N. J. (2000). Networks of interneurons with fast and slow gamma-aminobutyric acid type A (GABAA) kinetics provide substrate for mixed gamma-theta rhythm. *Proc Natl Acad Sci U S A, 97*(14), 8128-8133.

Williams, L. M., Palmer, D., Liddell, B. J., Song, L., & Gordon, E. (2006). The 'when' and 'where' of perceiving signals of threat versus non-threat. *Neuroimage, 31*(1), 458-467.

Williams, L. M., Whitford, T. J., Gordon, E., Gomes, L., Brown, K. J., & Harris, A. W. (2009). Neural synchrony in patients with a first episode of schizophrenia:

tracking relations with grey matter and symptom profile. *J Psychiatry Neurosci, 34*(1), 21-29.

Williams, L. M., Whitford, T. J., Nagy, M., Flynn, G., Harris, A. W., Silverstein, S. M., et al. (2009). Emotion-elicited gamma synchrony in patients with first-episode schizophrenia: a neural correlate of social cognition outcomes. *J Psychiatry Neurosci, 34*(4), 303-313.

Winston, J. S., Vuilleumier, P., & Dolan, R. J. (2003). Effects of low-spatial frequency components of fearful faces on fusiform cortex activity. *Curr Biol, 13*(20), 1824-1829.

Winterer, G., Coppola, R., Goldberg, T. E., Egan, M. F., Jones, D. W., Sanchez, C. E., et al. (2004). Prefrontal broadband noise, working memory, and genetic risk for schizophrenia. *Am J Psychiatry, 161*(3), 490-500.

Winterer, G., Ziller, M., Dorn, H., Frick, K., Mulert, C., Wuebben, Y., et al. (2000). Schizophrenia: reduced signal-to-noise ratio and impaired phase-locking during information processing. *Clin Neurophysiol, 111*(5), 837-849.

Womelsdorf, T., Schoffelen, J. M., Oostenveld, R., Singer, W., Desimone, R., Engel, A. K., et al. (2007). Modulation of neuronal interactions through neuronal synchronization. *Science, 316*(5831), 1609-1612.

Wynn, J. K., Lee, J., Horan, W. P., & Green, M. F. (2008). Using event related potentials to explore stages of facial affect recognition deficits in schizophrenia. *Schizophr Bull, 34*(4), 679-687.

Wynn, J. K., Light, G. A., Breitmeyer, B., Nuechterlein, K. H., & Green, M. F. (2005). Event-related gamma activity in schizophrenia patients during a visual backward-masking task. *Am J Psychiatry, 162*(12), 2330-2336.

Yeap, S., Kelly, S. P., Sehatpour, P., Magno, E., Javitt, D. C., Garavan, H., et al. (2006). Early visual sensory deficits as endophenotypes for schizophrenia: high-density electrical mapping in clinically unaffected first-degree relatives. *Arch Gen Psychiatry, 63*(11), 1180-1188.

Yoon, J. H., D'Esposito, M., & Carter, C. S. (2006). Preserved function of the fusiform face area in schizophrenia as revealed by fMRI. *Psychiatry Res, 148*(2-3), 205-216.

Young, A. W., Hellawell, D., & Hay, D. C. (1987). Configurational information in face perception. *Perception, 16*(6), 747-759.

Yuval-Greenberg, S., & Deouell, L. Y. (2007). What you see is not (always) what you hear: induced gamma band responses reflect cross-modal interactions in familiar object recognition. *J Neurosci, 27*(5), 1090-1096.

Zemon, V., & Gordon, J. (2006). Luminance-contrast mechanisms in humans: visual evoked potentials and a nonlinear model. *Vision Res, 46*, 4163-4180.

CHAPTER 2

Abd-El-Barr, M. M., Pennesi, M. E., Saszik, S. M., Barrow, A. J., Lem, J., Bramblett, D. E., et al. (2009). Genetic dissection of rod and cone pathways in the dark-adapted mouse retina. *J Neurophysiol, 102*(3), 1945-1955.

Andreasen, N. C. (1984). *The scale for the assessment of negative symptoms (SANS).* Iowa City: The University of Iowa.

Benedek, G., Benedek, K., Keri, S., & Janaky, M. (2003). The scotopic low-frequency spatial contrast sensitivity develops in children between the ages of 5 and 14 years. *Neurosci Lett, 345*(3), 161-164.

Braff, D. L., & Saccuzzo, D. P. (1982). Effect of antipsychotic medication on speed of information processing in schizophrenic patients. *Am J Psychiatry, 139*(9), 1127-1130.

Braff, D. L., & Saccuzzo, D. P. (1985). The time course of information-processing deficits in schizophrenia. *Am J Psychiatry, 142*(2), 170-174.

Brenner, C. A., Lysaker, P. H., Wilt, M. A., & O'Donnell, B. F. (2002). Visual processing and neuropsychological function in schizophrenia and schizoaffective disorder. *Psychiatry Res, 111*(2-3), 125-136.

Butler, P. D., Abeles, I. Y., Weiskopf, N. G., Tambini, A., Jalbrzikowski, M., Legatt, M. E., et al. (2009). Sensory contributions to impaired emotion processing in schizophrenia. *Schizophr Bull, 35*(6), 1095-1107.

Butler, P. D., Gur, R. C., Jalbrzikowski, M., Loughead, J., Saperstein, A. M., Schechter, I., et al. (2005). Visual processing impairment and emotion recognition dysfunction in schizophrenia. *Internation Congress on Schizophrenia Research Abstract, Savannah, Georgia.*

Butler, P. D., Harkavy-Friedman, J. M., Amador, X. F., & Gorman, J. M. (1996). Backward masking in schizophrenia: relationship to medication status, neuropsychological functioning, and dopamine metabolism. *Biol Psychiatry, 40*(4), 295-298.

Butler, P. D., Martinez, A., Foxe, J. J., Kim, D., Zemon, V., Silipo, G., et al. (2007). Subcortical visual dysfunction in schizophrenia drives secondary cortical impairments. *Brain, 130*, 417-430.

Butler, P. D., Schechter, I., Zemon, V., Schwartz, S. G., Greenstein, V. C., Gordon, J., et al. (2001). Dysfunction of early stage visual processing in schizophrenia. *Am J Psychiatry, 158*(7), 1126-1133.

Butler, P. D., Tambini, A., Yovel, G., Jalbrzikowski, M., Ziwich, R., Silipo, G., et al. (2008). What's in a face? Effects of stimulus duration and inversion on face processing in schizophrenia. *Schizophr Res*.

Butler, P. D., Zemon, V., Schechter, I., Saperstein, A. M., Hoptman, M. J., Lim, K. O., et al. (2005). Early-stage visual processing and cortical amplification deficits in schizophrenia. *Arch Gen Psychiatry, 62*(5), 495-504.

Cadenhead, K. S., Geyer, M. A., Butler, R. W., Perry, W., Sprock, J., & Braff, D. L. (1997). Information processing deficits of schizophrenia patients: relationship to clinical ratings, gender and medication status. *Schizophr Res, 28*(1), 51-62.

Cadenhead, K. S., Serper, Y., & Braff, D. L. (1998). Transient versus sustained visual channels in the visual backward masking deficits of schizophrenia patients. *Biol Psychiatry, 43*(2), 132-138.

Cattapan-Ludewig, K., Hilti, C. C., Ludewig, S., Vollenweider, F. X., & Feldon, J. (2005). Rapid visual information processing in schizophrenic patients: the impact of cognitive load and duration of stimulus presentation. A pilot study. *Neuropsychobiology, 52*(3), 130-134.

Chen, Y., Levy, D. L., Sheremata, S., & Holzman, P. S. (2004). Compromised late-stage motion processing in schizophrenia. *Biol Psychiatry, 55*(8), 834-841.

Chen, Y., Nakayama, K., Levy, D. L., Matthysse, S., & Holzman, P. S. (1999). Psychophysical isolation of a motion-processing deficit in schizophrenics and their relatives and its association with impaired smooth pursuit. *Proc Natl Acad Sci U S A, 96*(8), 4724-4729.

Dacey, D. M., & Petersen, M. R. (1992). Dendritic field size and morphology of midget and parasol ganglion cells of the human retina. *Proc Natl Acad Sci U S A, 89*(20), 9666-9670.

Daitch, J. M., & Green, D. G. (1969). Contrast sensitivity of the human peripheral retina. *Vision Res, 9*(8), 947-952.

Derrington, A. M., & Lennie, P. (1984). Spatial and temporal contrast sensitivities of neurones in lateral geniculate nucleus of macaque. *J Physiol, 357*, 219-240.

Dowling, J. E. (Ed.). (1987). *The Retina, an Approachable Part of the Brain*. Cambridge: Harvard University Press.

Enroth-Cugell, C., Hertz, B. G., & Lennie, P. (1977). Convergence of rod and cone signals in the cat's retina. *J Physiol, 269*(2), 297-318.

Fox, K., Sato, H., & Daw, N. (1990). The effect of varying stimulus intensity on NMDA-receptor activity in cat visual cortex. *J Neurophysiol, 64*(5), 1413-1428.

Gouras, P., & Link, K. (1966). Rod and cone interaction in dark-adapted monkey ganglion cells. *J Physiol, 184*(2), 499-510.

Green, M. F., Nuechterlein, K. H., & Breitmeyer, B. (1997). Backward masking performance in unaffected siblings of schizophrenic patients. Evidence for a vulnerability indicator [published erratum appears in Arch Gen Psychiatry 1997 Sep;54(9):846]. *Arch Gen Psychiatry, 54*(5), 465-472.

Harvey, P. D., Keefe, R. S., Moskowitz, J., Putnam, K. M., Mohs, R. C., & Davis, K. L. (1990). Attentional markers of vulnerability to schizophrenia: performance of medicated and unmedicated patients and normals. *Psychiatry Res, 33*(2), 179-188.

Hawken, M. J., & Parker, A. J. (1984). Contrast sensitivity and orientation selectivity in lamina IV of the striate cortex of Old World monkeys. *Exp Brain Res, 54*(2), 367-372.

Hicks, T. P., Lee, B. B., & Vidyasagar, T. R. (1983). The responses of cells in macaque lateral geniculate nucleus to sinusoidal gratings. *J Physiol, 337*, 183-200.

Hofmann, M. I., Barnes, C. S., & Hallett, P. E. (1990). Detection of briefly flashed sine-gratings in dark-adapted vision. *Vision Res, 30*(10), 1453-1466.

Hollingshead, A. (1975). Four Factor Index of Social Status. Yale University Department of Sociology.

Hyman SE, A. G., Rosenbaum JF (Ed.). (1995). *Handbook of Psychiatric Drug Therapy*. Boston: Little, Brown and Company.

Javitt, D. C., & Zukin, S. R. (1991). Recent advances in the phencyclidine model of schizophrenia. *Am J Psychiatry, 148*(10), 1301-1308.

Jibson, M. D., & Tandon, R. (1998). New atypical antipsychotic medications. *J Psychiatr Res, 32*(3-4), 215-228.

Kaplan, E. (1991). The receptive field structure of retinal ganglion cells in cat and monkey. In A. G. Leventhal (Ed.), *Vision and Visual Dysfunction* (pp. 10-40). Boston: CRC Press.

Kaplan, E., Lee, B., & Shapley, R. (1990). *New Views of primate retinal function.* (Vol. 9). Oxford: Pergamon.

Kelly, D. H. (1972). Adaptation effects on spatio-temporal sine-wave thresholds. *Vision Res, 12*(1), 89-101.

Keri, S., Antal, A., Szekeres, G., Benedek, G., & Janka, Z. (2002). Spatiotemporal visual processing in schizophrenia. *J Neuropsychiatry Clin Neurosci, 14*(2), 190-196.

Keri, S., & Benedek, G. (2007). Visual contrast sensitivity alterations in inferred magnocellular pathways and anomalous perceptual experiences in people at high-risk for psychosis. *Vis Neurosci, 24*(2), 183-189.

Keri, S., Kelemen, O., Benedek, G., & Janka, Z. (2004). Vernier threshold in patients with schizophrenia and in their unaffected siblings. *Neuropsychology, 18*(3), 537-542.

Keri, S., Kiss, I., Kelemen, O., Benedek, G., & Janka, Z. (2005). Anomalous visual experiences, negative symptoms, perceptual organization and the magnocellular pathway in schizophrenia: a shared construct? *Psychol Med, 35*(10), 1445-1455.

Kim, D., Wylie, G., Pasternak, R., Butler, P. D., & Javitt, D. C. (2006). Magnocellular contributions to impaired motion processing in schizophrenia. *Schizophr Res, 82*(1), 1-8.

Kim, D., Zemon, V., Saperstein, A., Butler, P. D., & Javitt, D. C. (2005). Dysfunction of early-stage visual processing in schizophrenia: harmonic analysis. *Schizophr Res, 76*(1), 55-65.

Kraepelin, E. (1904). *Psychiatrie ein lehrbuch for studierende und arzte*. Liepzig: Verlag von Johann Ambrosius Barth.

Kwon, Y. H., Esguerra, M., & Sur, M. (1991). NMDA and non-NMDA receptors mediate visual responses of neurons in the cat's lateral geniculate nucleus. *J Neurophysiol, 66*(2), 414-428.

Laycock, R., Crewther, S. G., & Crewther, D. P. (2007). A role for the 'magnocellular advantage' in visual impairments in neurodevelopmental and psychiatric disorders. *Neurosci Biobehav Rev, 31*(3), 363-376.

Lee, B. B., Smith, V. C., Pokorny, J., & Kremers, J. (1997). Rod inputs to macaque ganglion cells. *Vision Res, 37*(20), 2813-2828.

Liddell, B. J., Brown, K. J., Kemp, A. H., Barton, M. J., Das, P., Peduto, A., et al. (2005). A direct brainstem-amygdala-cortical 'alarm' system for subliminal signals of fear. *Neuroimage, 24*(1), 235-243.

Lund, J. S. (1973). Organization of neurons in the visual cortex, area 17, of the monkey (Macaca mulatta). *J Comp Neurol, 147*(4), 455-496.

Martinez, A., Hillyard, S. A., Dias, E. C., Hagler, D. J., Butler, P. D., Guilfoyle, D. N., et al. (2008). Magnocellular pathway impairment in schizophrenia: evidence from fMRI. *J Neuroscience, 28*(30), 7492-7500.

Merigan, W. H., & Maunsell, J. H. R. (1993). How parallel are the primate visual pathways? In W. M. Cowan, E. M. Shooter, C. F. Stevens & R. F. Thompson (Eds.), *Ann Rev Neuroscience* (pp. 369-402). Palo Alto, CA: Annual Reviews, Inc.

Olney, J. W., & Farber, N. B. (1995). Glutamate receptor dysfunction and schizophrenia. *Arch Gen Psychiatry, 52*(12), 998-1007.

Overall, J. E., & Gorham, D. R. (1962). The brief psychiatric rating scale. *Psychological Reports, 10*, 799-812.

Patel, A. S. (1966). Spatial resolution by the human visual system. The effect of mean retinal illuminance. *J Opt Soc Am, 56*(5), 689-694.

Peuskens, J., & Link, C. G. (1997). A comparison of quetiapine and chlorpromazine in the treatment of schizophrenia. *Acta Psychiatr Scand, 96*(4), 265-273.

Purpura, K., Kaplan, E., & Shapley, R. M. (1988). Background light and the contrast gain of primate P and M retinal ganglion cells. *Proc Natl Acad Sci U S A, 85*(12), 4534-4537.

Saccuzzo, D. P., & Braff, D. L. (1981). Early information processing deficit in schizophrenia. New findings using schizophrenic subgroups and manic control subjects. *Arch Gen Psychiatry, 38*(2), 175-179.

Saccuzzo, D. S., Cadenhead, K. S., & Braff, D. L. (1996). Backward versus forward visual masking deficits in schizophrenic patients: centrally, not peripherally, mediated? *Am J Psychiatry, 153*(12), 1564-1570.

Savage, G. L., & Banks, M. S. (1992). Scotopic visual efficiency: constraints by optics, receptor properties, and rod pooling. *Vision Res, 32*(4), 645-656.

Schechter, I., Butler, P. D., Silipo, G., Zemon, V., & Javitt, D. C. (2003). Magnocellular and parvocellular contributions to backward masking dysfunction in schizophrenia. *Schizophrenia Research, 64*, 91-101.

Schiller, P. H., Malpeli, J. G., & Schein, S. J. (1979). Composition of geniculostriate input ot superior colliculus of the rhesus monkey. *J Neurophysiol, 42*(4), 1124-1133.

Schroeder, C. E., Mehta, A. D., & Givre, S. J. (1998). A spatiotemporal profile of visual system activation revealed by current source density analysis in the awake macaque. *Cereb Cortex, 8*(7), 575-592.

Schwartz, B. D., Evans, W. J., Sautter, F., Pena, J. M., & Winstead, D. K. (1992). Deficits in initial feature registration of schizophrenics and substance abusers. *Schizophr Res, 7*(3), 217-224.

Sergi, M. J., & Green, M. F. (2003). Social perception and early visual processing in schizophrenia. *Schizophr Res, 59*(2-3), 233-241.

Sergi, M. J., Rassovsky, Y., Nuechterlein, K. H., & Green, M. F. (2006). Social perception as a mediator of the influence of early visual processing on functional status in schizophrenia. *Am J Psychiatry, 163*(3), 448-454.

Slaghuis, W. L. (1998). Contrast sensitivity for stationary and drifting spatial frequency gratings in positive- and negative-symptom schizophrenia. *J Abnorm Psychol, 107*(1), 49-62.

Slaghuis, W. L. (2004). Spatio-temporal luminance contrast sensitivity and visual backward masking in schizophrenia. *Exp Brain Res, 156*(2), 196-211.

Slaghuis, W. L., & Bakker, V. J. (1995). Forward and backward visual masking of contour by light in positive- and negative-symptom schizophrenia. *J Abnorm Psychol, 104*(1), 41-54.

Slaghuis, W. L., & Bishop, A. M. (2001). Luminance flicker sensitivity in positive- and negative-symptom schizophrenia. *Exp Brain Res, 138*(1), 88-99.

Slaghuis, W. L., & Thompson, A. K. (2003). The effect of peripheral visual motion on focal contrast sensitivity in positive- and negative-symptom schizophrenia. *Neuropsychologia, 41*(8), 968-980.

Tootell, R. B., Hamilton, S. L., & Switkes, E. (1988). Functional anatomy of macaque striate cortex. IV. Contrast and magno-parvo streams. *J Neurosci, 8*(5), 1594-1609.

Tootell, R. B., Silverman, M. S., Hamilton, S. L., Switkes, E., & De Valois, R. L. (1988). Functional anatomy of macaque striate cortex. V. Spatial frequency. *J Neurosci, 8*(5), 1610-1624.

Tsai, G., & Coyle, J. T. (2002). Glutamatergic mechanisms in schizophrenia. *Annu Rev Pharmacol Toxicol, 42*, 165-179.

Weiner, R. U., Opler, L. A., Kay, S. R., Merriam, A. E., & Papouchis, N. (1990). Visual information processing in positive, mixed, and negative schizophrenic syndromes. *J Nerv Ment Dis, 178*(10), 616-626.

Yeap, S., Kelly, S. P., Sehatpour, P., Magno, E., Javitt, D. C., Garavan, H., et al. (2006). Early visual sensory deficits as endophenotypes for schizophrenia: high-density electrical mapping in clinically unaffected first-degree relatives. *Arch Gen Psychiatry, 63*(11), 1180-1188.

CHAPTER 3

Addington, J., & Addington, D. (1998). Facial affect recognition and information processing in schizophrenia and bipolar disorder. *Schizophr Res, 32*(3), 171-181.

Addington, J., Addington, D., & Gasbarre, L. (2001). Neurocognitive and social functioning in schizophrenia and other diagnoses. *Schizophr Res, 48*(2-3), 367-368.

Adolphs, R., Tranel, D., & Buchanan, T. W. (2005). Amygdala damage impairs emotional memory for gist but not details of complex stimuli. *Nat Neurosci, 8*(4), 512-518.

Aggleton, J. P., Burton, M. J., & Passingham, R. E. (1980). Cortical and subcortical afferents to the amygdala of the rhesus monkey (Macaca mulatta). *Brain Res, 190*(2), 347-368.

Amaral, D. G., Behniea, H., & Kelly, J. L. (2003). Topographic organization of projections from the amygdala to the visual cortex in the macaque monkey. *Neuroscience, 118*(4), 1099-1120.

Andreasen, N. C. (1984). *The scale for the assessment of negative symptoms (SANS)*. Iowa City: The University of Iowa.

Balconi, M., & Pozzoli, U. (2003). Face-selective processing and the effect of pleasant and unpleasant emotional expressions on ERP correlates. *Int J Psychophysiol, 49*(1), 67-74.

Bar, M., Neta, M., & Linz, H. (2006). Very first impressions. *Emotion, 6*(2), 269-278.

Batty, M., & Taylor, M. J. (2003). Early processing of the six basic facial emotional expressions. *Brain Res Cogn Brain Res, 17*(3), 613-620.

Bentin, S., Allison, T., Puce, A., Perez, E., & McCarthy, G. (1996). Electrophysiological studies of face perception in humans. *Journal of Cognitive Neuroscience, 8*, 551-565.

Blau, V. C., Maurer, U., Tottenham, N., & McCandliss, B. D. (2007). The face-specific N170 component is modulated by emotional facial expression. *Behav Brain Funct, 3*, 7.

Borod, J. C., Martin, C. C., Alpert, M., Brozgold, A., & Welkowitz, J. (1993). Perception of facial emotion in schizophrenic and right brain-damaged patients. *J Nerv Ment Dis, 181*(8), 494-502.

Brekke, J., Kay, D. D., Lee, K. S., & Green, M. F. (2005). Biosocial pathways to functional outcome in schizophrenia. *Schizophr Res, 80*(2-3), 213-225.

Brenner, C. A., Wilt, M. A., Lysaker, P. H., Koyfman, A., & O'Donnell, B. F. (2003). Psychometrically matched visual-processing tasks in schizophrenia spectrum disorders. *J Abnorm Psychol, 112*(1), 28-37.

Butler, P. D., Abeles, I. Y., Weiskopf, N. G., Tambini, A., Jalbrzikowski, M., Legatt, M. E., et al. (2009). Sensory contributions to impaired emotion processing in schizophrenia. *Schizophr Bull, 35*(6), 1095-1107.

Butler, P. D., Kim, D., Foxe, J. J., Piesco, J. R., Hoptman, M. J., Lim, K. O., et al. (2004). Decreased signal amplification in schizophrenia: evidence from visual studies. *Society for Neuroscience Abstracts*, Program No. 348.341.

Butler, P. D., Martinez, A., Foxe, J. J., Kim, D., Zemon, V., Silipo, G., et al. (2007). Subcortical visual dysfunction in schizophrenia drives secondary cortical impairments. *Brain, 130*, 417-430.

Butler, P. D., Silverstein, S. M., & Dakin, S. C. (2008). Visual perception and its impairment in schizophrenia. *Biol Psychiatry, 64*(1), 40-47.

Butler, P. D., Tambini, A., Yovel, G., Jalbrzikowski, M., Ziwich, R., Silipo, G., et al. (2008). What's in a face? Effects of stimulus duration and inversion on face processing in schizophrenia. *Schizophr Res*.

Butler, P. D., Zemon, V., Schechter, I., Saperstein, A. M., Hoptman, M. J., Lim, K. O., et al. (2005). Early-stage visual processing and cortical amplification deficits in schizophrenia. *Arch Gen Psychiatry, 62*(5), 495-504.

Caharel, S., Bernard, C., Thibaut, F., Haouzir, S., Di Maggio-Clozel, C., Allio, G., et al. (2007). The effects of familiarity and emotional expression on face processing examined by ERPs in patients with schizophrenia. *Schizophr Res, 95*(1-3), 186-196.

Caharel, S., Courtay, N., Bernard, C., Lalonde, R., & Rebai, M. (2005). Familiarity and emotional expression influence an early stage of face processing: an electrophysiological study. *Brain Cogn, 59*(1), 96-100.

Calder, A. J., Rowland, D., Young, A. W., Nimmo-Smith, I., Keane, J., & Perrett, D. I. (2000). Caricaturing facial expressions. *Cognition, 76*(2), 105-146.

Campanella, S., Montedoro, C., Streel, E., Verbanck, P., & Rosier, V. (2006). Early visual components (P100, N170) are disrupted in chronic schizophrenic patients: an event-related potentials study. *Neurophysiol Clin, 36*(2), 71-78.

Campanella, S., Quinet, P., Bruyer, R., Crommelinck, M., & Guerit, J. M. (2002). Categorical perception of happiness and fear facial expressions: an ERP study. *J Cogn Neurosci, 14*(2), 210-227.

Carretie, L., Martin-Loeches, M., Hinojosa, J. A., & Mercado, F. (2001). Emotion and attention interaction studied through event-related potentials. *J Cogn Neurosci, 13*(8), 1109-1128.

Carretie, L., Mercado, F., Tapia, M., & Hinojosa, J. A. (2001). Emotion, attention, and the 'negativity bias', studied through event-related potentials. *Int J Psychophysiol, 41*(1), 75-85.

Chen, Y., Nakayama, K., Levy, D., Matthysse, S., & Holzman, P. (2003). Processing of global, but not local, motion direction is deficient in schizophrenia. *Schizophr Res, 61*(2-3), 215-227.

Cowey, A., & Stoerig, P. (1991). The neurobiology of blindsight. *Trends Neurosci, 14*(4), 140-145.

Doniger, G. M., Foxe, J. J., Murrary, M. M., Higgins, B. A., & Javitt, D. C. (2002). Impaired visual object recogntion and dorsal/ventral stream interaction in schizophrenia. *Arch Gen Psychiatry, 59*, 1011-1020.

Edwards, J., Jackson, H. J., & Pattison, P. E. (2002). Emotion recognition via facial expression and affective prosody in schizophrenia: a methodological review. *Clin Psychol Rev, 22*, 789-832.

Edwards, J., Pattison, P. E., Jackson, H. J., & Wales, R. J. (2001). Facial affect and affective prosody recognition in first-episode schizophrenia. *Schizophr Res, 48*(2-3), 235-253.

Eimer, M. (2000). The face-specific N170 component reflects late stages in the structural encoding of faces. *Neuroreport, 11*(10), 2319-2324.

Eimer, M., & Holmes, A. (2002). An ERP study on the time course of emotional face processing. *Neuroreport, 13*(4), 427-431.

Eimer, M., & Holmes, A. (2007). Event-related brain potential correlates of emotional face processing. *Neuropsychologia, 45*(1), 15-31.

Eimer, M., Holmes, A., & McGlone, F. P. (2003). The role of spatial attention in the processing of facial expression: an ERP study of rapid brain responses to six basic emotions. *Cogn Affect Behav Neurosci, 3*(2), 97-110.

Ekman, P., & Friesen, W. V. (1976). *Pictures of facial affect*. Palo Alto: Consulting Psychologists Press.

Feinberg, T. E., Rifkin, A., Schaffer, C., & Walker, E. (1986). Facial discrimination and emotional recognition in schizophrenia and affective disorders. *Arch Gen Psychiatry, 43*(3), 276-279.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (1997). *Structured Clinical Interview for DSM-IV Axis I Disorders- Patient Edition*. New York: New York State Psychiatric Institute.

Foxe, J. J., Doniger, G. M., & Javitt, D. C. (2001). Early visual processing deficits in schizophrenia: impaired PI generation revealed by high-density electrical mapping. *NeuroReport, 12*(17).

Foxe, J. J., Murray, M. M., & Javitt, D. C. (2005). Filling-in in Schizophrenia: a High-density Electrical Mapping and Source-analysis Investigation of Illusory Contour Processing. *Cereb Cortex, 15*(12), 1914-1927.

Freese, J. L., & Amaral, D. G. (2005). The organization of projections from the amygdala to visual cortical areas TE and V1 in the macaque monkey. *J Comp Neurol, 486*(4), 295-317.

Fukuda, M., Ono, T., & Nakamura, K. (1987). Functional relations among inferotemporal cortex, amygdala, and lateral hypothalamus in monkey operant feeding behavior. *J Neurophysiol, 57*(4), 1060-1077.

Galletly, C. A., Clark, C. R., & McFarlane, A. C. (2005). Clozapine improves working memory updating in schizophrenia. *Eur Neuropsychopharmacol, 15*(6), 601-608.

Goffaux, V., Gauthier, I., & Rossion, B. (2003). Spatial scale contribution to early visual differences between face and object processing. *Brain Res Cogn Brain Res, 16*(3), 416-424.

Gosselin, F., & Schyns, P. G. (2001). Bubbles: a technique to reveal the use of information in recognition tasks. *Vision Res, 41*(17), 2261-2271.

Gur, R. E., McGrath, C., Chan, R. M., Schroeder, L., Turner, T., Turetsky, B. I., et al. (2002). An fMRI study of facial emotion processing in patients with schizophrenia. *Am J Psychiatry, 159*(12), 1992-1999.

Gur, R. E., Turetsky, B. I., Cowell, P. E., Finkelman, C., Maany, V., Grossman, R. I., et al. (2000). Temporolimbic volume reductions in schizophrenia. *Arch Gen Psychiatry, 57*(8), 769-775.

Haenschel, C., Waltz, J., Bittner, R. A., Hartling, F., Rotarska-Jagiela, A., Maurer, K., et al. (2004). Intertrial synchronization deficits account for reduced P1 and high-frequency EEG activity in schizophrenia. *Society for Neuroscience Abstracts*, Program No. 348.343.

Halit, H., de Haan, M., Schyns, P. G., & Johnson, M. H. (2006). Is high-spatial frequency information used in the early stages of face detection? *Brain Res, 1117*(1), 154-161.

Heimberg, C., Gur, R. E., Erwin, R. J., Shtasel, D. L., & Gur, R. C. (1992). Facial emotion discrimination: III. Behavioral findings in schizophrenia. *Psychiatry Res, 42*(3), 253-265.

Herbener, E. S., Rosen, C., Khine, T., & Sweeney, J. A. (2007). Failure of positive but not negative emotional valence to enhance memory in schizophrenia. *J Abnorm Psychol, 116*(1), 43-55.

Herrmann, M. J., Ehlis, A. C., Muehlberger, A., & Fallgatter, A. J. (2005). Source localization of early stages of face processing. *Brain Topogr, 18*(2), 77-85.

Herrmann, M. J., Ellgring, H., & Fallgatter, A. J. (2004). Early-Stage face processing dysfunction in patients with schizophrenia. *Am J Psychiatry, 161*(5), 915-917.

Holmes, A., Winston, J. S., & Eimer, M. (2005). The role of spatial frequency information for ERP components sensitive to faces and emotional facial expression. *Brain Res Cogn Brain Res, 25*(2), 508-520.

Hollingshead, A. (1975). Four Factor Index of Social Status. Yale University Department of Sociology.

Holt, D. J., Kunkel, L., Weiss, A. P., Goff, D. C., Wright, C. I., Shin, L. M., et al. (2006). Increased medial temporal lobe activation during the passive viewing of emotional and neutral facial expressions in schizophrenia. *Schizophr Res, 82*(2-3), 153-162.

Horan, W. P., Green, M. F., Kring, A. M., & Nuechterlein, K. H. (2006). Does anhedonia in schizophrenia reflect faulty memory for subjectively experienced emotions? *J Abnorm Psychol, 115*(3), 496-508.

Horley, K., Gonsalvez, C., Williams, L., Lazzaro, I., Bahramali, H., & Gordon, E. (2001). Event-related potentials to threat-related faces in schizophrenia. *Int J Neurosci, 107*(1-2), 113-130.

Hyman SE, A. G., Rosenbaum JF (Ed.). (1995). *Handbook of Psychiatric Drug Therapy*. Boston: Little, Brown and Company.

Itier, R. J., & Taylor, M. J. (2004). Source analysis of the N170 to faces and objects. *Neuroreport, 15*(8), 1261-1265.

Iwai, E., Yukie, M., Suyama, H., & Shirakawa, S. (1987). Amygdalar connections with middle and inferior temporal gyri of the monkey. *Neurosci Lett, 83*(1-2), 25-29.

Iwai, E., Yukie, M., Watanabe, J., Hikosaka, K., Suyama, H., & Ishikawa, S. (1990). A role of amygdala in visual perception and cognition in macaque monkeys (Macaca fuscata and Macaca mulatta). *Tohoku J Exp Med, 161 Suppl*, 95-120.

Javitt, D. C., & Zukin, S. R. (1991). Recent advances in the phencyclidine model of schizophrenia. *Am J Psychiatry, 148*(10), 1301-1308.

Jibson, M. D., & Tandon, R. (1998). New atypical antipsychotic medications. *J Psychiatr Res, 32*(3-4), 215-228.

Johnston, P. J., Stojanov, W., Devir, H., & Schall, U. (2005). Functional MRI of facial emotion recognition deficits in schizophrenia and their electrophysiological correlates. *Eur J Neurosci, 22*(5), 1221-1232.

Joyce, C., & Rossion, B. (2005). The face-sensitive N170 and VPP components manifest the same brain processes: the effect of reference electrode site. *Clin Neurophysiol, 116*(11), 2613-2631.

Kee, K. S., Green, M. F., Mintz, J., & Brekke, J. S. (2003). Is emotion processing a predictor of functional outcome in schizophrenia? *Schizophr Bull, 29*(3), 487-497.

Keil, A., Muller, M. M., Gruber, T., Wienbruch, C., Stolarova, M., & Elbert, T. (2001). Effects of emotional arousal in the cerebral hemispheres: a study of oscillatory brain activity and event-related potentials. *Clin Neurophysiol, 112*(11), 2057-2068.

Keri, S., Antal, A., Szekeres, G., Benedek, G., & Janka, Z. (2002). Spatiotemporal visual processing in schizophrenia. *J Neuropsychiatry Clin Neurosci, 14*(2), 190-196.

Keri, S., Kelemen, O., Benedek, G., & Janka, Z. (2004). Vernier threshold in patients with schizophrenia and in their unaffected siblings. *Neuropsychology, 18*(3), 537-542.

Kerr, S. L., & Neale, J. M. (1993). Emotion perception in schizophrenia: specific deficit or further evidence of generalized poor performance? *J Abnorm Psychol, 102*(2), 312-318.

Kim, D., Zemon, V., Saperstein, A., Butler, P. D., & Javitt, D. C. (2005). Dysfunction of early-stage visual processing in schizophrenia: harmonic analysis. *Schizophr Res, 76*(1), 55-65.

Kohler, C. G., Bilker, W., Hagendoorn, M., Gur, R. E., & Gur, R. C. (2000). Emotion recognition deficit in schizophrenia: association with symptomatology and cognition. *Biol Psychiatry, 48*(2), 127-136.

Kohler, C. G., Turner, T. H., Bilker, W. B., Brensinger, C. M., Siegel, S. J., Kanes, S. J., et al. (2003). Facial emotion recognition in schizophrenia: intensity effects and error pattern. *Am J Psychiatry, 160*(10), 1768-1774.

Kring, A. M., Kerr, S. L., Smith, D. A., & Neale, J. M. (1993). Flat affect in schizophrenia does not reflect diminished subjective experience of emotion. *J Abnorm Psychol, 102*(4), 507-517.

Kring, A. M., & Moran, E. K. (2008). Emotional response deficits in schizophrenia: insights from affective science. *Schizophr Bull, 34*(5), 819-834.

Krolak-Salmon, P., Fischer, C., Vighetto, A., & Mauguiere, F. (2001). Processing of facial emotional expression: spatio-temporal data as assessed by scalp event-related potentials. *Eur J Neurosci, 13*(5), 987-994.

Kveraga, K., Boshyan, J., & Bar, M. (2007). Magnocellular projections as the trigger of top-down facilitation in recognition. *J Neurosci, 27*(48), 13232-13240.

Kwon, Y. H., Nelson, S. B., Toth, L. J., & Sur, M. (1992). Effect of stimulus contrast and size on NMDA receptor activity in cat lateral geniculate nucleus. *J Neurophysiol, 68*(1), 182-196.

Lee, J., Gosselin, F., Wynn, J. K., & Green, M. F. (2010). How Do Schizophrenia Patients Use Visual Information to Decode Facial Emotion? *Schizophr Bull.*

Lee, S. H., Kim, E. Y., Kim, S., & Bae, S. M. (2010). Event-related potential patterns and gender effects underlying facial affect processing in schizophrenia patients. *Neurosci Res, 67*(2), 172-180.

Li, H., Chan, R. C., McAlonan, G. M., & Gong, Q. Y. (2009). Facial emotion processing in schizophrenia: a meta-analysis of functional neuroimaging data. *Schizophr Bull, 36*(5), 1029-1039.

Liddell, B. J., Brown, K. J., Kemp, A. H., Barton, M. J., Das, P., Peduto, A., et al. (2005). A direct brainstem-amygdala-cortical 'alarm' system for subliminal signals of fear. *Neuroimage, 24*(1), 235-243.

Lynn, S. K., & Salisbury, D. F. (2008). Attenuated modulation of the N170 ERP by facial expressions in schizophrenia. *Clin EEG Neurosci, 39*(2), 108-111.

Mandal, M. K., Pandey, R., & Prasad, A. B. (1998). Facial expressions of emotions and schizophrenia: a review. *Schizophr Bull, 24*(3), 399-412.

Martinez, A., Hillyard, S. A., Dias, E. C., Hagler, D. J., Butler, P. D., Guilfoyle, D. N., et al. (2008). Magnocellular pathway impairment in schizophrenia: evidence from fMRI. *J Neuroscience, 28*(30), 7492-7500.

Morris, J. S., deBonis, M., & Dolan, R. J. (2002). Human amygdala responses to fearful eyes. *Neuroimage, 17*(1), 214-222.

Morris, J. S., DeGelder, B., Weiskrantz, L., & Dolan, R. J. (2001). Differential extrageniculostriate and amygdala responses to presentation of emotional faces in a cortically blind field. *Brain, 124*(Pt 6), 1241-1252.

Morris, J. S., Ohman, A., & Dolan, R. J. (1998). Conscious and unconscious emotional learning in the human amygdala. *Nature, 393*(6684), 467-470.

Morris, J. S., Ohman, A., & Dolan, R. J. (1999). A subcortical pathway to the right amygdala mediating "unseen" fear. *Proc Natl Acad Sci U S A, 96*(4), 1680-1685.

Mueser, K. T., Doonan, R., Penn, D. L., Blanchard, J. J., Bellack, A. S., Nishith, P., et al. (1996). Emotion recognition and social competence in chronic schizophrenia. *J Abnorm Psychol, 105*(2), 271-275.

Nakashima, T., Kaneko, K., Goto, Y., Abe, T., Mitsudo, T., Ogata, K., et al. (2008). Early ERP components differentially extract facial features: evidence for spatial frequency-and-contrast detectors. *Neurosci Res, 62*(4), 225-235.

Neuhaus, A. H., Karl, C., Hahn, E., Trempler, N. R., Opgen-Rhein, C., Urbanek, C., et al. (2011). Dissection of early bottom-up and top-down deficits during visual attention in schizophrenia. *Clin Neurophysiol, 122*(1), 90-98.

Norton, D., McBain, R., Holt, D. J., Ongur, D., & Chen, Y. (2009). Association of impaired facial affect recognition with basic facial and visual processing deficits in schizophrenia. *Biol Psychiatry, 65*(12), 1094-1098.

O'Donnell, B. F., Potts, G. F., Nestor, P. G., Stylianopoulos, K. C., Shenton, M. E., & McCarley, R. W. (2002). Spatial frequency discrimination in schizophrenia. *J Abnorm Psychol, 111*(4), 620-625.

Obayashi, C., Nakashima, T., Onitsuka, T., Maekawa, T., Hirano, Y., Hirano, S., et al. (2009). Decreased spatial frequency sensitivities for processing faces in male patients with chronic schizophrenia. *Clin Neurophysiol, 120*(8), 1525-1533.

Ojanpaa, H., & Nasanen, R. (2003). Utilisation of spatial frequency information in face search. *Vision Res, 43*(24), 2505-2515.

Overall, J. E., & Gorham, D. R. (1962). The brief psychiatric rating scale. *Psychological Reports, 10*, 799-812.

Penn, D. L., Corrigan, P. W., Bentall, R. P., Racenstein, J. M., & Newman, L. (1997). Social cognition in schizophrenia. *Psychol Bull, 121*, 114-132.

Peuskens, J., & Link, C. G. (1997). A comparison of quetiapine and chlorpromazine in the treatment of schizophrenia. *Acta Psychiatr Scand, 96*(4), 265-273.

Pizzagalli, D., Regard, M., & Lehmann, D. (1999). Rapid emotional face processing in the human right and left brain hemispheres: an ERP study. *Neuroreport, 10*(13), 2691-2698.

Pizzagalli, D. A., Lehmann, D., Hendrick, A. M., Regard, M., Pascual-Marqui, R. D., & Davidson, R. J. (2002). Affective judgments of faces modulate early activity (approximately 160 ms) within the fusiform gyri. *Neuroimage, 16*(3 Pt 1), 663-677.

Pourtois, G., Dan, E. S., Grandjean, D., Sander, D., & Vuilleumier, P. (2005). Enhanced extrastriate visual response to bandpass spatial frequency filtered fearful faces: time course and topographic evoked-potentials mapping. *Hum Brain Mapp, 26*(1), 65-79.

Sabatinelli, D., Lang, P. J., Bradley, M. M., Costa, V. D., & Keil, A. (2009). The timing of emotional discrimination in human amygdala and ventral visual cortex. *J Neurosci, 29*(47), 14864-14868.

Schechter, I., Butler, P. D., Silipo, G., Zemon, V., & Javitt, D. C. (2003). Magnocellular and parvocellular contributions to backward masking dysfunction in schizophrenia. *Schizophrenia Research, 64*, 91-101.

Schechter, I., Butler, P. D., Zemon, V. M., Revheim, N., Saperstein, A. M., Jalbrzikowski, M., et al. (2005). Impairments in generation of early-stage transient visual evoked potentials to magno- and parvocellular-selective stimuli in schizophrenia. *Clin Neurophysiol, 116*(9), 2204-2215.

Schiller, P. H., Malpeli, J. G., & Schein, S. J. (1979). Composition of geniculostriate input ot superior colliculus of the rhesus monkey. *J Neurophysiol, 42*(4), 1124-1133.

Schroeder, C. E., Mehta, A. D., & Givre, S. J. (1998). A spatiotemporal profile of visual system activation revealed by current source density analysis in the awake macaque. *Cereb Cortex, 8*(7), 575-592.

Schutter, D. J., de Haan, E. H., & van Honk, J. (2004). Functionally dissociated aspects in anterior and posterior electrocortical processing of facial threat. *Int J Psychophysiol, 53*(1), 29-36.

Schyns, P. G., & Oliva, A. (1999). Dr. Angry and Mr. Smile: when categorization flexibly modifies the perception of faces in rapid visual presentations. *Cognition, 69*(3), 243-265.

Sehatpour, P., Dias, E. C., Butler, P. D., Revheim, N., Guilfoyle, D. N., Foxe, J. J., et al. (2010). Impaired visual object processing across an occipital-frontal-hippocampal brain network in schizophrenia: an integrated neuroimaging study. *Arch Gen Psychiatry, 67*(8), 772-782.

Sergi, M. J., Rassovsky, Y., Nuechterlein, K. H., & Green, M. F. (2006). Social perception as a mediator of the influence of early visual processing on functional status in schizophrenia. *Am J Psychiatry, 163*(3), 448-454.

Shibata, T., Nishijo, H., Tamura, R., Miyamoto, K., Eifuku, S., Endo, S., et al. (2002). Generators of visual evoked potentials for faces and eyes in the human brain as determined by dipole localization. *Brain Topogr, 15*(1), 51-63.

Slaghuis, W. L. (1998). Contrast sensitivity for stationary and drifting spatial frequency gratings in positive- and negative-symptom schizophrenia. *J Abnorm Psychol, 107*(1), 49-62.

Slaghuis, W. L. (2004). Spatio-temporal luminance contrast sensitivity and visual backward masking in schizophrenia. *Exp Brain Res, 156*(2), 196-211.

Slaghuis, W. L., & Thompson, A. K. (2003). The effect of peripheral visual motion on focal contrast sensitivity in positive- and negative-symptom schizophrenia. *Neuropsychologia, 41*(8), 968-980.

Spencer, K. M., Nestor, P. G., Niznikiewicz, M. A., Salisbury, D. F., Shenton, M. E., & McCarley, R. W. (2003). Abnormal neural synchrony in schizophrenia. *J Neurosci, 23*(19), 7407-7411.

Spiegler, B. J., & Mishkin, M. (1981). Evidence for the sequential participation of inferior temporal cortex and amygdala in the acquisition of stimulus-reward associations. *Behav Brain Res, 3*(3), 303-317.

Streit, M., Wolwer, W., Brinkmeyer, J., Ihl, R., & Gaebel, W. (2001). EEG-correlates of facial affect recognition and categorisation of blurred faces in schizophrenic patients and healthy volunteers. *Schizophr Res, 49*(1-2), 145-155.

Streit, M., Wolwer, W., & Gaebel, W. (1997). Facial-affect recognition and visual scanning behaviour in the course of schizophrenia. *Schizophr Res, 24*(3), 311-317.

Tanaka, J. W., Curran, T., Porterfield, A. L., & Collins, D. (2006). Activation of preexisting and acquired face representations: the N250 event-related potential as an index of face familiarity. *J Cogn Neurosci, 18*(9), 1488-1497.

Turetsky, B. I., Kohler, C. G., Indersmitten, T., Bhati, M. T., Charbonnier, D., & Gur, R. C. (2007). Facial emotion recognition in schizophrenia: when and why does it go awry? *Schizophr Res, 94*(1-3), 253-263.

Vlamings, P. H., Goffaux, V., & Kemner, C. (2009). Is the early modulation of brain activity by fearful facial expressions primarily mediated by coarse low spatial frequency information? *J Vis, 9*(5), 12 11-13.

Vuilleumier, P., Armony, J. L., Driver, J., & Dolan, R. J. (2003). Distinct spatial frequency sensitivities for processing faces and emotional expressions. *Nat Neurosci, 6*(6), 624-631.

Vuilleumier, P., Richardson, M. P., Armony, J. L., Driver, J., & Dolan, R. J. (2004). Distant influences of amygdala lesion on visual cortical activation during emotional face processing. *Nat Neurosci, 7*(11), 1271-1278.

Walker, E., McGuire, M., & Bettes, B. (1984). Recognition and identification of facial stimuli by schizophrenics and patients with affective disorders. *Br J Clin Psychol, 23 (Pt 1)*, 37-44.

Whalen, P. J., Kagan, J., Cook, R. G., Davis, F. C., Kim, H., Polis, S., et al. (2004). Human amygdala responsivity to masked fearful eye whites. *Science, 306*(5704), 2061.

Winston, J. S., Vuilleumier, P., & Dolan, R. J. (2003). Effects of low-spatial frequency components of fearful faces on fusiform cortex activity. *Curr Biol, 13*(20), 1824-1829.

Woods, S. W. (2003). Chlorpromazine equivalent doses for the newer atypical antipsychotics. *J Clin Psychiatry, 64*(6), 663-667.

Wynn, J. K., Lee, J., Horan, W. P., & Green, M. F. (2008). Using event related potentials to explore stages of facial affect recognition deficits in schizophrenia. *Schizophr Bull, 34*(4), 679-687.

Yeap, S., Kelly, S. P., Sehatpour, P., Magno, E., Javitt, D. C., Garavan, H., et al. (2006). Early visual sensory deficits as endophenotypes for schizophrenia: high-density electrical mapping in clinically unaffected first-degree relatives. *Arch Gen Psychiatry, 63*(11), 1180-1188.

Yoon, J. H., D'Esposito, M., & Carter, C. S. (2006). Preserved function of the fusiform face area in schizophrenia as revealed by fMRI. *Psychiatry Res, 148*(2-3), 205-216.

CHAPTER 4

Andreasen, N. C. (1984). *The scale for the assessment of negative symptoms (SANS)*. Iowa City: The University of Iowa.

Axmacher, N., Henseler, M. M., Jensen, O., Weinreich, I., Elger, C. E., & Fell, J. (2010). Cross-frequency coupling supports multi-item working memory in the human hippocampus. *Proc Natl Acad Sci U S A, 107*(7), 3228-3233.

Basar-Eroglu, C., Brand, A., Hildebrandt, H., Karolina Kedzior, K., Mathes, B., & Schmiedt, C. (2007). Working memory related gamma oscillations in schizophrenia patients. *Int J Psychophysiol, 64*(1), 39-45.

Bastiaansen, M. C., Bocker, K. B., Brunia, C. H., de Munck, J. C., & Spekreijse, H. (2001). Event-related desynchronization during anticipatory attention for an upcoming stimulus: a comparative EEG/MEG study. *Clin Neurophysiol, 112*(2), 393-403.

Bates, A. T., Kiehl, K. A., Laurens, K. R., & Liddle, P. F. (2009). Low-frequency EEG oscillations associated with information processing in schizophrenia. *Schizophr Res, 115*(2-3), 222-230.

Battaglia, F. P., Sutherland, G. R., & McNaughton, B. L. (2004). Hippocampal sharp wave bursts coincide with neocortical "up-state" transitions. *Learn Mem, 11*(6), 697-704.

Bishop, G. (1932). Cyclical changes in excitability of the optic pathways of the rabbit. *American Journal of Physiology, 103*, 213-224.

Boutros, N. N., Arfken, C., Galderisi, S., Warrick, J., Pratt, G., & Iacono, W. (2008). The status of spectral EEG abnormality as a diagnostic test for schizophrenia. *Schizophr Res, 99*(1-3), 225-237.

Boutros, N. N., & Arfken, C. L. (2007). A four-step approach for developing diagnostic tests in psychiatry. *Clin EEG Neurosci, 38*(2), 62-65.

Butler, P. D., Martinez, A., Foxe, J. J., Kim, D., Zemon, V., Silipo, G., et al. (2007). Subcortical visual dysfunction in schizophrenia drives secondary cortical impairments. *Brain, 130*, 417-430.

Butler, P. D., Zemon, V., Schechter, I., Saperstein, A. M., Hoptman, M. J., Lim, K. O., et al. (2005). Early-stage visual processing and cortical amplification deficits in schizophrenia. *Arch Gen Psychiatry, 62*(5), 495-504.

Buzsaki, G. (2005). Theta rhythm of navigation: link between path integration and landmark navigation, episodic and semantic memory. *Hippocampus, 15*(7), 827-840.

Buzsaki, G. (2006). *Rhythms of the Brain*. USA: Oxford University Press.

Canolty, R. T., Edwards, E., Dalal, S. S., Soltani, M., Nagarajan, S. S., Kirsch, H. E., et al. (2006). High gamma power is phase-locked to theta oscillations in human neocortex. *Science, 313*(5793), 1626-1628.

Canolty, R. T., & Knight, R. T. (2010). The functional role of cross-frequency coupling. *Trends Cogn Sci, 14*(11), 506-515.

Cho, R. Y., Konecky, R. O., & Carter, C. S. (2006). Impairments in frontal cortical gamma synchrony and cognitive control in schizophrenia. *Proc Natl Acad Sci U S A, 103*(52), 19878-19883.

Dakin, S., Carlin, P., & Hemsley, D. (2005). Weak suppression of visual context in chronic schizophrenia. *Curr Biol, 15*(20), R822-824.

Daw, N. W., Stein, P. S. G., & Fox, K. (1993). The role of NMDA receptors in information processing. *Ann Rev Neurosci, 16*, 207-222.

Ekman, P., & Friesen, W. V. (1976). *Pictures of facial affect*. Palo Alto: Consulting Psychologists Press.

Ergen, M., Marbach, S., Brand, A., Basar-Eroglu, C., & Demiralp, T. (2008). P3 and delta band responses in visual oddball paradigm in schizophrenia. *Neurosci Lett, 440*(3), 304-308.

Fehr, T., Kissler, J., Wienbruch, C., Moratti, S., Elbert, T., Watzl, H., et al. (2003). Source distribution of neuromagnetic slow-wave activity in schizophrenic patients--effects of activation. *Schizophr Res, 63*(1-2), 63-71.

Fenton, G. W., Fenwick, P. B., Dollimore, J., Dunn, T. L., & Hirsch, S. R. (1980). EEG spectral analysis in schizophrenia. *Br J Psychiatry, 136*, 445-455.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (1997). *Structured Clinical Interview for DSM-IV Axis I Disorders- Patient Edition*. New York: New York State Psychiatric Institute.

Flynn, G., Alexander, D., Harris, A., Whitford, T., Wong, W., Galletly, C., et al. (2008). Increased absolute magnitude of gamma synchrony in first-episode psychosis. *Schizophr Res, 105*(1-3), 262-271.

Fox, K., Sato, H., & Daw, N. (1990). The effect of varying stimulus intensity on NMDA-receptor activity in cat visual cortex. *J Neurophysiol, 64*(5), 1413-1428.

Foxe, J. J., Doniger, G. M., & Javitt, D. C. (2001). Early visual processing deficits in schizophrenia: impaired PI generation revealed by high-density electrical mapping. *NeuroReport, 12*(17).

Foxe, J. J., Simpson, G. V., & Ahlfors, S. P. (1998). Parieto-occipital approximately 10 Hz activity reflects anticipatory state of visual attention mechanisms. *Neuroreport, 9*(17), 3929-3933.

Fries, P., Reynolds, J. H., Rorie, A. E., & Desimone, R. (2001). Modulation of oscillatory neuronal synchronization by selective visual attention. *Science, 291*(5508), 1560-1563.

Friston, K. J. (1999). Schizophrenia and the disconnection hypothesis. *Acta Psychiatr Scand Suppl, 395*, 68-79.

Gallinat, J., Winterer, G., Herrmann, C. S., & Senkowski, D. (2004). Reduced oscillatory gamma-band responses in unmedicated schizophrenic patients indicate impaired frontal network processing. *Clin Neurophysiol, 115*(8), 1863-1874.

Gattaz, W. F., Mayer, S., Ziegler, P., Platz, M., & Gasser, T. (1992). Hypofrontality on topographic EEG in schizophrenia. Correlations with neuropsychological and psychopathological parameters. *Eur Arch Psychiatry Clin Neurosci, 241*(6), 328-332.

Gomez-Ramirez, M., Higgins, B. A., Rycroft, J. A., Owen, G. N., Mahoney, J., Shpaner, M., et al. (2007). The deployment of intersensory selective attention: a high-density electrical mapping study of the effects of theanine. *Clin Neuropharmacol, 30*(1), 25-38.

Gomez-Ramirez, M., Kelly, S. P., Montesi, J. L., & Foxe, J. J. (2009). The effects of L-theanine on alpha-band oscillatory brain activity during a visuo-spatial attention task. *Brain Topogr, 22*(1), 44-51.

Gray, C. M., Konig, P., Engel, A. K., & Singer, W. (1989). Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties. *Nature, 338*(6213), 334-337.

Herrmann, C. S., & Demiralp, T. (2005). Human EEG gamma oscillations in neuropsychiatric disorders. *Clin Neurophysiol, 116*(12), 2719-2733.

Higashima, M., Tsukada, T., Nagasawa, T., Oka, T., Okamoto, T., Okamoto, Y., et al. (2007). Reduction in event-related alpha attenuation during performance of an auditory oddball task in schizophrenia. *Int J Psychophysiol, 65*(2), 95-102.

Hong, L. E., Summerfelt, A., Mitchell, B. D., McMahon, R. P., Wonodi, I., Buchanan, R. W., et al. (2008). Sensory gating endophenotype based on its neural oscillatory pattern and heritability estimate. *Arch Gen Psychiatry, 65*(9), 1008-1016.

Hyman SE, A. G., Rosenbaum JF (Ed.). (1995). *Handbook of Psychiatric Drug Therapy*. Boston: Little, Brown and Company.

Javitt, D. C. (2009). When doors of perception close: bottom-up models of disrupted cognition in schizophrenia. *Annu Rev Clin Psychol, 5*, 249-275.

Jensen, O., & Mazaheri, A. Shaping functional architecture by oscillatory alpha activity: gating by inhibition. *Front Hum Neurosci, 4*, 186.

Jibson, M. D., & Tandon, R. (1998). New atypical antipsychotic medications. *J Psychiatr Res, 32*(3-4), 215-228.

Jones, M. W., & Wilson, M. A. (2005). Theta rhythms coordinate hippocampal-prefrontal interactions in a spatial memory task. *PLoS Biol, 3*(12), e402.

Jones, S. R., Pinto, D. J., Kaper, T. J., & Kopell, N. (2000). Alpha-frequency rhythms desynchronize over long cortical distances: a modeling study. *J Comput Neurosci, 9*(3), 271-291.

Kahana, M. J., Seelig, D., & Madsen, J. R. (2001). Theta returns. *Curr Opin Neurobiol, 11*(6), 739-744.

Keil, A., Muller, M. M., Ray, W. J., Gruber, T., & Elbert, T. (1999). Human gamma band activity and perception of a gestalt. *J Neurosci, 19*(16), 7152-7161.

Kelly, S. P., Foxe, J. J., Newman, G., & Edelman, J. A. (2010). Prepare for conflict: EEG correlates of the anticipation of target competition during overt and covert shifts of visual attention. *Eur J Neurosci, 31*(9), 1690-1700.

Kelly, S. P., Gomez-Ramirez, M., & Foxe, J. J. (2009). The strength of anticipatory spatial biasing predicts target discrimination at attended locations: a high-density EEG study. *Eur J Neurosci, 30*(11), 2224-2234.

Kelly, S. P., Gomez-Ramirez, M., Montesi, J. L., & Foxe, J. J. (2008). L-theanine and caffeine in combination affect human cognition as evidenced by oscillatory alpha-band activity and attention task performance. *J Nutr, 138*(8), 1572S-1577S.

Kelly, S. P., Lalor, E. C., Finucane, C., McDarby, G., & Reilly, R. B. (2005). Visual spatial attention control in an independent brain-computer interface. *IEEE Trans Biomed Eng, 52*(9), 1588-1596.

Kelly, S. P., Lalor, E. C., Reilly, R. B., & Foxe, J. J. (2006). Increases in alpha oscillatory power reflect an active retinotopic mechanism for distracter suppression during sustained visuospatial attention. *J Neurophysiol, 95*(6), 3844-3851.

Kim, D., Zemon, V., Saperstein, A., Butler, P. D., & Javitt, D. C. (2005). Dysfunction of early-stage visual processing in schizophrenia: harmonic analysis. *Schizophr Res, 76*(1), 55-65.

Klimesch, W., Doppelmayr, M., Russegger, H., Pachinger, T., & Schwaiger, J. (1998). Induced alpha band power changes in the human EEG and attention. *Neurosci Lett, 244*(2), 73-76.

Klimesch, W., Sauseng, P., & Hanslmayr, S. (2007). EEG alpha oscillations: the inhibition-timing hypothesis. *Brain Res Rev, 53*(1), 63-88.

Knott, V., Labelle, A., Jones, B., & Mahoney, C. (2001). Quantitative EEG in schizophrenia and in response to acute and chronic clozapine treatment. *Schizophr Res, 50*(1-2), 41-53.

Knyazev, G. G. (2007). Motivation, emotion, and their inhibitory control mirrored in brain oscillations. *Neurosci Biobehav Rev, 31*(3), 377-395.

Koh, Y., Shin, K. S., Kim, J. S., Choi, J. S., Kang, D. H., Jang, J. H., et al. (2010). An MEG study of alpha modulation in patients with schizophrenia and in subjects at high risk of developing psychosis. *Schizophr Res*.

Kwon, Y. H., Nelson, S. B., Toth, L. J., & Sur, M. (1992). Effect of stimulus contrast and size on NMDA receptor activity in cat lateral geniculate nucleus. *J Neurophysiol, 68*(1), 182-196.

Lakatos, P., Chen, C. M., O'Connell, M. N., Mills, A., & Schroeder, C. E. (2007). Neuronal oscillations and multisensory interaction in primary auditory cortex. *Neuron, 53*(2), 279-292.

Lakatos, P., Karmos, G., Mehta, A. D., Ulbert, I., & Schroeder, C. E. (2008). Entrainment of neuronal oscillations as a mechanism of attentional selection. *Science, 320*(5827), 110-113.

Lakatos, P., O'Connell, M. N., Barczak, A., Mills, A., Javitt, D. C., & Schroeder, C. E. (2009). The leading sense: supramodal control of neurophysiological context by attention. *Neuron, 64*(3), 419-430.

Lakatos, P., Shah, A. S., Knuth, K. H., Ulbert, I., Karmos, G., & Schroeder, C. E. (2005). An oscillatory hierarchy controlling neuronal excitability and stimulus processing in the auditory cortex. *J Neurophysiol, 94*(3), 1904-1911.

Leavitt, V. M., Molholm, S., Ritter, W., Shpaner, M., & Foxe, J. J. (2007). Auditory processing in schizophrenia during the middle latency period (10-50 ms): high-density electrical mapping and source analysis reveal subcortical antecendents to early cortical deficits. *J Psychiatr Neurosci, 32*(5), 339-353.

Lisman, J. (2010). Working memory: the importance of theta and gamma oscillations. *Curr Biol, 20*(11), R490-492.

Lisman, J. E., Coyle, J. T., Green, R. W., Javitt, D. C., Benes, F. M., Heckers, S., et al. (2008). Circuit-based framework for understanding neurotransmitter and risk gene interactions in schizophrenia. *Trends Neurosci, 31*(5), 234-242.

Lorincz, M. L., Kekesi, K. A., Juhasz, G., Crunelli, V., & Hughes, S. W. (2009). Temporal framing of thalamic relay-mode firing by phasic inhibition during the alpha rhythm. *Neuron, 63*(5), 683-696.

Mann, E. O., & Paulsen, O. (2007). Role of GABAergic inhibition in hippocampal network oscillations. *Trends Neurosci, 30*(7), 343-349.

Martinez, A., Hillyard, S. A., Dias, E. C., Hagler, D. J., Butler, P. D., Guilfoyle, D. N., et al. (2008). Magnocellular pathway impairment in schizophrenia: evidence from fMRI. *J Neuroscience, 28*(30), 7492-7500.

Mulholland, T., Goodman, D., & Boudrot, R. (1983). Attention and regulation of EEG alpha-attenuation responses. *Biofeedback Self Regul, 8*(4), 585-600.

Neuper, C., Wortz, M., & Pfurtscheller, G. (2006). ERD/ERS patterns reflecting sensorimotor activation and deactivation. *Prog Brain Res, 159*, 211-222.

Norra, C., Waberski, T. D., Kawohl, W., Kunert, H. J., Hock, D., Gobbele, R., et al. (2004). High-frequency somatosensory thalamocortical oscillations and psychopathology in schizophrenia. *Neuropsychobiology, 49*(2), 71-80.

Ojanpaa, H., & Nasanen, R. (2003). Utilisation of spatial frequency information in face search. *Vision Res, 43*(24), 2505-2515.

Omori, M., Koshino, Y., Murata, T., Murata, I., Nishio, M., Sakamoto, K., et al. (1995). Quantitative EEG in never-treated schizophrenic patients. *Biol Psychiatry, 38*(5), 305-309.

Peuskens, J., & Link, C. G. (1997). A comparison of quetiapine and chlorpromazine in the treatment of schizophrenia. *Acta Psychiatr Scand, 96*(4), 265-273.

Pfurtscheller, G., & Neuper, C. (2006). Future prospects of ERD/ERS in the context of brain-computer interface (BCI) developments. *Prog Brain Res, 159*, 433-437.

Pfurtscheller, G., Neuper, C., & Mohl, W. (1994). Event-related desynchronization (ERD) during visual processing. *Int J Psychophysiol, 16*(2-3), 147-153.

Phillips, W. A., & Silverstein, S. M. (2003). Convergence of biological and psychological perspectives on cognitive coordination in schizophrenia. *Behavioral and Brain Sciences, 26*, 65-138.

Raghavachari, S., Kahana, M. J., Rizzuto, D. S., Caplan, J. B., Kirschen, M. P., Bourgeois, B., et al. (2001). Gating of human theta oscillations by a working memory task. *J Neurosci, 21*(9), 3175-3183.

Rutishauser, U., Ross, I. B., Mamelak, A. N., & Schuman, E. M. (2010). Human memory strength is predicted by theta-frequency phase-locking of single neurons. *Nature, 464*(7290), 903-907.

Sauseng, P., Klimesch, W., Freunberger, R., Pecherstorfer, T., Hanslmayr, S., & Doppelmayr, M. (2006). Relevance of EEG alpha and theta oscillations during task switching. *Exp Brain Res, 170*(3), 295-301.

Schechter, I., Butler, P. D., Zemon, V. M., Revheim, N., Saperstein, A. M., Jalbrzikowski, M., et al. (2005). Impairments in generation of early-stage transient visual evoked potentials to magno- and parvocellular-selective stimuli in schizophrenia. *Clin Neurophysiol, 116*(9), 2204-2215.

Schnitzler, A., & Gross, J. (2005). Normal and pathological oscillatory communication in the brain. *Nat Rev Neurosci, 6*(4), 285-296.

Sederberg, P. B., Kahana, M. J., Howard, M. W., Donner, E. J., & Madsen, J. R. (2003). Theta and gamma oscillations during encoding predict subsequent recall. *J Neurosci, 23*(34), 10809-10814.

Singer, W., & Gray, C. M. (1995). Visual feature integration and the temporal correlation hypothesis. *Annu Rev Neurosci, 18*, 555-586.

Spencer, K. M. (2008). Visual gamma oscillations in schizophrenia: implications for understanding neural circuitry abnormalities. *Clin EEG Neurosci, 39*(2), 65-68.

Spencer, K. M., Nestor, P. G., Niznikiewicz, M. A., Salisbury, D. F., Shenton, M. E., & McCarley, R. W. (2003). Abnormal neural synchrony in schizophrenia. *J Neurosci, 23*(19), 7407-7411.

Spencer, K. M., Nestor, P. G., Perlmutter, R., Niznikiewicz, M. A., Klump, M. C., Frumin, M., et al. (2004). Neural synchrony indexes disordered perception and cognition in schizophrenia. *Proc Natl Acad Sci U S A, 101*(49), 17288-17293.

Spencer, K. M., Niznikiewicz, M. A., Shenton, M. E., & McCarley, R. W. (2008). Sensory-evoked gamma oscillations in chronic schizophrenia. *Biol Psychiatry, 63*(8), 744-747.

Sponheim, S. R., Clementz, B. A., Iacono, W. G., & Beiser, M. (1994). Resting EEG in first-episode and chronic schizophrenia. *Psychophysiology, 31*(1), 37-43.

Steriade, M. (1997). Synchronized activities of coupled oscillators in the cerebral cortex and thalamus at different levels of vigilance. *Cereb Cortex, 7*(6), 583-604.

Strik, W. K., Fallgatter, A. J., Brandeis, D., & Pascual-Marqui, R. D. (1998). Three-dimensional tomography of event-related potentials during response inhibition: evidence for phasic frontal lobe activation. *Electroencephalogr Clin Neurophysiol, 108*(4), 406-413.

Symond, M. P., Harris, A. W., Gordon, E., & Williams, L. M. (2005). "Gamma synchrony" in first-episode schizophrenia: a disorder of temporal connectivity? *Am J Psychiatry, 162*(3), 459-465.

Taylor, K., Mandon, S., Freiwald, W. A., & Kreiter, A. K. (2005). Coherent oscillatory activity in monkey area v4 predicts successful allocation of attention. *Cereb Cortex, 15*(9), 1424-1437.

Thut, G., Nietzel, A., Brandt, S. A., & Pascual-Leone, A. (2006). Alpha-band electroencephalographic activity over occipital cortex indexes visuospatial attention bias and predicts visual target detection. *J Neurosci, 26*(37), 9494-9502.

Uhlhaas, P. J., Linden, D. E., Singer, W., Haenschel, C., Lindner, M., Maurer, K., et al. (2006). Dysfunctional long-range coordination of neural activity during Gestalt perception in schizophrenia. *J Neurosci, 26*(31), 8168-8175.

Uhlhaas, P. J., & Singer, W. (2010). Abnormal neural oscillations and synchrony in schizophrenia. *Nat Rev Neurosci, 11*(2), 100-113.

Williams, L. M., Whitford, T. J., Nagy, M., Flynn, G., Harris, A. W., Silverstein, S. M., et al. (2009). Emotion-elicited gamma synchrony in patients with first-episode schizophrenia: a neural correlate of social cognition outcomes. *J Psychiatry Neurosci, 34*(4), 303-313.

Womelsdorf, T., & Fries, P. (2006). Neuronal coherence during selective attentional processing and sensory-motor integration. *J Physiol Paris, 100*(4), 182-193.

Worden, M. S., Foxe, J. J., Wang, N., & Simpson, G. V. (2000). Anticipatory biasing of visuospatial attention indexed by retinotopically specific alpha-band electroencephalography increases over occipital cortex. *J Neurosci, 20*(6), RC63.

Wynn, J. K., Light, G. A., Breitmeyer, B., Nuechterlein, K. H., & Green, M. F. (2005). Event-related gamma activity in schizophrenia patients during a visual backward-masking task. *Am J Psychiatry, 162*(12), 2330-2336.

Yuval-Greenberg, S., & Deouell, L. Y. (2007). What you see is not (always) what you hear: induced gamma band responses reflect cross-modal interactions in familiar object recognition. *J Neurosci, 27*(5), 1090-1096.