NEURAL SUBSTRATES OF VISUAL PROCESSING AND OBJECT RECOGNITION DEFICITS IN SCHIZOPHRENIA

by

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Abstract

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Mounting evidence has shown that patients with schizophrenia have preferential deficits of the magnocellular versus the parvocellular visual system. Experiment 1 examined this deficit in schizophrenia patients utilizing an electrophysiological paradigm. Patients showed preferential magnocellular deficits in electrophysiological response indicative of impaired contrast gain (response amplification at low contrast) and contrast gain control (inhibition of responses at high contrast), which are used preferentially by this pathway to optimize responses. Patients also displayed deficits in psychophysical contrast sensitivity, further showing deficient contrast gain in the magnocellular pathway. These electrophysiological and psychophysical deficits were associated with neuropsychological and emotion processing deficits, which predicted functional outcome.

Experiment 2 utilized functional magnetic resonance imaging (fMRI) to examine the neural underpinnings of the paradigms used in Experiment 1. fMRI responses to magnocellular- and parvocellular-biased contrast stimuli from the electrophysiological paradigm showed that contrast gain (i.e., signal amplification) was related to increases in volume of relatively weak occipital activation, while contrast gain control (i.e., signal inhibition) was related to strong a occipital activation over a smaller volume. Inhibitory contrast gain control was also linked to negative parafoveal activation, which was less apparent for patients. fMRI responses to a contrast sensitivity procedure showed reduced volume of occipital activation to low spatial frequency (LSF), but not high spatial frequency (HSF), stimuli for patients, indicating a general deficit in activation volume for LSF stimuli which are preferentially processed by the magnocellular system.

Experiment 3 examined consequences of magnocellular dysfunction for object recognition in schizophrenia. Patients showed deficits in fMRI activation to LSF object stimuli over a widespread cortical network, indicating a loss of early-stage low resolution object information. Patients instead showed an increase in activation to HSF object stimuli in some areas, suggesting compensation for LSF deficits with HSF information. Together, these three experiments further elucidated the neural substrates of preferential magnocellular deficits in schizophrenia, and demonstrated that such deficits may propagate to higher cognitive processes such as object recognition.

Dedication

To my baby daughter Pamela Jane, my greatest inspiration for completing this work and my greatest impediment to doing so.

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1.1 Overview

High-level cognitive dysfunction is a core component of schizophrenia (Cohen and Servan-Schreiber, 1992, Goldman-Rakic and Selemon, 1997, Weinberger and Gallhofer, 1997, Callicott et al., 2003, Reichenberg and Harvey, 2007, Minzenberg et al., 2009) and is related to functional outcome (Green, 2006). In addition, sensory deficits have long been recognized as a key feature of schizophrenia (Foxe et al., 2001, Braus et al., 2002, Ardekani et al., 2003, Butler et al., 2006, Yeap et al., 2006, Javitt, 2009), but have traditionally been thought of as secondary to cognitive dysfunction (Silverstein et al., 1996, Potts et al., 2002, van der Stelt et al., 2004, Rassovsky et al., 2005). More recent findings indicate that these sensory deficits directly contribute to high-level cognitive deficits (Goff and Coyle, 2001, Javitt, 2009, Kantrowitz and Javitt, 2010b, a). In particular, early-stage visual deficits may propagate to higher cognitive functions such as object recognition (Doniger et al., 2002, Sehatpour et al., 2010, Calderone et al., 2012), motion processing (Kim et al., 2006), perceptual grouping and organization (Kurylo et al., 2007, Silverstein and Keane, 2011), reading (Revheim et al., 2006), and emotion recognition (Leitman et al., 2005, Turetsky et al., 2007, Butler et al., 2009, Leitman et al., 2011).

The visual system consists of two major subcortical pathways, the magnocellular and parvocellular pathways, which both show deficits in schizophrenia (Slaghuis, 1998). However, a growing literature shows that the magnocellular pathway is preferentially impaired in schizophrenia, due to the fact that this pathway uses gain control more than the parvocellular pathway (Butler et al., 2001, Schechter et al., 2003, Butler et al., 2005, Kéri et al., 2005, Kim et al., 2005, Schechter et al., 2005, Butler et al., 2008a, Martinez et al., 2008, Green et al., 2009). Gain control refers to processes allowing sensory systems to optimize their response levels based on their immediate context, thus making the best use of a limited dynamic signaling range

(Butler et al., 2008a, Butler et al., 2012). Gain control in the visual system is thought to be mediated by N-Methyl-D-aspartate (NMDA) glutamate receptors (Fox et al., 1990, Kwon et al., 1992, Daw et al., 1993, Zemon and Gordon, 2006, Lisman et al., 2008) and NMDA function appears to be impaired in schizophrenia (Goff and Coyle, 2001, Javitt, 2004, Krystal et al., 2005, Javitt, 2009, Kantrowitz and Javitt, 2010b, a).

Experiment 1 of this dissertation uses an electrophysiological paradigm examining visual contrast response functions, as well as a psychophysical contrast sensitivity paradigm, to further elucidate gain control deficits in schizophrenia. These two paradigms have previously shown a preferential magnocellular deficit in schizophrenia linked to impaired gain control across several cohorts (Butler et al., 2001, Butler et al., 2005, Butler et al., 2008a, Butler et al., 2009, Butler et al., 2012). Experiment 1 replicated these findings in a large sample of schizophrenia patients and healthy controls, and further characterized the components of gain control in the magnocellular pathway using a biophysical model (Zemon and Gordon, 2006). In addition, measures of early-stage visual functioning including gain control related to higher cognitive functions as well as functional outcome.

Although preferential magnocellular deficits in schizophrenia have been well documented with electrophysiological and behavioral methods, these deficits have yet to be localized. Experiment 2 of this dissertation utilized the same stimuli from the tasks of Experiment 1 in a functional magnetic resonance imaging (fMRI) task. The electrophysiological and psychophysical results of Experiment 1 were replicated, and additionally the neural substrates of these deficits in gain control were examined in terms of both strength and extent of fMRI occipital activation.

Magnocellular pathway deficits in schizophrenia have also been linked to higher cognitive deficits, such as impaired object recognition (Doniger et al., 2002, Sehatpour et al., 2010). The “frame and fill” model of object recognition posits that low resolution information is rapidly transmitted by the magnocellular pathway to the cortical dorsal stream and prefrontal cortex, where a rough approximation of an object’s shape is generated (Ullman, 1995, Bar, 2003, Bar et al., 2006, Chen et al., 2007, Kveraga et al., 2007). This “frame” then quickly feeds back to the ventral temporal cortex, where slower high resolution parvocellular information is integrated into a perceptual whole (Tanaka, 1993, 1996, Bar et al., 2001, Grill-Spector et al., 2001, Malach et al., 2002). The frame information aids this integrative process by constraining it to the general shape of the object. Magnocellular deficits in schizophrenia may thus impair the framing function of the PFC during object recognition (Sehatpour et al., 2010). Experiment 3 of this dissertation applied an fMRI object recognition task previously used by Bar and colleagues (Bar et al., 2006) to examine the cortical circuitry underlying object recognition deficits in schizophrenia by biasing object stimuli toward magnocellular or parvocellular processing. Functionally determined regions of interest showed a lack of magnocellular information processing in the PFC for schizophrenia, and compensation with parvocellular information. Resting state functional connectivity also revealed a lack of connectivity between early visual areas and PFC for schizophrenia.

In summary, this dissertation sought to examine the specific nature of gain control deficits underlying preferential magnocellular dysfunction in schizophrenia, and to relate this dysfunction to object recognition and functional measures. Gain control impairment was studied in a large sample to allow characterization of individual processes contributing to the impairment. The neural substrates of gain control impairment were examined with fMRI, and fMRI also revealed altered cortical circuitry in schizophrenia for object recognition related to a lack of magnocellular information.

1.2 Theories of schizophrenia

Schizophrenia is a debilitating mental disorder affecting approximately one percent of the worldwide population. Two main categories of symptoms have classically been emphasized in this disorder. Positive symptoms such as delusions, hallucinations, and incoherent thought patterns are phenomena present in schizophrenia in contrast to healthy individuals. Negative symptoms such as flat affect, lack of motivation, and lack of socialization represent characteristics that are absent in schizophrenia in contrast to healthy individuals. In addition, cognitive decline as measured by neuropsychological tests and IQ is a core feature of schizophrenia (Reichenberg and Harvey, 2007, Javitt, 2009).

Basic sensory deficits in schizophrenia were described as early as 1904 by Kraeplin in his conceptualization of the disorder as “dementia praecox” (Kraepelin, 1904). In the 1950s, Bleuler influentially ascribed sensory deficits to failures of high-level cognitive processes, denying that sensory systems were impaired at basic levels in schizophrenia (Bleuler, 1950). The notion that abnormal perception in schizophrenia is due to higher-level deficits, rather than fundamental sensory dysfunction, forms the basis of the top-down theory of schizophrenia. This theory claims that advanced brain systems in the prefrontal cortex governing attention, cognitive control, and executive functioning are directly impaired, and that this results in secondary impairments in lower processes overseen by these systems, such as perception (Cohen and Servan-Schreiber, 1992, Goldman-Rakic and Selemon, 1997, Weinberger and Gallhofer, 1997, Callicott et al., 2003, Reichenberg and Harvey, 2007, Minzenberg et al., 2009). For example, visual deficits have been ascribed to failures of attention (Silverstein et al., 1996, Potts et al., 2002, van der Stelt et al., 2004, Rassovsky et al., 2005, Barch et al., 2012). While the top-down theory remains influential, a bottom-up theory arose in the 1960s when self reported perceptual disturbances in schizophrenia led to the investigation of basic sensory deficits (McGhie and Chapman, 1961, McGhie et al., 1964). This investigation was aided by the advent of electrophysiological and eye-tracking techniques in the 1970s (Holzman, 1972). Today, there is a large and growing literature supporting fundamental dysfunction of low-level sensory systems in schizophrenia (Butler et al., 2001, Foxe et al., 2001, Braus et al., 2002, Ardekani et al., 2003, Schechter et al., 2003, Butler et al., 2005, Kéri et al., 2005, Kim et al., 2005, Schechter et al., 2005, Butler et al., 2006, Yeap et al., 2006, Butler et al., 2008a, Martinez et al., 2008, Green et al., 2009). The bottom-up theory thus postulates that in addition to top-down deficits, basic sensory deficits propagate upward to higher cognitive functions such as object recognition (Doniger et al., 2002, Sehatpour et al., 2010, Calderone et al., 2012), reading (Revheim et al., 2006), and emotion recognition (Leitman et al., 2005, Turetsky et al., 2007, Butler et al., 2009, Leitman et al., 2011). The top-down and bottom-up theories of dysfunction in schizophrenia have been associated with the neurochemical dopaminergic and glutamatergic theories of schizophrenia respectively.

1.2.1 Dopaminergic theory of schizophrenia

The dopaminergic theory of schizophrenia has been used to support the top-down theory of impaired high-level processes. In primates, dopaminergic neurons tend to project to areas responsible for high-order functions, such as the prefrontal cortex, and only sparsely project to primary sensory areas (Lewis et al., 1987). The dopaminergic theory posits excessive dopamine release into high-level areas, causing aberrant processing in functions such as attention and cognitive control. This hypothesis originated from the apparent success of dopamine agonists in producing positive schizophrenia symptoms, and the success of dopamine antagonists in treating positive symptoms (Davis et al., 1991). Specifically, the dopamine antagonist chlorpromazine and related antipsychotic drugs were found to reduce positive symptoms in schizophrenia patients as well reverse positive symptoms caused by dopamine agonists (Delay et al., 1956a, b, Krystal et al., 2005). Despite the success of these medications, these antipsychotic drugs do not treat and sometimes intensify cognitive symptoms of schizophrenia (Castner et al., 2000, Dorph-Petersen et al., 2005, Tandon, 2011). While significant evidence exists for dopaminergic dysfunction in schizophrenia, this theory does not explain the wide range of cognitive symptoms, nor does it offer a remedy for them.

1.2.2 Glutamatergic theory of schizophrenia

The glutamatergic theory of schizophrenia lends support to the bottom-up theory of fundamentally impaired sensory systems. In contrast to dopaminergic neurons, NMDA glutamate receptors are found in both higher cortical areas and primary sensory areas (Javitt, 2004, 2009). Of specific interest to this dissertation, NMDA glutamate receptors are preferentially involved in the functioning of the magnocellular visual pathway (Fox et al., 1990, Kwon et al., 1992). Preferential magnocellular deficits in schizophrenia may thus be due to glutamate hypofunction. This theory arose from the ability of NMDA antagonists such as ketamine and phencyclidine (PCP) to reproduce positive, negative, and cognitive symptoms of schizophrenia, and thus provide a more complete model of the disorder than dopamine agonists alone (Javitt, 1987, Javitt and Zukin, 1991). In addition, NMDA agonists such as N-acetyl cysteine (Berk et al., 2008, Lavoie et al., 2008), glycine (Javitt et al., 1994, Heresco-Levy et al., 1999, Javitt et al., 2001, Heresco-Levy et al., 2004, Tsai et al., 2004, Javitt, 2006, 2008), D-alanine (Tsai et al., 2006), D-serine (Tsai et al., 1998, Heresco-Levy et al., 2005), and sarcosine

(Lane et al., 2005, Lane et al., 2008) have been found to alleviate positive, negative, and cognitive symptoms in schizophrenia patients (Javitt, 2004). NMDA abnormalities in schizophrenia may therefore underlie a wide range of fundamental sensory and perceptual deficits, which may in turn feed forward to higher level processes.

1.3 Visual system basics

The visual system is exceptionally well characterized in both animals and humans. The primate subcortical visual system is divided into two primary pathways that project from the retina through the lateral geniculate nucleus of the thalamus to primary visual cortex (V1) (Kaplan and Shapley, 1982, 1986, Wurtz and Kandel, 2000). The magnocellular pathway projects to cellular layer 4Cα of V1 and relays information to the dorsal visual stream, including the middle temporal cortex and inferior parietal cortex. The parvocellular pathway projects to cellular layer 4Cβ of V1 and relays information to the ventral visual stream, including the lateral occipital complex and inferior temporal cortex (Hubel and Wiesel, 1972, Tootell et al., 1988, Shapley, 1990). These two cortical streams are separated anatomically and functionally, though they interact significantly (Ungerleider and Mishkin, 1982, Maunsell et al., 1990, Merigan and Maunsell, 1993, Schroeder et al., 1998a). The magnocellular pathway transmits information rapidly, and is sensitive to low spatial frequencies, high temporal frequencies, and low luminance contrasts. The magnocellular pathway and the dorsal stream process global information about the visual scene, such as general shapes and locations, and are important in attentional capture and eye-movement guidance. The parvocellular pathway relays information more slowly, and is sensitive to high spatial frequencies, low temporal frequencies, high luminance contrasts, and chromatic contrasts. The parvocellular pathway and the ventral stream process the fine details of a visual scene, and are important for color perception and discernment of subtle structure

(Ungerleider and Mishkin, 1982, Derrington and Lennie, 1984, Maunsell et al., 1990, Shapley, 1990, Merigan and Maunsell, 1993, Schroeder et al., 1998a, Wurtz and Kandel, 2000, Norman, 2002, Chen et al., 2007).

This dissertation makes extensive use of the different luminance contrast sensitivities of the two pathways. The magnocellular pathway exhibits strong gain control in its contrast response function, while the parvocellular pathway does not, indicating that these two pathways utilize separate cellular mechanisms. Contrast gain and contrast gain control are two examples of the broader mechanism of gain control, and were first described in the visual system by Shapley and Victor (Shapley and Victor, 1978, Shapley and Victor, 1979, Shapley and Victor, 1981) in cat retinal ganglion cells, and were later found in the monkey (Kaplan and Shapley, 1982, Derrington and Lennie, 1984, Kaplan and Shapley, 1986, Shapley, 1990) and human visual systems (Zemon and Gordon, 2006, García-Quispe et al., 2009). The contrast response function of the magnocellular pathway is nonlinear, showing a steep initial slope over the low contrast region followed by a decrease in slope as contrast increases above about 12%. The initial steep slope is referred to as contrast gain, and reflects amplification of responses to low contrasts. Response saturation at 12% contrast is referred to as contrast gain control, and reflects response attenuation at higher contrasts. Both contrast gain and contrast gain control in the magnocellular contrast response function are therefore examples of gain control optimizing response levels in this visual pathway. The parvocellular pathway, however, does not respond to low contrasts below about 10% and has a shallow linear slope throughout its contrast response function as contrast increases. The magnocellular pathway is thus optimized for keen discernment of lower contrasts, and is not sensitive to differences among higher contrasts. The

P-pathway, on the other hand, while insensitive to lower contrasts, can differentiate higher contrasts throughout the range above 10% (Kaplan and Shapley, 1982, 1986, Shapley, 1990).

This dissertation uses steady-state visual evoked potentials (ssVEP) to measure magnocellular and parvocellular pathway functioning in humans. This technique makes use of the different contrast sensitivities and processing speeds of the two pathways to preferentially stimulate one or the other pathway using visual stimuli. Rapidly appearing and disappearing low contrast stimuli bias processing toward the magnocellular pathway, while sustained high contrast stimuli bias processing toward the parvocellular pathway (Butler et al., 2001, Butler et al., 2005, Zemon and Gordon, 2006, García-Quispe et al., 2009). The electrophysiological responses obtained during these two types of stimuli reflect the processing characteristics of the particular pathway being stimulated (Greenstein et al., 1998, Zemon and Gordon, 2006). The ssVEP responses obtained from magnocellular- and parvocellular-biased stimuli mirror the response obtained from single cell recordings in animal studies (Butler et al., 2001, Butler et al., 2005, Zemon and Gordon, 2006, Butler et al., 2008a, García-Quispe et al., 2009, Green et al., 2009).

Experiments 1 and 2 of this dissertation replicate this finding in healthy controls and the finding of preferential impairment in magnocellular contrast response function for schizophrenia patients. Experiment 1 also further characterizes the nature of this impairment using a nonlinear biophysical model developed by Zemon and Gordon (Zemon and Gordon, 2006) to characterize these ssVEP responses. This model provides quantitative estimates of the contrast gain and contrast gain control present in magnocellular contrast response functions. Experiment 2 additionally localizes the cortical underpinnings of this ssVEP response in humans, for both healthy controls and schizophrenia patients.

Another reliable method of measuring magnocellular pathway functioning is the psychophysical contrast sensitivity paradigm. This paradigm measures the lowest contrast level at which participants can reliably detect visual spatial frequency gratings, and therefore indicates the ability of the visual system to process low contrast stimuli (Butler et al., 2005, Butler et al., 2008a). These gratings can be manipulated in luminance, contrast, spatial frequency, and temporal frequency in order to bias the task toward the magnocellular or parvocellular pathway (Slaghuis, 1998, O'Donnell et al., 2002), though sufficiently low contrast stimuli are always biased toward magnocellular processing (Butler et al., 2005). In addition to the ssVEP and biophysical model parameters, contrast sensitivity measures are also used in Experiments 1 and 2 to replicate previous findings of contrast sensitivity deficits in schizophrenia, and to examine the neural underpinnings of contrast sensitivity in healthy controls and schizophrenia patients.

1.4 Early-stage visual processing deficits in schizophrenia

Visual deficits have long been recognized as a feature of schizophrenia (McGhie and Chapman, 1961, McGhie et al., 1964, Holzman, 1972, Foxe et al., 2001, Braus et al., 2002, Ardekani et al., 2003, Butler et al., 2006, Yeap et al., 2006). Under the top-down theory, these deficits have sometimes been attributed to failures of higher-level processes such as attention (Silverstein et al., 1996, Potts et al., 2002, van der Stelt et al., 2004, Rassovsky et al., 2005). However, an increasing body of evidence suggests that visual deficits are fundamental in schizophrenia, occur at low levels of processing, and include preferential magnocellular pathway impairment (Butler et al., 2001, Schechter et al., 2003, Butler et al., 2005, Kéri et al., 2005, Kim et al., 2005, Schechter et al., 2005, Butler et al., 2008a, Martinez et al., 2008, Butler et al., 2009, Green et al., 2009). This is consistent with the glutamatergic theory of schizophrenia, due to the dependence of magnocellular functioning on NMDA glutamate receptors (Fox et al., 1990, Kwon et al., 1992, Daw et al., 1993, Zemon and Gordon, 2006, Lisman et al., 2008).

Behavioral tasks have been used to demonstrate that visual deficits in schizophrenia are specific to low contrast, magnocellular-biased stimuli. Keri et al. (Kéri et al., 2004, Kéri et al., 2005) used variations of vernier tasks to demonstrate that patients had deficits in discriminating low contrast and low spatial frequency stimuli, as opposed to high contrast and color contrast stimuli. Schizophrenia patients also have reliable deficits in the backward masking visual task, specifically when stimuli are biased toward magnocellular processing (Saccuzzo and L., 1986, Slaghuis and Bakker, 1995, Butler et al., 1996, Butler et al., 2002, Schechter et al., 2003, Slaghuis, 2004). Backward masking paradigms examine rapid visual processing at short latencies, and thus these findings support the notion that the visual system in schizophrenia is impaired before the influence of top-down processes.

Contrast sensitivity tasks have also been developed with magnocellular- and parvocellular-biased stimuli in order to investigate differential visual pathway deficits in schizophrenia. The magnocellular pathway optimally processes low spatial frequency information, while the parvocellular pathway optimally processes high spatial frequency information (Wurtz and Kandel, 2000). Schizophrenia patients show preferential deficits in contrast sensitivity when low spatial frequency stimuli are used (Slaghuis, 1998, Kéri et al., 2002, Slaghuis and Thompson, 2003, Slaghuis, 2004, Butler et al., 2005). However, contrast sensitivity studies using high spatial frequency stimuli have had mixed results. Patients have demonstrated deficits with such stimuli (Slaghuis, 1998, Kéri et al., 2002, Slaghuis and Thompson, 2003, Slaghuis, 2004), while Butler and colleagues (Butler et al., 2005, Butler et al., 2009) found no difference between patient and control performance at high spatial frequencies.

An explanation for this discrepancy between studies may be that deficits are generally found when contrast threshold is very low, regardless of spatial frequency, because the parvocellular pathway is insensitive to these very low contrasts (Butler et al., 2005). Experiment 1 of this dissertation examined contrast sensitivity deficits in a large population of schizophrenia patients, and Experiment 2 localized the cortical underpinnings of this deficit in occipital cortex.

Preferential magnocellular pathway deficits have also been demonstrated in schizophrenia using electrophysiological measures. Of particular interest to this dissertation, ssVEP studies by Butler and colleagues (Butler et al., 2001, Butler et al., 2005, Butler et al., 2008a, Butler et al., 2009, Butler et al., 2012) have manipulated contrast levels of isolated check patterns to bias them toward the magnocellular or parvocellular pathway. For controls, contrast response functions to magnocellular- and parvocellular-biased stimuli mimic the responses obtained from single cell recordings in animals. Patients, however, show reduced contrast gain and contrast gain control for magnocellular-biased stimuli, resulting in a shallower initial slope and lower saturation level in contrast response function. Schizophrenia patients also show reduced responses to parvocellular-biased stimuli, but interactions showed significantly greater dysfunction to magnocellular- than parvocellular-biased stimuli, and parvocellular-biased contrast response functions maintained their characteristic linear shape for patients. This ssVEP task measures early-stage visual processing in V1, and thus demonstrates that visual deficits in schizophrenia occur before the influence of top-down mechanisms. Experiment 1 of this dissertation examined this preferential magnocellular deficit in contrast response function in a large population of schizophrenia patients, and Experiment 2 localized the cortical underpinnings of this deficit in occipital cortex.

Event-related potential (ERP) studies have also been used to study visual processing in schizophrenia. The P1 component of the ERP response occurs approximately 100ms after stimulus onset, is driven by magnocellular-biased stimuli, and has been localized to the dorsal processing stream (Goffaux and Rossion, 2006). The C1 and N1 components are sensitive to parvocellular-biased stimuli, and are thought to reflect early (~90ms) V1 activity and slightly later (~150ms) ventral stream activity respectively (Allison et al., 1999, Bentin et al., 1999, Doniger et al., 2000). ERP studies have demonstrated a robust P1 deficit in Schizophrenia, indicative of dorsal stream dysfunction. The N1 component, on the other hand, remains intact in schizophrenia, indicating a relatively intact ventral stream (Butler et al., 2004, Caharel et al., 2007).

1.5 Propagation of early-stage visual processing deficits to higher functions

The magnocellular pathway relays information more rapidly than the parvocellular pathway, and is thus crucial for the initial stages of processing visual input (Schmolesky et al., 1998, Schroeder et al., 1998b, Chen et al., 2007, Tapia and Breitmeyer, 2011). Processes such as emotion recognition and object recognition have traditionally been studied as occurring in the ventral cortical stream, which receives parvocellular pathway input. However, these processes also receive rapid magnocellular mediated information, which is critical to their functioning. Early-stage magnocellular pathway deficits in schizophrenia therefore predict a loss of magnocellular input to these higher level processes. Indeed, preferential magnocellular deficits in schizophrenia have been linked to deficits in motion processing (Kim et al., 2006), perceptual grouping (Kurylo et al., 2007, Silverstein and Keane, 2011), reading (Revheim et al., 2006), emotion recognition (Leitman et al., 2005, Turetsky et al., 2007, Butler et al., 2009, Leitman et al., 2011), and object recognition (Doniger et al., 2002, Sehatpour et al., 2010, Calderone et al., 2012). Experiment 3 of this dissertation focused on localizing deficits in object recognition for schizophrenia patients, and revealed altered patterns of cortical activity for magnocellular- and parvocellular-biased object stimuli.

1.5.1 The magnocellular pathway in object recognition

Normal object recognition makes use of converging magnocellular and parvocellular information in the ventral temporal cortex (VTC) (Hubel and Wiesel, 1962, Tanaka, 1993, Pasupathy and Connor, 1999, Vogels et al., 2001). Under the "frame and fill" model of object recognition, the magnocellular pathway rapidly relays low spatial frequency information about an object stimulus to the dorsal stream (Ungerleider and Mishkin, 1982, Shapley, 1990, Merigan and Maunsell, 1993), which, in turn, transmits this information to the preferontal cortex (PFC) (Wise et al., 1997, Endo et al., 1999, Petrides and Pandya, 1999, Saron et al., 2001). This information is used by the PFC to create a low resolution "frame," or general shape, of the object stimulus, which is fed back to the VTC (Ullman, 1995, Schmolesky et al., 1998, Lamme and Roelfsema, 2000, Bar, 2003, Bar et al., 2006, Kveraga et al., 2007, Sehatpour et al., 2010, Tapia and Breitmeyer, 2011). The parvocellular pathway, on the other hand, more slowly relays high spatial frequency information directly to the VTC (Ungerleider and Mishkin, 1982, Shapley, 1990, Merigan and Maunsell, 1993). Because the magnocellular pathway is faster than the parvocellular pathway, the "frame" feedback from the PFC arrives first (Schmolesky et al., 1998, Schroeder et al., 1998b, Chen et al., 2007, Tapia and Breitmeyer, 2011), followed by the fine detailed parvocellular pathway information which is used to "fill" the frame (Ullman, 1995, Bar, 2003, Bar et al., 2006, Kveraga et al., 2007, Sehatpour et al., 2010). Object recognition ultimately occurs through integration of fine detailed information into a coherent whole (Tanaka, 1993, 1996, Bar et al., 2001, Grill-Spector et al., 2001, Malach et al., 2002), and the PFC frame feedback constrains this process to a limited number of possible objects matching the general shape of the stimulus (Bar, 2003, Bar et al., 2006, Kveraga et al., 2007).

The work of Bar and colleagues is of particular interest to this dissertation, as it utilizes one of their object recognition paradigms. Using MEG and fMRI, they found that magnocellular-biased object stimuli activated the PFC, whereas parvocellular-biased stimuli produced more VTC activation and less PFC activation (Bar et al., 2006, Kveraga et al., 2007). Analysis of MEG time courses for magnocellular-biased stimuli, but not parvocellular-biased stimuli, revealed that early visual areas and PFC interacted initially, with later interactions between PFC and VTC (Bar et al., 2006). These results are consistent with the frame and fill model, in which the PFC creates a low resolution object frame based on rapid magnocellular pathway information and feeds this frame back to the VTC to assist the slower process of integrating fine details into a coherent object.

1.5.2 Object recognition deficits in schizophrenia

Behavioral findings using the perceptual closure task in schizophrenia indicate deficits in the ability to integrate fragmented objects into whole object perceptions (Doniger et al., 2002, Sehatpour et al., 2010). Additionally, preferential magnocellular pathway deficits in Schizophrenia may propagate in a bottom-up fashion during object recognition, resulting in a loss of low spatial frequency information arriving at the PFC. This would result in impaired “frame” generation. Evidence for this has been found with impaired ERP components associated with perceptual closure and dorsal stream activity, while a ventral stream ERP component remained intact (Doniger et al., 2002). A recent replication of these ERP findings extended the perceptual closure task to fMRI, and found an impaired network of dorsal stream, ventral stream, PFC, and hippocampal activity in Schizophrenia (Sehatpour et al., 2010). Effective connectivity analysis of the fMRI data suggested that dorsal stream deficits influenced PFC deficits, which in turn influenced ventral stream deficits. These studies indicate that the dorsal stream/PFC framing circuit is impaired in Schizophrenia, consistent with preferential magnocellular deficits. The cognitive task of object recognition may therefore be impaired due to a bottom-up propagation of basic visual dysfunction.

1.6 Objectives

Experiment 1 (Chapter 2) used previously developed ssVEP and psychophysical contrast sensitivity tasks to replicate preferential magnocellular deficits in a large population of schizophrenia patients, and to further characterize these deficits and relate them to functional measures and symptoms. For the ssVEP task, stimuli were biased toward magnocellular or parvocellular processing using luminance contrast. Contrast response functions for these stimuli were characterized with a biophysical model to assess contrast gain and contrast gain control. For the contrast sensitivity task, stimuli were also biased toward the magnocellular or parvocellular pathway using different spatial frequencies and stimulus durations. Hypotheses were 1) schizophrenia patients would show the expected preferential magnocellular deficit in ssVEP contrast response functions, as well as preferential contrast sensitivity deficits to magnocellular-biased stimuli, 2) schizophrenia patients would show reductions in measures of contrast gain and contrast gain control as characterized by a nonlinear biophysical model of the magnocellular contrast response function, and 3) early-stage visual functioning would correlate with higher cognitive functions as well as functional outcome.

Experiment 2 (Chapter 3) used the same stimuli from the ssVEP and contrast sensitivity tasks from Experiment 1 in an fMRI paradigm to localize cortical activity related to preferential magnocellular deficits in schizophrenia. Hypotheses were 1) schizophrenia patients would show the expected preferential magnocellular deficit in ssVEP contrast response functions, as well as preferential contrast sensitivity deficits to magnocellular-biased stimuli, 2) schizophrenia patients would show altered patterns of occipital activation to magnocellular-biased stimuli more so than to parvocellular-biased stimuli.

Experiment 3 (Chapter 4) utilized an object recognition fMRI task developed by Bar and colleagues (Bar et al., 2006) and extended it to study object recognition in schizophrenia. This paradigm biased object stimuli toward magnocellular or parovcellular processing by filtering them to contain only low or high spatial frequencies respectively. This experiment also extends the findings of Sehatpour and colleagues (Sehatpour et al., 2010) that showed an impaired dorsal stream/PFC circuit for object recognition in schizophrenia by examining the specific contributions of different spatial frequencies to object recognition. In addition, resting state functional connectivity was used to examine the cortical networks used during object recognition for healthy controls and schizophrenia patients. Hypotheses were 1) healthy control participants would demonstrate a dorsal stream/PFC circuit that uses magnocellular information to generate an object “frame” that feeds back to the VTC, 2) schizophrenia patients would have deficits in this circuit specifically related to magnocellular biased information, and 3) patients would have deficits in functional connectivity between primary visual areas, dorsal stream areas, and PFC, consistent with impaired magnocellular pathway input.

The overall goal of this dissertation is to elucidate the nature of early-stage visual deficits in schizophrenia and understand how such deficits contribute to higher cognitive dysfunction as well as functional outcome.

CHAPTER 2

Visual gain control impairment in schizophrenia and its relationship to higher-order cognition and functional outcome

1. Abstract

Early-stage visual processing deficits in schizophrenia relate to higher-order cognitive deficits as well as functional outcome. This study examined deficits in visual gain control in a large sample of schizophrenia patients using two methods: steady-state visual evoked potential (ssVEP) contrast response functions and psychophysical contrast sensitivity. A biophysical model fit was used to characterize the magnocellular-biased ssVEP contrast response function to measure contrast gain and contrast gain control, two specific instances of the more general process of gain control. Neuropsychological function, emotion processing, symptoms, and functional status were also assessed, and structural equation modeling explored the relationships between these variables and early-stage visual processing. ssVEP revealed a preferential deficit in magnocellular-biased contrast response functions for patients. Deficits were also found in schizophrenia for biophysical model estimates of contrast gain and contrast gain control. Patients showed contrast sensitivity deficits across a wide range of spatial frequencies, indicating a broad deficit in detecting low contrasts. In the structural equation modeling, these measures of early-stage visual processing significantly predicted neuropsychological and emotion processing measures across groups. For patients, neuropsychological function predicted symptoms and functional status, while emotion processing only predicted the degree to which patients were able to live independently. These results show links between early-stage visual processing deficits and functional outcome, mediated by neuropsychological and emotion processing cognitive functions.

2. Introduction

Recent evidence has shown that sensory processing impairment in various modalities is a key feature of schizophrenia (Javitt, 2009, Koychev et al., 2011, Leitman et al., 2011, Silverstein and Keane, 2011, Butler et al., 2012) and is related to functional outcome (Sergi et al., 2006). In the visual system, early-stage sensory deficits have been found for processing contrast (Slaghuis, 1998, Kéri et al., 2002, Kéri et al., 2004, Butler et al., 2005, Butler et al., 2009, Green et al., 2009), motion (Chen et al., 2003b, Chen et al., 2004, Kim et al., 2006), and spatial frequency (O'Donnell et al., 2002, Martinez et al., 2008, Calderone et al., 2012, Martinez et al., 2012). In addition, visual sensory deficits contribute to higher level impairments in emotion processing (Turetsky et al., 2007, Butler et al., 2009), object processing (Doniger et al., 2002, Kurylo et al., 2007, Sehatpour et al., 2010, Calderone et al., 2012), motion processing (Kim et al., 2006) and reading (Revheim et al., 2006). Such higher level cognitive processes may also mediate a link between early-stage visual functioning and outcome measures for schizophrenia (Sergi et al., 2006).

Gain control has been identified as a useful construct for assessing perceptual function in schizophrenia by the NIH-sponsored Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) (Green et al., 2009, Butler et al., 2012). Gain control refers to processes allowing sensory systems to optimize response levels by amplifying or attenuating neuronal responses based on their immediate context, thus making the best use of a limited dynamic signaling range (Butler et al., 2008a, Butler et al., 2012). One method for assessing gain control in the visual system is a steady-state visual evoked potential (ssVEP) task using luminance contrast stimuli biased toward the magnocellular or parvocellular visual pathway (Zemon and Gordon, 2006, Butler et al., 2008a). Patients with schizophrenia have shown a deficit on this task which has been replicated in several cohorts (Butler et al., 2001, Butler et al., 2005, Butler et al., 2008a, Butler et al., 2009, Butler et al., 2012). In addition, Zemon and Gordon (Zemon and Gordon, 2006) developed a biophysical model fit to estimate measures of gain control in this task. The current study utilizes this ssVEP task and biophysical model in a large cohort to further characterize the specific nature of gain control deficits in schizophrenia. This study also employs another method of assessing gain control, a psychophysical contrast sensitivity task utilizing various spatial frequencies and stimulus durations that has also shown deficits across cohorts of schizophrenia patients (Butler et al., 2001, Butler et al., 2005, Butler et al., 2008a, Butler et al., 2009, Butler et al., 2012).

The subcortical visual system consists of two major pathways projecting from the retina, through the lateral geniculate nucleus of the thalamus, to cortical visual areas (Kaplan and Shapley, 1982, 1986, Wurtz and Kandel, 2000). The magnocellular pathway rapidly transmits information to dorsal stream cortical areas, which preferentially process global visual information. The parvocellular pathway more slowly transmits information to ventral stream cortical areas, which process fine details of a visual scene (Ungerleider and Mishkin, 1982, Shapley, 1990, Merigan and Maunsell, 1993, Schroeder et al., 1998a, Wurtz and Kandel, 2000, Norman, 2002, Chen et al., 2007). Magnocellular responses to luminance contrast stimuli exhibit gain control more so than parvocellular responses, as evidenced by monkey intracortical (Shapley and Victor, 1979, Kaplan and Shapley, 1982, 1986, Shapley, 1990) and human ssVEP studies (Butler et al., 2001, Butler et al., 2005, Zemon and Gordon, 2006, Butler et al., 2008a, García-Quispe et al., 2009, Butler et al., 2012). The nonlinear contrast response function of the magnocellular pathway shows a steep initial slope over the low contrast region followed by a decrease in slope as contrast increases above about 12%. Initial steep slope indicates amplification of responses to low contrasts, and is referred to as initial contrast gain. Response saturation at 12% contrast indicates response attenuation at higher contrasts, and is referred to as contrast gain control. Both contrast gain and contrast gain control in the magnocellular contrast response function are examples of gain control being utilized by the visual system to optimize responses. The parvocellular pathway, however, does not respond to low contrasts below about 10% and has a shallow linear slope throughout its contrast response function as contrast increases. The preferential use of gain control by the magnocellular, rather than by the parvocellular, pathway may be due to differences in cellular mechanisms. Initial contrast gain in the magnocellular pathway may be mediated by N-Methyl-D-aspartate (NMDA) glutamate receptors (Fox et al., 1990, Kwon et al., 1992, Daw et al., 1993, Zemon and Gordon, 2006, Lisman et al., 2008), and contrast gain control is thought to be due to shunting inhibition mediated by Gamma Amino Butyric Acid (GABA) (Borg-Graham et al., 1998, Kandel and Siegelbaum, 2000).

Visual processing deficits in gain control propagate in a bottom-up manner to higher-order cognitive functions in schizophrenia, which in turn predict functional outcome. For instance, preferential magnocellular deficits have been shown to contribute to emotion processing deficits (Butler et al., 2009), such that a loss of magnocellular visual information results in a decreased ability to perceive emotional cues. Early-stage visual dysfunction has also been related to impaired social perception, which similarly involves the ability to perceive social cues (Sergi et al., 2006). Social perception predicts functional outcome in schizophrenia (Horan et al., 2011), and Sergi and colleagues (Sergi et al., 2006) used structural equation modeling to show that social perception mediates the link between early-stage visual processing and functional status. Rassovsky and colleagues (Rassovsky et al., 2011) recently used this method to demonstrate that negative symptoms in schizophrenia, as well as social perception, mediate this link between visual processing and functional status. The current study employed structural equation modeling to investigate the link between early-stage visual deficits and both functional status and symptoms. This model posited emotion processing and neuropsychological function as "mediators" of these links.

The goal of this study was to examine gain control impairment in the visual system for schizophrenia patients and its relationship with neuropsychological measures, emotion processing, and functional outcome. Previous ssVEP and contrast sensitivity results have indicated deficits in contrast gain and contrast gain control in schizophrenia (Butler et al., 2001, Butler et al., 2005, Butler et al., 2008a, Butler et al., 2009). This study used a far larger sample size, and thus aimed to further characterize these deficits. In addition, this study examined the relationships between these deficits, higher-order processes, symptoms, and functional status.

3. Methods

Participants

150 patients who met DSM-IV criteria for schizophrenia and 157 healthy volunteers participated. Patients were recruited through inpatient and outpatient 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 available clinical information. Controls were recruited through the Volunteer Recruitment Program at the Nathan Kline Institute. All participants provided informed consent and received cash compensation for their time. The study was approved by the Nathan Kline Institutional Review Board. 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 ophthalmological disorders, including

glaucoma or cataracts, that might affect performance or if they met criteria for alcohol or substance dependence within the last 6 months or abuse within the last month. All participants had normal or corrected-to-normal visual acuity of 20/32 or better on the Logarithmic Visual Acuity Chart (Precision Vision). All patients were receiving antipsychotic medication at the time of testing. Chlorpromazine equivalents were calculated as previously described (Woods, 2003, 2005, 2011). All data reported below are mean ± standard deviation.

A greater number of controls than patients were female (patients: 126 males, 24 females; controls: 107 males, 50 females; $\chi^2 = 10.530$, $p = .001$) and controls were significantly younger than patients (patients: 37.12 ± 10.49; controls: 33.55 ± 11.74; $t(292.811) = 2.774$, $p = .006$). These effects may be due to the large sample size of this study, as recent work from our group reported a similar difference in age as non-significant in a smaller sample (Martinez et al., 2012). Patients had significantly lower socioeconomic status (SES) as measured by the 4-factor Hollingshead Scale (Hollingshead, 1975) (patients: 25.75 ± 11.06; controls: 43.30 ± 12.13; $t(291) = -12.942$, $p < .001$), but parental SES did not differ between groups (patients: 44.44 ± 22.78; controls: 44.46 ± 13.91; $p = .99$). Patients had significantly reduced IQ (patients: 96.24 ± 9.56; controls: 107.12 ± 11.34; $t(282)= -8.743$, $p < .001$) and education as measured by highest grade achieved (patients: 11.77 ± 2.36; controls: 15.17 ± 2.47; $t(289)= -12.02$, $p < .001$). Patients were ill for 15.25 ± 8.94 years, had an average Global Assessment of Functioning (GAF) score of 43.46 ± 12.01, and were receiving antipsychotic doses equivalent to an average of 858.07 ± 725.60 mg of chlorpromazine per day. Although demographic data for some variables were unavailable for some participants, the overall sample characteristics were similar to those in recent publications from our group (Dias et al., 2011, Calderone et al., 2012, Martinez et al., 2012).

Steady-State Visual Evoked Potentials (ssVEP)

Isolated dark checks, subtending 15 minutes of arc of visual angle each, were shown in 16 x 16 check arrays subtending a total of 8 x 8° of visual angle. The background luminance was ~100 cd/m^2. Check luminance was modulated sinusoidally at 12 Hz. Seven depths of modulation (DOM) (0, 1, 2, 4, 8, 16, and 32%) were presented for one second each in a seven second swept-parameter run. Ten such runs were obtained for magnocellular- and parvocellular-biased stimuli separately, for each participant. For all runs, a standing check luminance (pedestal) was used, with checks modulated above and below the pedestal according to the DOM. In magnocellular-biased runs, the pedestal equaled the DOM, creating appearing and disappearing stimuli. In parvocellular-biased runs, the pedestal was constant at 48% contrast, so that stimuli never dropped below 16% contrast (Figure 1). A discrete Fourier transform was used to analyze the fundamental frequency component of averaged magnocellular- and parvocellular-biased runs separately. Signal-to-noise ratios (SNR) of the fundamental frequency were used as the dependent measure in a three-way ANOVA with group, DOM, and bias condition as factors.

A nonlinear biophysical model developed by Zemon and Gordon (Zemon and Gordon, 2006) was fit to SNRs from the magnocellular-biased condition (see Appendix A for a detailed description of the following parameters and fitting procedure). This model estimates four free parameters for the magnocellular-biased contrast response function. The initial contrast gain parameter (g_0) estimates the linear slope of the function over the low contrast range, and reflects response amplification to low contrast. The contrast gain control parameter (m) estimates the degree of response attenuation at high contrast, and reflects shunting inhibition, a process by which excitatory current is shunted out of a neuron when GABA-mediated ion channels are opened in the cell membrane (Borg-Graham et al., 1998, Kandel and Siegelbaum, 2000). The threshold parameter (d_0) estimates the lowest DOM at which shunting inhibition occurs, and reflects the point in the contrast response function where contrast gain control is first observed. The initial phase parameter (ϕ_0) estimates the phase of the ssVEP response with respect to the stimulus frequency, and reflects the speed of ssVEP response separate from contrast-induced changes in response speed. Such changes in response speed are measured by an integrative time constant parameter calculated from the contrast gain and contrast gain control parameters for 1% DOM (τ_1) and 32% DOM (τ_{32}) (Appendix A). This time constant parameter estimates the speed of the ssVEP response at each DOM, and reflects increased membrane conductance due to shunting inhibition as contrast increases. As GABA-mediated ion channels are opened during shunting inhibition, increased membrane conductance results in faster signal propagation (Kandel and Siegelbaum, 2000), and this is observed as a reduction in the time constant parameter with increasing DOM.

Magnocellular-biased contrast response functions were also characterized as having responses to contrasts below 16% DOM (individuals with low contrast responses) or showing a lack of responses to these contrasts (individuals with low contrast deficits). “Responses” consisted of SNRs above the noise level (>1). 90 controls and 82 patients had low contrast responses, while 16 controls and 28 patients had low contrast deficits.

Psychophysical Contrast Sensitivity

Horizontal sine-wave gratings were presented on the left or right of a computer screen, with the mean luminance of the stimuli shown on the other. Participants indicated which side the grating stimulus appeared on in a two alternative forced-choice paradigm. Gratings contained 0.5, 1, 4, 7 or 21 horizontal light/dark bars (cycles) per degree of visual angle (c/deg). Stimuli were shown at short 32 ms duration and longer 500 ms (Figure 2). The entire display subtended 10 x 10 degrees of visual angle, viewed from a distance of 190 cm. For each spatial frequency, an up-down transformed response (UDTR) procedure estimated the threshold contrast at which 70.7% of responses were correct. Contrast was changed by 6 decibels until two errors were made, after which 3 decibel changes were used. The threshold contrast was taken as the mean of ten reversals, and contrast sensitivity was calculated as the reciprocal of the threshold. Contrast sensitivity was used as the dependent measure in a three-way ANOVA with group, stimulus duration, and spatial frequency as factors.

Neuropsychological Assessment

Five domains were chosen from the NIMH-sponsored Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (Kern et al., 2008, Nuechterlein et al., 2008). These included speed of processing, attention vigilance, working memory, verbal learning, and visual learning.

Penn Emotion Tasks

In the Penn Emotion Recognition task (ER-40), 40 images of faces expressing either happiness, sadness, anger, fear, or a neutral expression were shown in a random order. Stimuli were balanced for poser’s age, gender, and ethnicity. Each emotion category contained four high-intensity and four low-intensity expressions. Participants verbally identified the expressed emotion from the five possible choices and the experimenter pressed response buttons to record participant answers. The outcome measure was the total percent of emotions correctly identified. A practice trial including feedback was given before the task. The task and scoring programs are available at http://penncnp.med.upenn.edu.

In the Penn Emotion Differentiation task (EMODIFF), participants differentiated the intensity of emotion expressed in two faces from the same poser shown side by side. Participants were asked to point to the face that was happier out of the two or sadder out of the two. If both faces showed equal intensity, participants were instructed to point to a box to indicate this. Twenty trials were shown for each emotion (happy and sad), and the outcome measure was the total percent of faces correctly discriminated.

In the Penn Emotion Acuity task (PEAT), participants determined the degree of emotion expressed in a face image along a seven point scale from very sad to very happy, with neutral in the middle (Erwin et al., 1992). Forty faces were presented in two blocks, the first containing sad and neutral faces, and the second containing happy and neutral faces.

Symptom and Functional Status Measures

The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1989), Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1984), and Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) were administered to schizophrenia patients to assess symptoms. The Global Assessment of Functioning (GAF) score as well as the Independent Living Scale (ILS) (Persel, 2012) were used to assess functional status. The ILS assessed the likelihood of successful independent living based on effective day-to-day strategies for negotiating life.

Structural Equation Modeling

Structural equation modeling was used to examine relationships between variables in this study. This statistical procedure determines relationships between constructs with a combination of confirmatory factor analysis and multiple regression. Constructs are termed “latent variables” and are estimated by factor analysis of measured operational definitions of the constructs, which are termed “observed variables.” Multiple regression is then used to estimate the relationships between latent variables, which are measured as partial correlations. The current analysis contained five latent variables. “Early-stage visual processing” was determined by two observed variables from the ssVEP biophysical model fit: initial contrast gain and contrast gain control, and two observed variables from the psychophysical task: contrast sensitivity to 1 c/deg at the 32 ms duration and to 4 c/deg at the 500 ms duration. “Emotion processing” was determined by the three observed variables from the Penn Emotion Tasks. “Neuropsychological function” was determined by the five variables from the MATRIX assessment. “Symptoms” was determined by the total scores from the PANSS, SANS, and BPRS. “Functional status” was determined by the observed variables GAF score and ILS.

The following relationships were hypothesized between the variables measured in this study. Early-stage visual processing was hypothesized to predict emotion processing as well as neuropsychological function. Emotion processing and neuropsychological function were both hypothesized to predict symptoms as well as functional status. Two separate models were constructed to examine emotion processing and neuropsychological function as providing a predictive link between early-stage visual processing and both symptoms and functional status. Models were estimated with a maximum-likelihood solution.

4. Results

Steady-State Visual Evoked Potentials

SNR of evoked potential responses were used as a dependent measure. A three-way ANOVA with group as a between subjects factor and condition (magncoellular- vs. parvocellular-biased) and DOM as within subjects factors showed that patients had significantly lower SNRs than healthy controls ($F(1,2996)=15.911$, $p<0.001$). A significant three-way interaction for group, condition, and DOM ($F(6,2996)=2.463$, $p<0.05$) indicated greater deficits for patients in the magnocellular-biased compared to the parvocellular-biased condition (Figure 3).

Patients had a higher percentage of individuals with low contrast deficits than controls (patients: 25.45%, controls: 15.09%), though this difference only reached trend level significance ($\chi^2(1)=3.572$, $p=0.059$). The three-way ANOVA described above was performed separately for participants with low contrast responses and participants with low contrast deficits (Figure 4). For participants with low contrast responses, (Figure 4A), patients again had significantly lower SNRs than healthy controls ($F(1,2380)=10.249$, $p<0.005$). However, the three-way interaction between group, condition, and DOM was not significant ($F(6,2380)=1.682$, $p=0.122$), indicating that patient deficits were not significantly greater for the magnocellular-biased than the parvocellular-biased condition. This shows that the preferential magnocellular deficit seen in Figure 3 and previous studies (Butler et al., 2001, Butler et al., 2005, Butler et al., 2008a, Butler et al., 2009, Butler et al., 2012) may be due to inclusion of patients with low contrast deficits, as low contrast responses were not previously categorized in this manner. However, the current finding of deficits for both magnocellular- and parvocellular-biased stimuli for patients with low contrast responses indicate that these responses are still reduced compared to controls. For participants with low contrast deficits (Figure 4B), no significant group differences or interactions including group were found.

Magnocellular-biased contrast response functions were fit with a nonlinear biophysical model (Zemon and Gordon, 2006) to characterize the components of gain control used by this pathway. When groups were not divided into those with and without low contrast responses, patients had significantly reduced initial contrast gain compared to controls (Figure 5), indicating a deficit in response amplification to low contrasts. Patients also showed lower contrast gain control, reflecting less response attenuation to higher contrasts, though this difference only reached trend level significance (*p*=0.075). In addition, patients had significantly lower threshold DOM, indicating that response attenuation occurs at lower contrasts than for controls. Together with reduced initial contrast gain, this finding shows a reduced signaling range over low contrasts for patients. Groups also differed in initial phase and time constants for 1 and 32% DOM. This showed that patients had slower overall responses as well as slower responses to both low and high DOM than controls.

These comparisons of model fit parameters were also carried out separately for participants with low contrast responses and participants with low contrast deficits (Figure 6). For participants with low contrast responses, the pattern of deficits for patients was identical to the pattern observed when all participants were considered, with one exception. The group difference for contrast gain control reached a trend level (*p*=0.075) when all participants were considered, but was highly non-significant when only participants with low contrast responses were considered (*p*=0.325). This was expected, due to the fact that contrast response functions with low contrast deficits only rise above the noise at the highest DOMs, and thus cannot show response attenuation at these DOMs. The trend level group difference in contrast gain control observed for all the participants together is therefore likely due to the greater number of low contrast deficits for patients over controls. However, the consistent pattern of significant group differences for all participants as well as only those with low contrast responses indicate that patients have deficits in initial contrast gain and response speed even when contrast gain control is intact. No significant group differences were found for participants with low contrast deficits, except that patients had significantly slower time constants for 1% DOM.

Initial contrast gain, contrast gain control, and the time constant for 1% DOM were chosen to be used in correlations with contrast sensitivity, neuropsychological measures, emotion recognition, and emotion differentiation. The time constant at 1% DOM was chosen as a measure of response speed because it has the largest range of the time constants, and time constants for all DOMs are directly proportional (see Appendix A).

Psychophysical Contrast Sensitivity

Contrast sensitivity was calculated as the reciprocal of the threshold contrast at which stimuli were detectable. A three-way ANOVA with group as a between subjects factor and stimulus duration (32 vs. 500 ms) and spatial frequency (0.5, 1, 4, 7, 21 c/deg) as within subjects factors showed that patients had significantly lower contrast sensitivities than healthy controls ($F(1,1940)=94.497$, $p<0.001$). A significant three-way interaction for group, stimulus duration, and spatial frequency ($F(4,1940)=8.427$, $p<0.001$) indicated that across groups, contrast sensitivity peaked at low spatial frequencies for 32 ms duration and at mid-range spatial frequencies for 500 ms duration (Figure 5). In addition, the difference between mean scores for controls and patients were larger in the 32 ms than in the 500 ms condition for 0.5, 1, and 4 c/deg, and larger in the 500 ms than in the 32 ms condition for 7 and 21 c/deg.

The spatial frequency that produced the highest contrast sensitivity for each stimulus duration (1 c/deg for 32 ms and 4 c/deg for 500 ms) was used to assess correlations between contrast sensitivity and ssVEP, neuropsychological measures, emotion recognition, and emotion differentiation.

Correlations between Steady-State Visual Evoked Potentials and Contrast Sensitivity

Previous work by our group found a correlation for schizophrenia patients between contrast sensitivity for 0.5 c/deg at 32 ms and ssVEP SNR for 16% DOM for the magnocellular-biased, but not parvocellular-biased, condition (Butler et al., 2005). The current results replicated and extended this finding, showing correlations for patients between magnocellular-biased SNR for 16% DOM and contrast sensitivity for 1 c/deg at 32 ms ($r = .373$, $p < 0.01$) and for 4 c/deg at 500 ms ($r = .284$, $p < 0.05$) (Figure 8). No correlations involving parvocellular-biased SNR were found.

Neuropsychological and Emotion Processing Measures

Patients had significantly lower scores than controls on all five neuropsychological measures: speed of processing ($t(58.325) = 9.802$, $p < .001$), attention vigilance ($t(129.404) = 9.748$, $p < .001$), working memory ($t(78.633) = 7.039$, $p < .001$), verbal learning ($t(92.278) = 5.991$, $p < .001$), and visual learning ($t(92.080) = 6.568$, $p < .001$). Patients also had significantly lower scores than controls for emotion processing seen on the ER-40 ($t(265) = 10.919$, $p < .001$), EMODIFF ($t(199.757) = 10.238$, $p < .001$), and PEAT ($t(191.933) = 7.997$, $p < .001$) tasks.

Structural Equation Modeling

Structural equation models estimated coefficients between variables for all participants (across groups) having scores on those variables. Controls were therefore included in all analyses except those involving symptoms and functional outcome, as only patients had scores for these measures. The model examining neuropsychological function provided a strong fit for the data ($\chi^2(74) = 180.247$, $p < .001$) (Figure 9). All observed variables had moderate to high loadings on their latent variables that were significant at the $p = .001$ level. Early-stage visual processing significantly predicted neuropsychological functioning (standardized coefficient = .521, $p < .001$), which in turn significantly predicted functional status (standardized coefficient = .964, $p < .001$) and symptoms (standardized coefficient = -.736, $p < .001$). The model examining emotion processing also provided a strong fit for the data ($\chi^2(51) = 170.149$, $p < .001$) (Figure

10). All observed variables had moderate to high loadings on their latent variables that were significant at the $p = .001$ level, except that GAF score had a weak, non-significant loading on functional status (standardized coefficient = .119, $p = .888$). Early-stage visual processing significantly predicted emotion processing (standardized coefficient = .558, $p < .001$), which in turn significantly predicted functional status (standardized coefficient = .148, $p < .001$) but not symptoms (standardized coefficient = -.157, $p = .117$).

5. Discussion

This study examined deficits in visual processing in schizophrenia and their relationships to higher-level processes, symptoms, and functional status. Contrast gain and contrast gain control have previously been found to be impaired in schizophrenia, and these impairments have been studied with psychophysical contrast sensitivity and an ssVEP paradigm (Butler et al., 2001, Butler et al., 2005, Butler et al., 2008a, Butler et al., 2009). This study replicated these past findings in a larger sample, and further characterized the ssVEP deficit using a biophysical model (Zemon and Gordon, 2006). Psychophysical contrast sensitivity also revealed patient deficits in the ability to perceive low contrast across spatial frequency and stimulus duration. Further, early-visual processing was found to significantly predict neuropsychological function, which in turn predicted functional status and symptoms, as well as emotion processing, which were related to functional outcome.

Gain Control Deficits in Schizophrenia

Schizophrenia patients showed a preferential deficit in ssVEP response to magnocellular-biased stimuli, replicating previous results (Butler et al., 2001, Butler et al., 2005, Butler et al., 2008a). ssVEP contrast response curves for magnocellular-biased stimuli were characterized using a nonlinear biophysical model (Zemon and Gordon, 2006) and categorized as having low contrast responses or low contrast deficits (see Methods). A greater number of patients, rather than controls, had low contrast deficits, with a trend toward significance. When only participants with low contrast responses were considered, the same pattern of a preferential magnocellular deficit for schizophrenia was observed. This indicates that not only were patients more likely to show low contrast deficits, but even for patients with low contrast responses, these responses were still impaired relative to controls.

The biophysical model allowed further examination of specific deficits for contrast gain and contrast gain control, and response speed in schizophrenia. When all participants in each group were considered together, patients showed significant deficits for all model fit parameters except contrast gain control, which trended toward significance. For patients with low contrast responses, contrast gain control was intact, but initial contrast gain as well as the speed of the ssVEP response was still impaired. Processing speed is generally impaired in schizophrenia (see (Kalkstein et al., 2010) for review), and relates to functional outcome (Puig et al., 2012). The current results of increased time constants for patients show that ssVEP response speed is slower, even when patients have intact contrast gain control. Impaired contrast gain, rather than contrast gain control, may therefore contribute to visual processing speed deficits. Individuals with low contrast deficits also showed significantly slower time constants for 1% DOM, and additionally had poor contrast gain control, as their model fits were typically linear. Together, these results reveal two types of visual gain control impairment in schizophrenia for this ssVEP paradigm: a deficit in responses to low contrast associated with poor contrast gain control (25% of patients), and a more common reduction in initial contrast gain with intact contrast gain control (75% of patients).

The loss or reduction of magnocellular-biased ssVEP response observed for patients is supported by previous studies in which diffusion tensor imaging revealed a loss of white matter integrity specific to the optic radiations in schizophrenia (Butler et al., 2006, Henze et al., 2012). Recent work has shown that reductions in white matter integrity of the optic nerve result in a loss of VEP response (Diem et al., 2008, Naismith et al., 2012). Indeed, one of our previous studies found a correlation between white matter integrity and SNR for magnocellular-biased ssVEP responses (Butler et al., 2005).

Across groups, contrast sensitivity curves showed the expected pattern in which the 32 ms stimulus duration produced the highest contrast sensitivities at low spatial frequencies, while the 500 ms stimulus duration produced the highest contrast sensitivities at mid-range spatial frequencies (Tolhurst, 1975, Legge, 1978). Patients with schizophrenia showed contrast sensitivity deficits to all stimulus conditions, indicating a reduced ability to perceive very low contrast at a wide range of spatial frequencies and at both short and longer stimulus duration. These results for the 32 ms condition generally agree with our previous findings for contrast sensitivity deficits in schizophrenia at this stimulus duration, which indicated selective deficits at low spatial frequencies (Butler et al., 2005, Butler et al., 2009). The larger sample of patients in the current study showed deficits across spatial frequencies, but patients did show greater deficits to low spatial frequencies at 32 ms. Results for the 500 ms condition again showed patient deficits across spatial frequencies, but in this case greater deficits were found at higher spatial frequencies. These results agree with other previous work showing selective deficits in schizophrenia for higher spatial frequencies at 500 ms stimulus duration (Kéri et al., 2002). Contrast sensitivity deficits in schizophrenia provide further evidence of impaired gain control. The ability to detect very low contrast stimuli, regardless of spatial frequency or stimulus duration, depends on the magnocellular pathway, as the parvocellular pathway does not respond to these very low levels of contrast. A loss of gain control as seen in the ssVEP paradigm may lead to a dysfunctional magnocellular response, which in turn impairs the ability of schizophrenia patients to detect very low contrast stimuli.

Though preferential magnocellular deficits in schizophrenia are supported by a diverse and increasing literature (Butler et al., 2001, Schechter et al., 2003, Butler et al., 2005, Kéri et al., 2005, Kim et al., 2005, Schechter et al., 2005, Butler et al., 2008a, Martinez et al., 2008, Butler et al., 2009, Coleman et al., 2009, Green et al., 2009, Brittain et al., 2010, Dias et al., 2011, Koychev et al., 2011, Martinez et al., 2011, Butler et al., 2012), some recent work has questioned this model. Lalor and colleagues (Lalor et al., 2012a) recently used the electrophysiological technique Visual Evoked Spread Spectrum Analysis (VESPA), along with visual evoked potentials (VEP), to investigate magnocellular and parvocellular functioning in schizophrenia. Deficits were found with VEP elicited by high contrast stimuli, but not with VESPA to either low or high contrast stimuli, which the authors interpreted as evidence against a magnocellular deficit in schizophrenia. Source localization for the VESPA response has indicated that it stems largely from early retinotopic visual areas (Lalor et al., 2012b, Murphy et al., 2012), but a recent study (Di Russo et al., 2007) has shown that the ssVEP response has major neural generators in both primary visual cortex V1 and in motion sensitive area MT, as well as minor generators in mid-occipital area V3A and ventral occipital areas V4 and V8. Thus, the VESPA response may not reflect gain control processes occurring outside of V1. Additionally, the VESPA assumes a linear relationship between input to the cortex and the estimated neural response function, which may not optimally capture the nonlinear contrast gain and contrast gain control of the magnocellular response. While Lalor and colleagues (Lalor et al., 2012a) looked at high and low contrast VESPA responses, they did not assess low contrast transient VEP and only show a VEP deficit at high contrast. Examination of low contrast VEP responses in relation to their VESPA findings is necessary before they conclude there is a lack of magnocellular deficit.

Skottun and Skoyles (Skottun and Skoyles, 2011) recently raised concerns regarding the ssVEP paradigm used in this study. These authors point out that cells in the koniocellular visual pathway, as well as cortical visual area MT, may have similar contrast response functions as magnocellular cells, and that the magnocellular-biased condition used in this study may elicit activity from these other cell types. However, the magnocellular-biased condition, regardless of the cell types it recruits, elicits contrast response functions that demonstrate contrast gain and contrast gain control. It is these mechanisms that are thought to be impaired in schizophrenia, and the preferential magnocellular deficit is thought to arise as a result of the magnocellular pathway's preferential use of these mechanisms (Fox et al., 1990, Kwon et al., 1992, Daw et al., 1993, Zemon and Gordon, 2006, Lisman et al., 2008). Even if the magnocellular-biased condition elicits activity from non-magnocellular neurons, the deficits in contrast gain and contrast gain control observed for schizophrenia are likely to affect the magnocellular pathway more so than the parvocellular pathway. Additionally, impaired contrast gain and contrast gain control importantly contribute to higher-order cognitive impairment and functional outcome, regardless of their underlying cellular mechanism. This being said, strong evidence supports the idea that the low contrast stimuli used in the magnocellular-biased condition preferentially activate magnocellular neurons. For example, koniocellular neurons contribute less to the cortical response and have a wider range of physiologic properties than magnocellular and parvocellular neurons (Lalor and Foxe, 2010). Area MT receives a variety of inputs, but these are dominated by a rapid magnocellular signal (Nassi and Callaway, 2009). Further, the contrast response functions of both the magnocellular- and parvocellular-biased stimuli used in the ssVEP paradigm match the contrast response functions of these pathways obtained from single-cell recordings (Green et al., 2009).

Skottun and Skoyles (Skottun and Skoyles, 2011) also posit that the best measure of magnocellular functioning is contrast sensitivity to low spatial frequencies (<1.5 c/deg) and high temporal frequencies. The current results show a correlation between contrast sensitivity to 1 c/deg at a rapid 32 ms stimulus duration and ssVEP SNR in the magnocellular- but not parvocellular-biased condition. This result was also previously obtained with 0.5 c/deg stimuli (Butler et al., 2005). This further supports the idea that the stimulus manipulations used in the ssVEP paradigm bias neural responses toward the magnocellular or parvocellular pathways.

The ssVEP paradigm and psychophysical contrast sensitivity paradigm both aim to measure specific examples of the general gain control process, which optimizes neural responses based on context (Butler et al., 2008a, Butler et al., 2012). A recent study by Barch and colleagues (Barch et al., 2012) investigated gain control impairment in the visual system in schizophrenia using the contrast-contrast task, in which healthy individuals perceive reduced contrast for a center stimulus if it is surrounded by a higher contrast stimulus (Chubb et al., 1989). This effect is due to inhibition of responses to the center stimulus by responses to the contextual high contrast surround (Zenger-Landolt and Heeger, 2003), and therefore reflects gain control. Schizophrenia patients have recently shown improved performance in judging the true contrast of the center stimulus relative to controls, demonstrating reduced gain control (Dakin et al., 2005, Barch et al., 2012). This result importantly isolates gain control impairment from general task impairment, as patients show improved performance on this task. However, Barch and colleagues (Barch et al., 2012) also used catch trials in their experiment to measure attentional mechanisms. When participants showing poor attention were eliminated from the analysis, improved task performance for patients was no longer significant. This result conflicts with the current finding of a preferential deficit in magnocellular-biased ssVEP response, as an attentional deficit would predict equally impaired responses to magnocellular- and parvocellular-biased stimuli. In addition, impaired gain control has also been found in the auditory system at the pre-attentive level.

Mismatch negativity is an event-related potential response elicited by a deviant auditory stimulus among a series of standard stimuli (Green et al., 2009). In this case, the response to the deviant stimulus depends on the context of the preceding standard stimuli, and thus this response reflects gain control in the auditory system. Reliable deficits in both the amplitude and latency of the mismatch negativity have been found in schizophrenia (Umbricht and Krljes, 2005, Javitt et al., 2008, Friedman et al., 2012). This task reflects early, pre-attentive processes, and thus further demonstrates impaired early-stage sensory gain control processes in schizophrenia.

Relationships between Early-Visual Processing, Higher-Order Cognitive Functions, Symptoms, and Functional Status

Structural equation modeling has previously been used to demonstrate links between early-stage visual processing and functional status in schizophrenia, with social perception (Sergi et al., 2006, Rassovsky et al., 2011) and negative symptoms (Rassovsky et al., 2011) found to mediate these links. Social perception includes emotion processing (Sergi and Green, 2003), and the current results show that emotion processing specifically mediates a link between early-stage visual processing and functional status. In this model, emotion processing predicted functional status but not symptoms, and functional status only significantly reflected the independent living scale and not the GAF score. This suggests that impaired emotion processing has consequences specifically for independent living, rather than symptoms or global functioning. Neuropsychological function, on the other hand, significantly predicted functional status as reflected by independent living and GAF score, as well as symptoms. This indicates that deficits in neuropsychological function have wide-ranging consequences for both disease status and functional status.

Emotion processing and neuropsychological function were also both significantly predicted by early-stage visual processing, suggesting that visual processing deficits in schizophrenia reflected by ssVEP and psychophysical contrast sensitivity have consequences for higher-level cognitive functions, disease status, and functional status. A caveat of these current results is that both controls and patients were included in the models. Thus, links between early-stage visual processing and higher-level cognitive functioning included control participants, and reflect the fact that patients showed deficits for these measures relative to controls. However, recent work by Gold and colleagues (Gold et al., 2012) demonstrated links between basic auditory processing impairment and auditory emotion recognition deficits in schizophrenia, and Leitman and colleagues (Leitman et al., 2010) found that both auditory emotion recognition and basic auditory perception were related to functional outcome. Together with the current findings in the visual system, these studies show that basic sensory processing dysfunction in schizophrenia across modalities affects higher cognitive functions as well as functional outcome.

Impairments in other cognitive functions have also recently been linked to early-stage visual processing deficits, particularly in the magnocellular system. Reading deficits in schizophrenia have been linked to impaired magnocellular function as measured by contrast sensitivity (Revheim et al., 2006). Altered cortical activity during object recognition has recently been tied to dorsal stream dysfunction (Sehatpour et al., 2010) and a loss of magnocellular-transmitted information (Calderone et al., 2012). While cognitive dysfunction in general is known to be related to functional outcome in schizophrenia (Green, 2006), relationships between some specific cognitive functions and functional outcome remain to be elucidated. The current results indicate that emotion processing, as opposed to general neuropsychological functioning, specifically relates to independent living. Future investigations of processes such as reading and object recognition are needed to further clarify how these cognitive functions may mediate links between early-stage sensory processing and functional outcome.

Summary and Conclusions

Two tasks were used to measure contrast gain and contrast gain control in a large sample of patients with schizophrenia. ssVEP and a related biophysical model revealed preferential magnocellular deficits in schizophrenia. These were further characterized by the biophysical model, which revealed low contrast deficits related to impaired contrast gain control in 25% of patients, as well as a general deficit in contrast gain in the other 75%. These two types of gain control deficits may relate to differential GABA and NMDA function respectively. Additionally, ssVEP response speed was significantly impaired in all patients, suggesting that contrast gain deficits may contribute to visual processing speed impairment in schizophrenia. Psychophysical contrast sensitivity revealed deficits for patients across spatial frequency and for both short- and long-duration stimuli. These results further indicate that schizophrenia is associated with impaired perception of low contrasts.

Structural equation modeling revealed that this impairment in contrast gain and contrast gain control as measured by ssVEP, as well as psychophysical contrast sensitivity, predicts impaired emotion processing and neuropsychological function. Emotion processing specifically predicted the degree to which patients were able to live independently, while neuropsychological function also predicted this in addition to global functioning and symptoms. These results underscore the importance of early-stage visual processing deficits in schizophrenia for understanding higher-level cognitive dysfunction that contributes to functional outcome.

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7. Appendix A

The Nonlinear Biophysical Model

The biophysical model used in this study was developed by Zemon and Gordon (Zemon and Gordon, 2006). Fitting the model to an individual's contrast response function yields estimates of four free parameters: initial contrast gain, initial phase, contrast gain control, and threshold depth of modulation (DOM). The integrative time constant of the system at any particular DOM can then be calculated from the initial contrast gain and contrast gain control parameters.

Initial contrast gain, g_0, reflects the initial specific conductance of the neural system responding to the stimuli, and estimates the membrane conductance in the absence of visual stimulation. This parameter also estimates the initial (Fatt and Katz, 1953)linear slope of the contrast response function. Initial phase, ϕ_0, is the phase of the response with respect to the stimulus frequency in the absence of stimulus-induced phase changes. Contrast gain control, m, measures shunting inhibition in the system. This parameter estimates the amount of nonlinear reduction in the slope of the contrast response function as DOM increases. Shunting inhibition was first described by Fatt and Katz (Fatt and Katz, 1953), and refers to a cellular process in which a portion of excitatory current entering the cell through ion channels in the membrane is shunted out through nearby channels (Kandel and Siegelbaum, 2000) regulated by Gamma Amino Butyric Acid (GABA) (Borg-Graham et al., 1998). The opening of these GABA mediated channels increases the membrane conductance of the cell, which has two consequences: a reduction in the overall voltage of the cell which decreases the probability of an action potential; and a reduction in the time needed for a voltage signal to travel along the membrane. Shunting inhibition therefore results in reduced amplitude of ssVEP responses with a simultaneous advance in their phase. This effect is also termed contrast gain control, as it demonstrates a context dependent modulation of the initial contrast gain of the system. Threshold DOM, d_0, is the lowest DOM at which shunting inhibition (i.e. contrast gain control) occurs in the contrast response function.

The integrative time constant, τ, measures the speed of the response dependent on the DOM of a stimulus. The total integrative time constant is given by:

$$\tau = \frac{C}{g_0 + g_s} = \frac{C}{g_0 + m(DOM - d_0)}$$

where C is the specific capacitance of the cellular membrane, which is assumed to be 0.8 μF/cm^2, and g_s is the amount of conductance due to shunting.

The model uses a differential equation to obtain the system's frequency response. Estimates of amplitude (A_R) and phase (ϕ_R) of the second harmonic frequency component of the response are then obtained:

$$A_R = (DOM - d_0)\left(k\frac{g_0/C}{\sqrt{p^2 + \omega^2}}\right)$$

$$\phi_R = -\tan^{-1}\left(\frac{\omega}{p}\right) + \phi_0$$

where p is the reciprocal of the total integrative time constant, ω is the angular temporal frequency of the second harmonic response component, and K is the gain setting which is assumed to be 10 (Zemon and Gordon, 2006, García-Quispe et al., 2009).

A discrete Fourier transform applied to the EEG data yielded cosine and sine coefficients for the second harmonic component of the response. The model used an algorithm based on the Generalized Reduced Gradient nonlinear optimization code found in the Microsoft Excel Solver program (Microsoft, 2006) to apply a least-squares criterion to fit the model to these cosine and sine coefficients. The model estimates for these coefficients were calculated from the previous response amplitude and phase equations:

$$cosine\ coefficient = A_R \cdot \cos \phi_R$$

$$sine\ coefficient = A_R \cdot \sin \phi_R$$

Contrast response functions were also visually inspected, and in some cases adjustments to the model fit were made by removing data points and re-running the Solver algorithm. In some cases, the amplitude of the response decreased at 32% DOM relative to 16% DOM. The model was only capable of producing monotonically increasing functions, and in these cases the reduced amplitude at 32% DOM artificially increased the value of the contrast gain control (i.e. shunting inhibition) parameter, m. In such cases, the response for 32% DOM was removed from the model to more accurately estimate contrast gain control.

8. Figure Captions

Figure 1. Sinusoidal modulation of isolated check stimuli used in the ssVEP paradigm. Stimuli were sinusoidally modulated at 12 Hz, such that each cycle through contrast levels shown in A and B occurred 12 times per second. A. Magnocellular-biased condition: pedestal around which contrast was modulated equaled the depth of modulation, resulting in appearance/disappearance stimuli. B. Parvocellular-biased condition: pedestal around which contrast was modulated equaled 48%, so that contrast remained high during modulation.

Figure 2. Psychophysical contrast sensitivity task. Participants indicated whether stimuli appeared on the left or right side of the screen. Two separate sessions showed stimuli for 32 and 500 ms. In each session, 0.5, 1, 4, 7, and 21 c/deg stimuli were intermixed. After the stimulus was shown, participants indicated whether the stimulus appeared on the left or right side of the screen by raising the left or right hand, and the experimenter recorded these responses.

Figure 3. Contrast response functions for the ssVEP paradigm. Error bars show standard error. $*p < .05$.

Figure 4. Contrast response functions for the ssVEP paradigm plotted separately for A. Individuals with low contrast responses, and B. Individuals with low contrast deficits. Error bars show standard error. $*p < .05$.

Figure 5. Variables estimated by the biophysical model fit of magnocellular-biased ssVEP contrast response functions. Error bars show standard error. $*p < .05$.

Figure 4. Variables estimated by the biophysical model fit of magnocellular-biased ssVEP contrast response functions plotted separately for A. Individuals with low contrast responses, and B. Individuals with low contrast deficits. Error bars show standard error. $*p < .05$.

Figure 7. Psychophysical contrast sensitivities displayed on a log base 10 scale. Error bars show standard error. $*p < .05$, $**p < .01$.

Figure 8. Correlations between ssVEP SNR to 16% DOM in the magnocellular-biased condition and peak contrast sensitivities for each stimulus duration.

Figure 9. Structural equation model hypothesizing neuropsychological function as a mediator for a link between early-stage visual processing and functional status as well as symptoms. Standardized regression coefficients are given. $*p < .001$.

Figure 10. Structural equation model hypothesizing emotion processing as a mediator for a link between early-stage visual processing and functional status as well as symptoms. Standardized regression coefficients are given. $*p < .001$.

9. Figures

<u>Figure 1:</u>
Steady-state visual evoked potential stimuli:

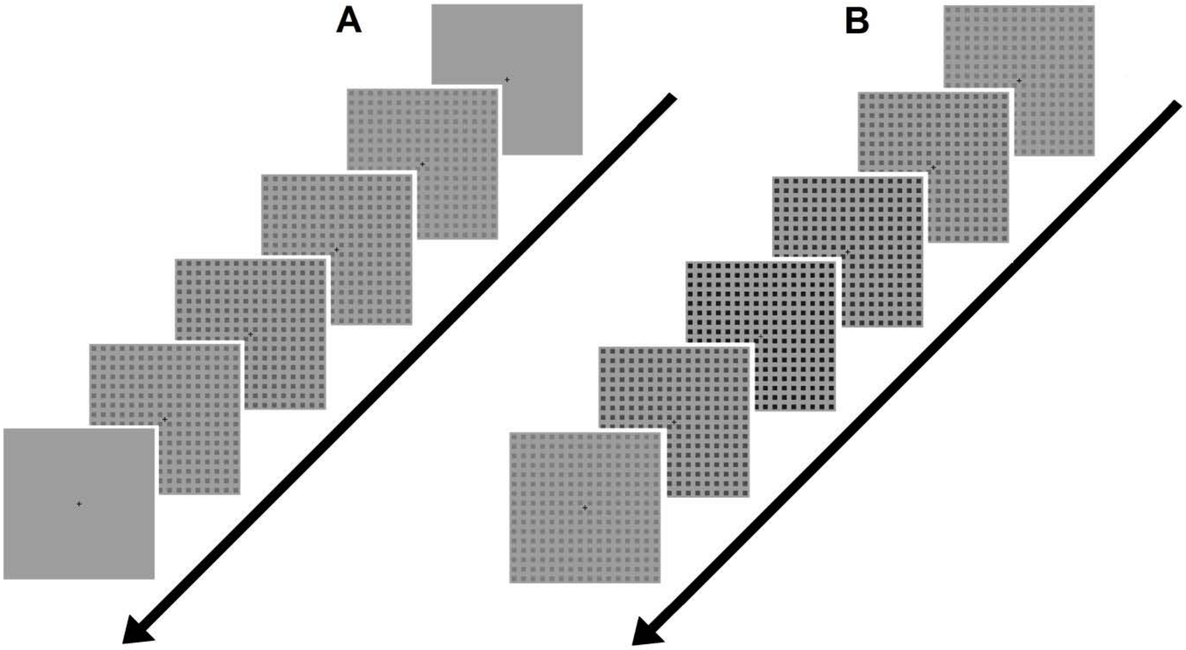


Figure 2:
Psychophysical contrast sensitivity stimuli:

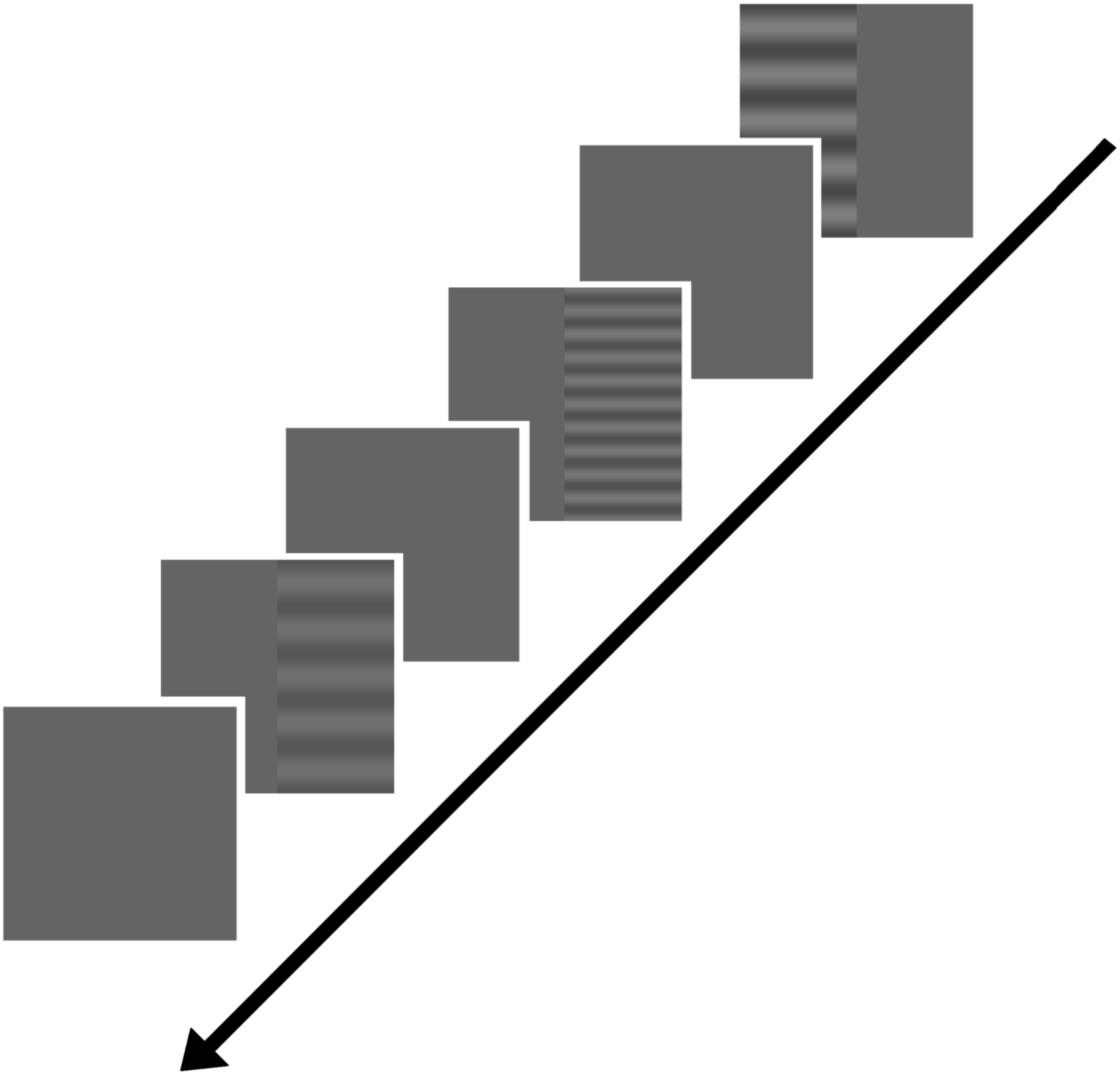
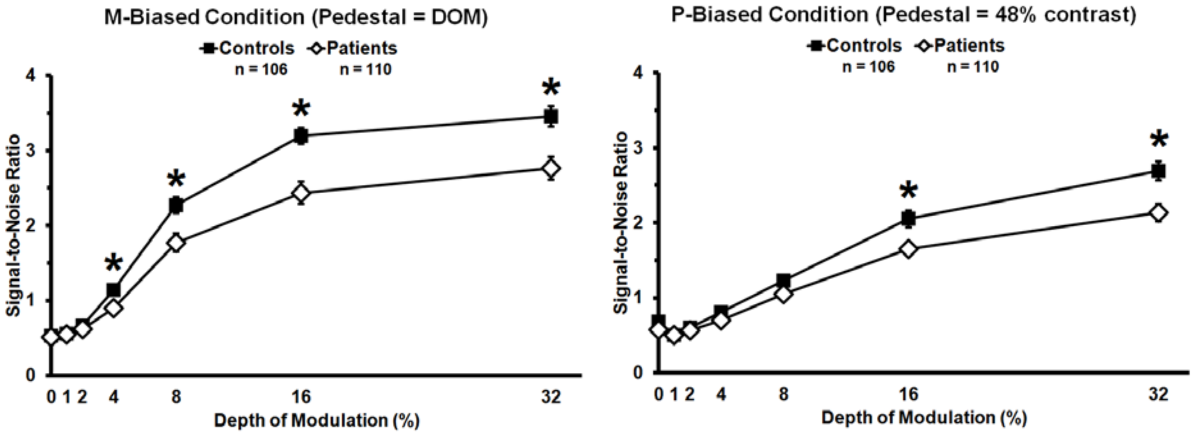


Figure 3:

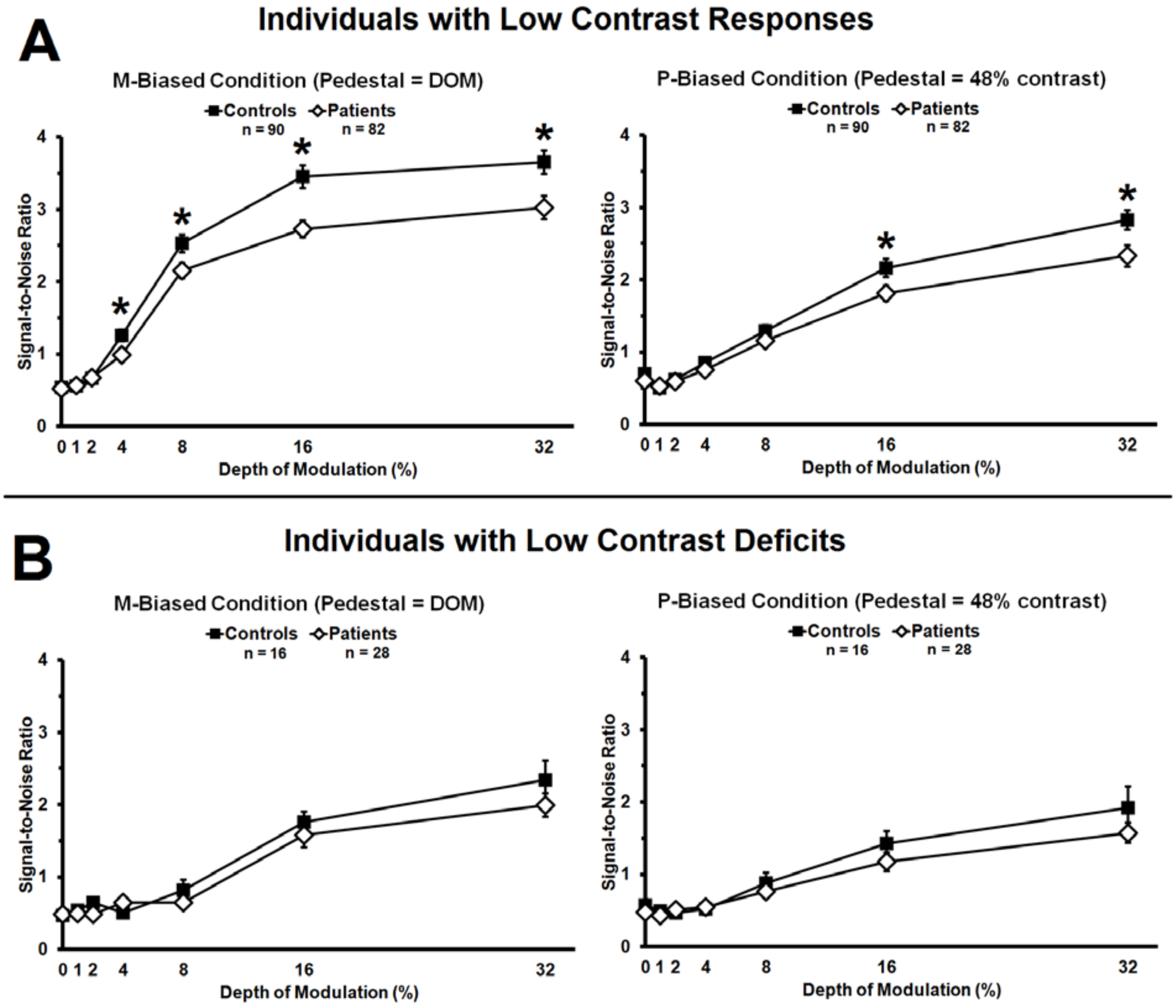
Contrast response functions:



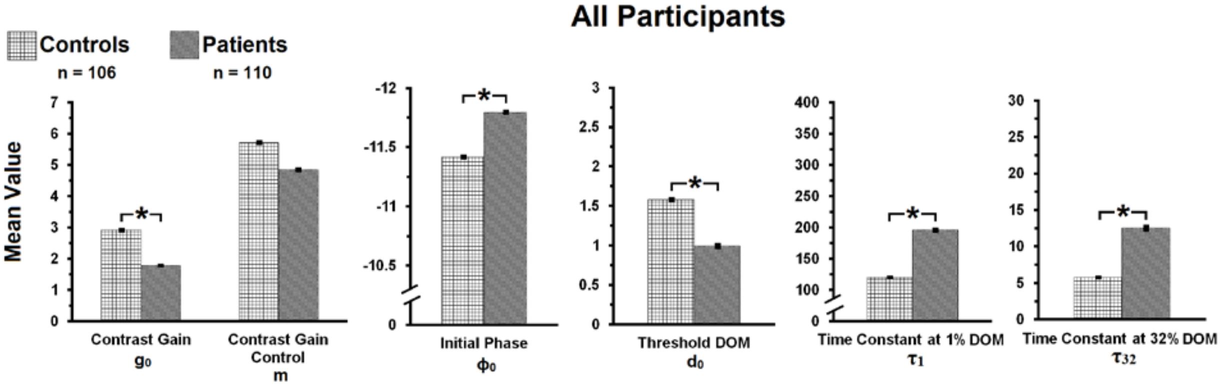
M-Biased Condition (Pedestal = DOM)

P-Biased Condition (Pedestal = 48% contrast)

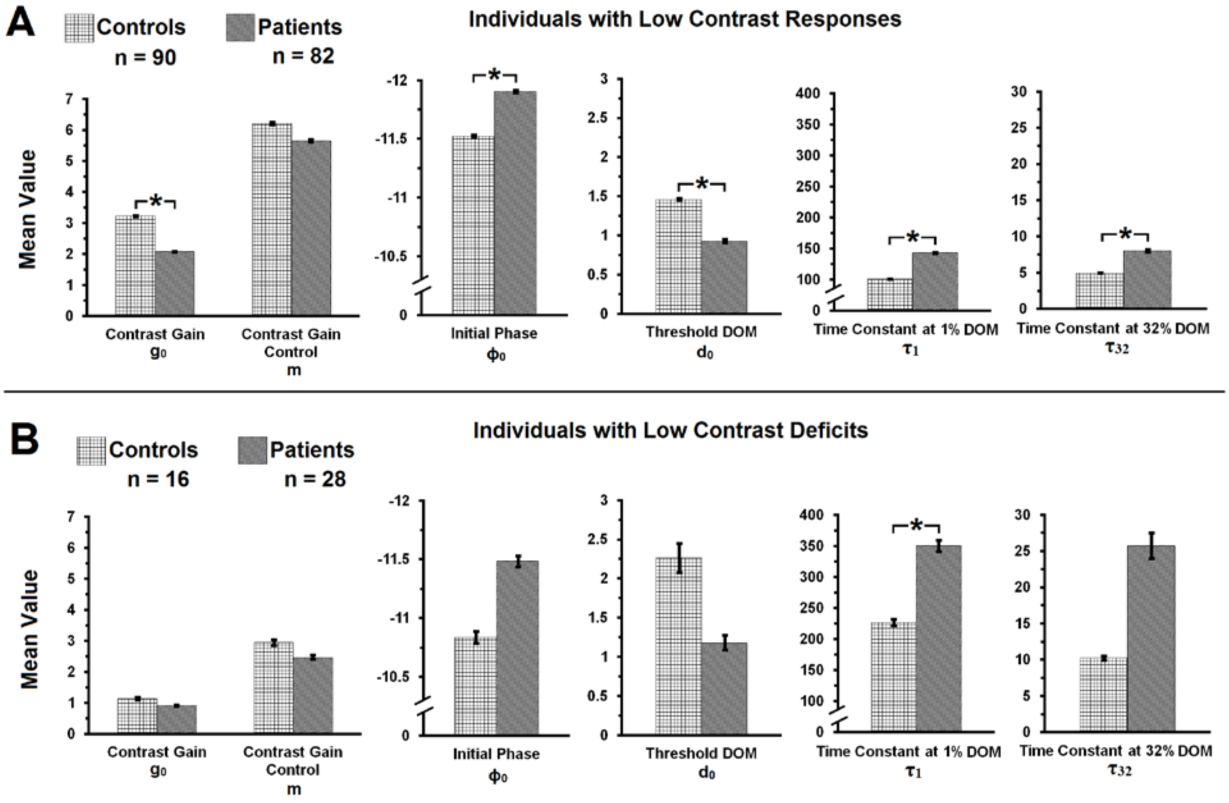
Figure 4:
Contrast response functions for individuals with and without low contrast responses:



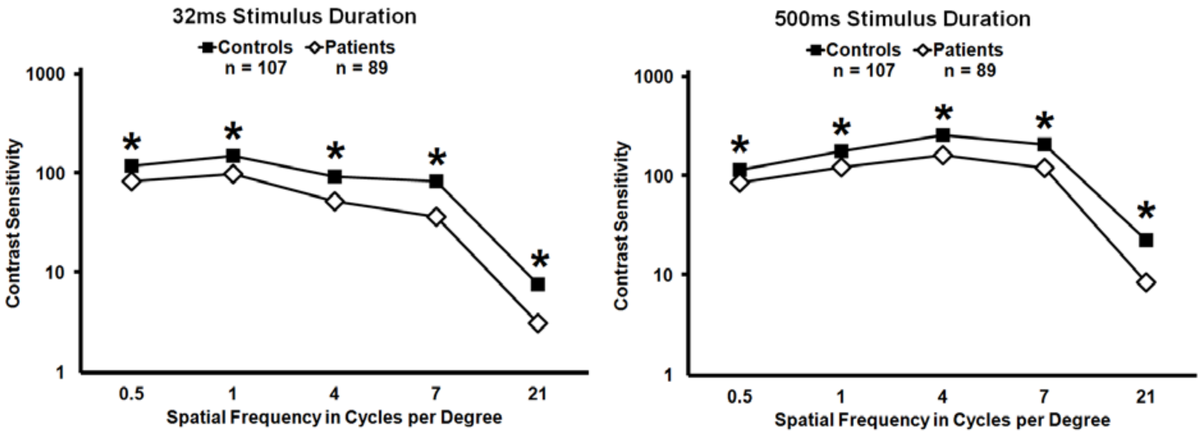
<u>Figure 5:</u>
Biophysical model fit parameters:



<u>Figure 6:</u>
Biophysical model fit parameters for individuals with and without low contrast responses:



<u>Figure 7:</u>
Psychophysical contrast sensitivity:



<u>Figure 8:</u>
Correlations between steady-state visual evoked potentials and contrast sensitivity:

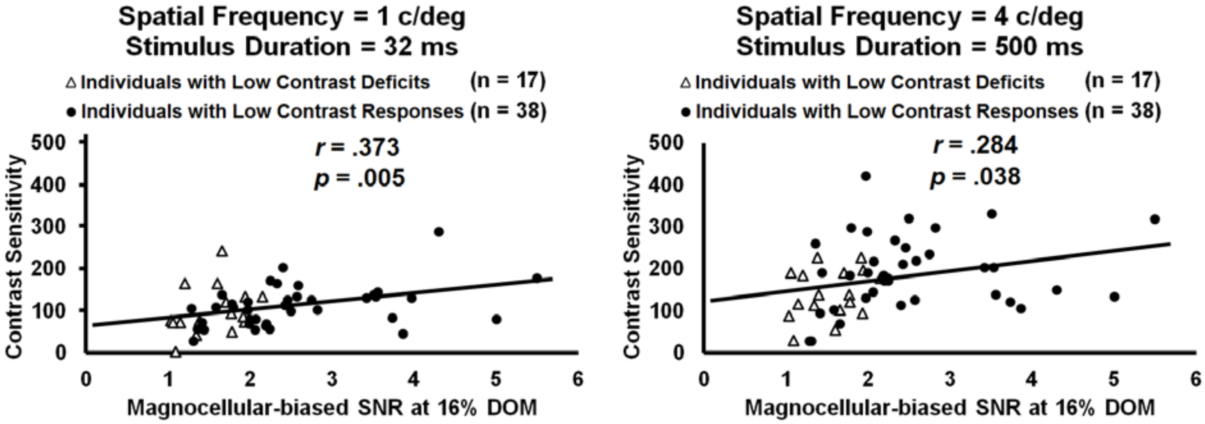


Figure 9:

Structural equation model including neuropsychological function:

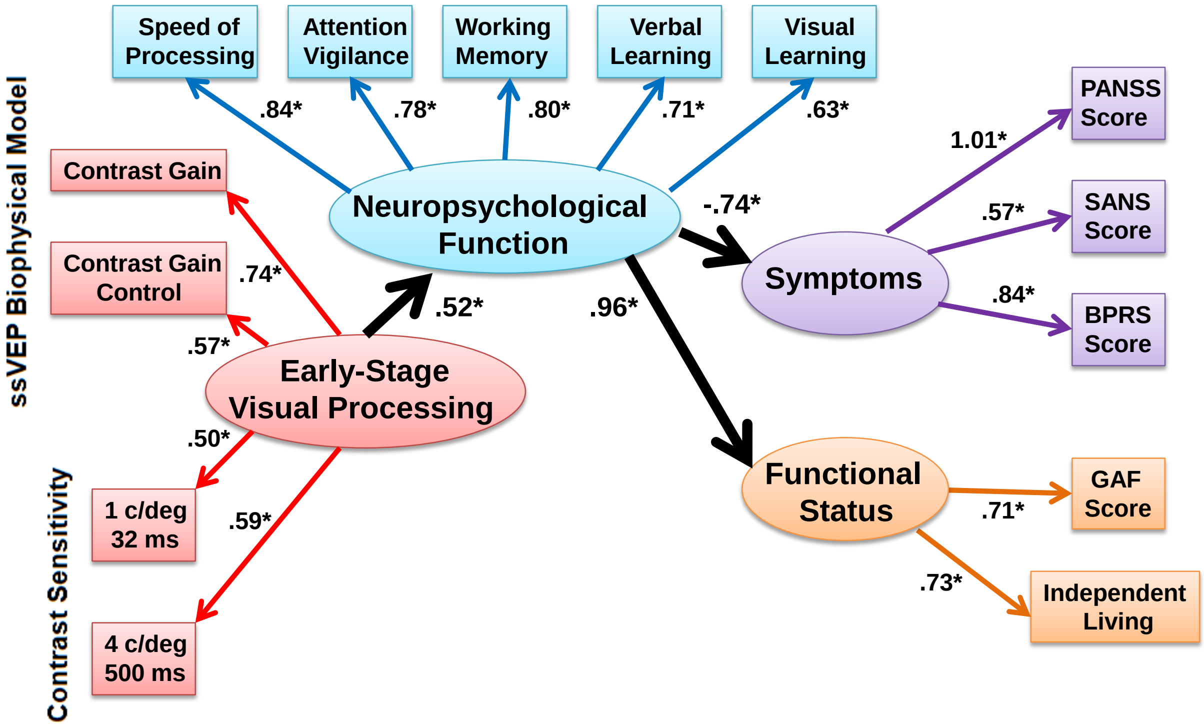
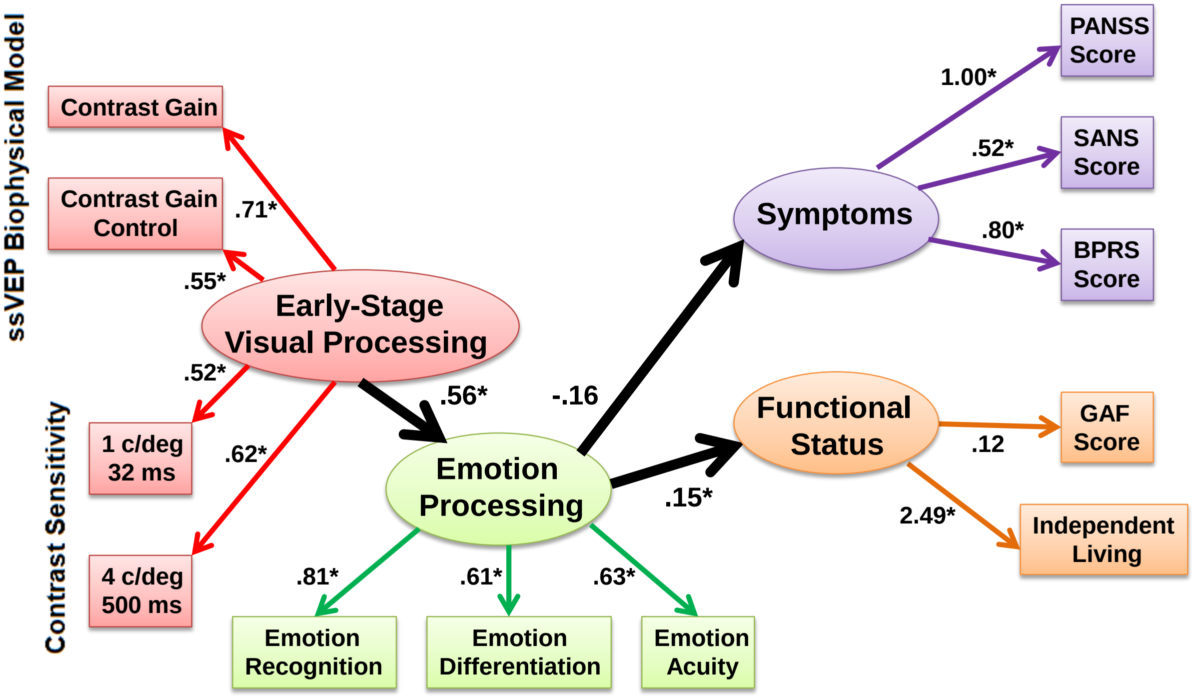


Figure 10:
Structural equation model including emotion processing:



CHAPTER 3

Neural substrates of visual gain control in healthy individuals and schizophrenia patients

1. Abstract

Gain control has been identified by an NIMH-sponsored group as a useful general construct for assessing perceptual deficits in patients with schizophrenia and in the evaluation of treatment efficacy for cognitive dysfunction in this population. Specific measures of contrast gain and contrast gain control derived from recordings of steady-state visual evoked potentials (ssVEP) have demonstrated neural deficits within the visual pathways of patients with schizophrenia. Psychophysical measures of contrast sensitivity have also shown functional loss in these patients. In the current study, functional magnetic resonance imaging (fMRI) was used in conjunction with ssVEPs and contrast sensitivity testing to elucidate the neural underpinnings of these deficits. During fMRI scanning, participants viewed 1) the same low and higher spatial frequency stimuli used in the psychophysical contrast sensitivity task performed at both individual detection threshold levels and at a high contrast; and 2) the same stimuli used in the ssVEP paradigm, which were designed to be biased toward either the magnocellular or parvocellular visual pathway. Patients showed a significant impairment in contrast sensitivity at both spatial frequencies in the psychophysical task and showed reduced occipital activation volume for low, but not higher, spatial frequency at threshold and high contrast in the magnet, consistent with other studies showing deficits in low spatial frequency processing for schizophrenia. As expected, patients exhibited selective deficits under the magnocellular-biased ssVEP condition. Occipital lobe fMRI responses were obtained for magnocellular- and parvocellular-biased contrast stimuli similar to those used in the ssVEP paradigm. These responses generally demonstrated increased activation volume, but low strength, with increases in low levels of contrast, and decreased activation volume, but high strength, at higher contrast,

for both magnocellular- and parvocellular-biased conditions across groups. Thus, for patients, the fMRI results showed intact recruitment of occipital areas while the ssVEP results indicated that these areas did not optimally utilize gain control. These results indicate a broad dissociation between fMRI and ssVEP measures. Findings are interpreted with respect to neural underpinnings of each type of signal.

2. Introduction

Over recent years it has become clear that patients with schizophrenia exhibit sensory processing deficits in a number of modalities (Javitt, 2009, Koychev et al., 2011, Leitman et al., 2011, Silverstein and Keane, 2011, Butler et al., 2012). Indeed, perception was chosen as one of the key domains for development of measures that could be used in clinical trials in schizophrenia by the NIH-sponsored Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) initiative (Green et al., 2009, Butler et al., 2012). In the visual system, behavioral, electrophysiological, and functional magnetic resonance imaging (fMRI) studies have revealed early-stage sensory deficits, including deficient processing of contrast (Slaghuis, 1998, Kéri et al., 2002, Kéri et al., 2004, Butler et al., 2005, Butler et al., 2009, Green et al., 2009), motion (Chen et al., 2003b, Chen et al., 2004, Kim et al., 2006), and spatial frequency information (O'Donnell et al., 2002, Martinez et al., 2008, Martinez et al., 2012). These visual sensory processing deficits appear to contribute to higher level dysfunction in reading (Revheim et al., 2006), object processing and grouping (Doniger et al., 2002, Kurylo et al., 2007, Sehatpour et al., 2010), and emotion processing (Turetsky et al., 2007, Butler et al., 2009, Calderone et al., 2012).

Within the domain of perception, the CNTRICS initiative identified two constructs as useful in clinical trials of treatments to improve cognition: gain control and integration. The focus of the current study is on gain control, which refers to processes that allow sensory systems to optimize their response levels based on their immediate context, to make the best use of limited dynamic signaling range (Butler et al., 2008a, Butler et al., 2012). Gain control processes amplify or attenuate neuronal responses using both the intrinsic properties of neurons as well as lateral connections between them (Green et al., 2009, Barch et al., 2012).

The anatomical correlates of two functional measures related to gain control were explored using an fMRI technique in the current study. These measures use visual stimuli designed to emphasize either the magnocellular or parvocellular contributions to visual processing. The subcortical magnocellular pathway contains rapidly conducting neurons that project preferentially to dorsal stream cortical areas while the parvocellular pathway contains smaller, more slowly conducting neurons that project preferentially to ventral stream areas, with extensive interaction between these pathways following activation of primary visual cortex (V1). While response properties of the two pathways overlap, they can be preferentially activated by stimuli that differ in contrast, spatial, and temporal frequency. With regard to contrast, magnocellular neurons show a nonlinear response to contrast with steep initial slope as contrast increases through the low contrast region followed by a decrease in slope as contrast increases above 12%. The steep initial slope reflects initial gain and is referred to as ‘contrast gain.’ Response saturation which occurs at higher contrasts reflects a nonlinear inhibitory mechanism and is referred to as ‘contrast gain control’ (Shapley and Victor, 1979). This nonlinear response to contrast is an aspect of the more general concept of gain control as defined by CNTRICS; it involves a dynamic signal adjustment to enhance responses to low contrast and restrict responses from rising past a certain level when contrast is high. This type of response is found at the subcortical level within the magnocellular pathway. The subcortical parvocellular pathway and its recipient cortical neurons, on the other hand, do not respond much at low contrast (<10%), and parvocellular responses exhibit a shallow linear slope in response magnitude vs. contrast as contrast increases, i.e., low contrast gain (Kaplan and Shapley, 1982, 1986, Tootell et al., 1988, Shapley, 1990, Benardete et al., 1992).

Patients with schizophrenia exhibit deficits in gain control in the visual system, which are seen in electrophysiological (Butler et al., 2005, Green et al., 2009, Butler et al., 2012) as well as behavioral studies (Slaghuis, 1998, Kéri et al., 2002, Kéri et al., 2004, Butler et al., 2005, Butler et al., 2009, Green et al., 2009, Barch et al., 2012). An electrophysiological steady-state visual evoked potential (ssVEP) task using isolated-check stimuli (Zemon and Gordon, 2006) has previously been used to demonstrate contrast gain and contrast gain control deficits in schizophrenia (Butler et al., 2001, Butler et al., 2005, Butler et al., 2008a, Butler et al., 2012). This task biases responses toward the magnocellular contribution by keeping stimuli in the low contrast range, and biases responses toward the parvocellular contribution by modulating stimulus contrast around a high contrast "pedestal" to keep stimuli above the level that induces magnocellular response saturation (Zemon and Gordon, 2006). Signal-to-noise ratios are obtained separately for magnocellular- and parvocellular-biased responses over a range of increasing contrasts. Schizophrenia patients have shown selective deficits in the magnocellular-biased vs. the parvocellular-biased contrast response function (Butler et al., 2001, Butler et al., 2005, Butler et al., 2008a, Butler et al., 2012). To better understand the neural underpinnings of these deficits in contrast gain and contrast gain control, the current study used the same stimuli from previous ssVEP studies (Butler et al., 2005, Zemon and Gordon, 2006, Butler et al., 2008a) in an fMRI paradigm.

Schizophrenia patients also exhibit visual deficits in the psychophysical contrast sensitivity task, in which contrast detection thresholds are found for different spatial frequencies by using sinusoidal spatial frequency gratings as stimuli. The ability to detect low contrast stimuli under particular spatiotemporal conditions arises from the greater sensitivity to contrast of the magnocellular over the parvocellular system. The magnocellular pathway responds preferentially to low spatial and high temporal frequencies, while the parvocellular pathway preferentially responds to high spatial and low temporal frequencies (Ungerleider and Mishkin, 1982, Shapley, 1990, Merigan and Maunsell, 1993, Wurtz and Kandel, 2000, Norman, 2002). For contrast sensitivity tasks, short duration stimuli (i.e. high temporal frequency), produce the highest contrast sensitivities at low spatial frequencies, whereas longer duration stimuli produce the highest contrast sensitivities at mid-range spatial frequencies (Tolhurst, 1975, Legge, 1978). A number of studies show that patients with schizophrenia have higher contrast thresholds (i.e., impaired contrast sensitivity) compared to healthy controls (Slaghuis, 1998, Kéri et al., 2002, Chen et al., 2003a, Slaghuis, 2004, Butler et al., 2005, Butler et al., 2008b, Norton et al., 2009, Dias et al., 2011). Selective deficits have been found at low spatial frequencies in some studies (Butler et al., 2005, Butler et al., 2009), though others found deficits across spatial frequencies (Slaghuis, 1998, Kéri et al., 2002) or showed contradictory results of increased contrast sensitivity for first-episode schizophrenia patients (Kiss et al., 2010). One reason for discrepancies between studies may be that deficits are generally found when contrast threshold is low, regardless of spatial frequency (Butler et al., 2005).

The goal of the current study was to explore the cortical areas that underlie the visual responses that reflect gain control and contrast sensitivity deficits in schizophrenia using stimuli from electrophysiological (Butler et al., 2005, Zemon and Gordon, 2006, Butler et al., 2008a) and psychophysical paradigms (Butler et al., 2001, Butler et al., 2005, Butler et al., 2009). It is hoped that this work will assist in task development for measures to be used in clinical trials aimed at assessing cognition in schizophrenia.

3. Methods

Participants

Fifteen patients who met DSM-IV criteria for schizophrenia and 15 healthy volunteers participated. Patients were recruited through inpatient and outpatient 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 available clinical information. Controls were recruited through the Volunteer Recruitment Program at the Nathan Kline Institute. All participants provided informed consent and received cash compensation for their time. The study was approved by the Nathan Kline Institutional Review Board. 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 ophthalmological disorders, including glaucoma or cataracts, that might affect performance or if they met criteria for alcohol or substance dependence within the last six months or abuse within the last month. All participants had normal or corrected-to-normal visual acuity of 20/32 or better on the Logarithmic Visual Acuity Chart (Precision Vision). All patients were receiving antipsychotic medication at the time of testing. Chlorpromazine equivalents were calculated as previously described (Woods, 2003, 2005, 2011). All data reported below are mean ± standard deviation.

Controls and patients did not differ in gender (patients: 13 males, 2 females; controls: 12 males, 3 females; $p = .64$) or age (patients: 39.12 ± 10.09; controls: 34.89 ± 10.36; $p = .27$). Patients had significantly lower socioeconomic status (SES) as measured by the 4-factor Hollingshead Scale (patients: 23.31 ± 6.80; controls: 44.57 ± 9.88; $t(25) = -6.463$, $p < .001$), but parental SES did not differ between groups (patients: 39.92 ± 9.39; controls: 46.68 ± 14.05; $p = .30$). Patients had significantly reduced IQ (patients: 97.46 ± 7.00; controls: 104.71 ± 8.65; $t(25) = -2.38$, $p = .03$) and education as measured by highest grade achieved (patients: 11.54 ± 1.20; controls: 14.50 ± 1.99; $t(25) = -4.64$, $p < .001$). Patients were ill for 14.58 ±

7.42 years, had an average Global Assessment of Functioning (GAF) score of 48.67 ± 13.84, and were receiving antipsychotic doses equivalent to an average of 783.33 ± 611.54 mg of chlorpromazine per day. Although demographic data for some variables were unavailable for some participants, the overall sample characteristics were similar to those in recent publications from our group (Dias et al., 2011, Calderone et al., 2012, Martinez et al., 2012).

Psychophysical Contrast Sensitivity

Horizontal sine-wave gratings were presented on the left or right half of a computer screen (VENUS system, Neuroscientific Corp., Farmingdale, NY), with the mean luminance of the stimuli shown on the other half. Participants indicated on which side the grating pattern appeared on in a two-alternative forced-choice paradigm (Figure 1). Two different spatial frequencies were used. The low spatial frequency (0.5 c/deg) stimuli were shown for a short (32 ms) duration and the higher spatial frequency (4 c/deg) stimuli were shown for a longer (500 ms) duration to bias stimuli toward eliciting responses from the magnocellular and parvocellular pathways, respectively. The entire display subtended 10 x 10 degrees of visual angle, viewed from a distance of 190 cm. For each spatial frequency, an up-down transformed rule (UDTR) procedure estimated the threshold contrast at which 70.7% of responses were correct. Contrast was changed by 6 decibels until two errors were made, after which 3 decibel changes were used. The threshold contrast was taken as the mean of ten reversals, and contrast sensitivity was calculated as the reciprocal of the threshold (Wetherill and Levitt, 1965).

Steady State Visual Evoked Potentials (ssVEP)

Apparatus

Stimulus presentation, ssVEP recording, and data analysis were performed with a Neucodia system (VeriSci Corp., Raritan, NJ). For improved measurement of responses, this system uses synchronized data collection: electroencephalographic (EEG) signal sampling at integer multiples of the stimulus display's frame rate. A single channel of EEG recording was used with one (active) electrode at O_z, referenced to a second one at C_z with a floating ground at P_z, in accordance with the 10-20 system (Jasper, 1958).

Stimuli and Procedure

Isolated dark checks, subtending 15 minutes of arc of visual angle each, were shown in 16 x 16 check arrays subtending a total of 8 x 8° of visual angle. The background luminance was ~50 cd/m^2. Check luminance was modulated sinusoidally at 12.5 Hz. Seven depths of modulation (DOM) (0, 1, 2, 4, 8, 16, and 32%) were presented for one second each in a seven second swept-parameter run. Ten such runs were obtained for M-biased and P-biased stimuli separately, for each participant. For all runs, a standing check luminance (pedestal) was used, with checks modulated above and below the pedestal according to the DOM. In M-biased runs, the pedestal equaled the DOM, creating appearing and disappearing stimuli (Figure 2). In P-biased runs, the pedestal was fixed at 48% contrast, so that stimuli never dropped below 16% contrast (Butler et al., 2005, Zemon and Gordon, 2006).

Analysis

A discrete Fourier transform was used to analyze the fundamental frequency component of averaged M- and P-biased runs separately. Signal-to-noise ratios (SNR) of the fundamental frequency component computed for each set of 10 runs were used as the dependent measure in a three-way ANOVA with group, DOM, and bias condition as factors. A measure of initial gain was calculated as the slope of the response function between 4 and 16% DOM, i.e. the change in SNR from 4 to 16% DOM divided by the increase in DOM (12%). A measure of plateau level was calculated as the average of the responses at 16 and 32% DOM.

Functional Magnetic Resonance Imaging (fMRI)

Apparatus

A 3T Siemens TIM Trio magnetic resonance scanner at the Nathan Kline Institute was used for all functional and structural scans. Functional scans contained 34 axial slices, with TR=2000ms, TE=30ms, and voxel size=2.5x2.5x2.8mm, with a 0.7mm gap. High-resolution structural scans were performed with a 3-D magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence, having 192 sagital slices with TR=2500ms, TE=3.5ms, FA=8°, and voxel size =1x1x1mm. Slice time correction, motion correction, normalization to a value of 100, smoothing (8mm FWHM Gaussian kernel), skull stripping, deconvolution of relevant time series, and first-order regression analyses were performed using the AFNI (http://afni.nimh.nih.gov/; (Cox, 1996)). Functional and structural scans were coregistered and transformed into a common Talairach space using the Automatic Registration Toolbox (Ardekani et al., 2004, Klein et al., 2009).

Stimuli and Procedure

Similar isolated-check stimuli as those used in the ssVEP paradigm were presented to create M-biased and P-biased fMRI scanning runs. Check size was slightly larger, with each isolated check subtending 24 minutes of arc of visual angle. Five DOMs (2, 4, 8, 16, and 32%) were presented in a block design for both M-biased and P-biased conditions. For each DOM, 12 seconds of pattern presentation was followed by 12 seconds of blank background luminance, and this cycle was repeated four times. To maintain attention to the stimuli, participants pressed a response button when a fixation cross in the center of the screen changed into a dot for 300ms. The dot appeared randomly during half of the stimulus presentations.

Contrast sensitivity tasks were performed during fMRI scanning for the same two stimulus conditions used in the psychophysical task: 0.5 c/deg displayed for 32 ms, and 4 c/deg displayed for 500 ms. During structural scans, participants performed the task beginning at 50% contrast. A UDTR procedure that estimated an accuracy of 84.09% decreased stimulus contrast by 6 decibels until the first reversal, and increased or decreased stimulus contrast by 3 decibels afterwards. When five reversals were obtained, the task paused until structural scanning was complete. The threshold contrast was taken as the mean of the two contrasts shown in the fifth reversal. During a subsequent functional scan, the task resumed at the contrast level reached at the end of the fifth reversal. Participants continued performing the task at threshold contrast for 45 TRs, and then performed the task at an unchanging high contrast of 71% for an additional 45 TRs. This entire procedure was completed for each spatial frequency separately. Display equipment used for the fMRI paradigm was limited to 256 gray levels, in contrast to the 4096 gray levels utilized by the VENUS system for the psychophysical contrast sensitivity task. Thus, the lowest contrast that could be displayed in the fMRI paradigm was ~1%. To compensate for this, a neutral density filter was used to dim the luminance of the display by 1 log unit during the contrast sensitivity paradigm only.

All stimuli were viewed through a mirror system mounted on the head coil that reflected a projection screen behind the scanner. The luminance of the projection screen was obtained for the complete range of grayscale values by using a photometer (Photoresearch, Inc. Model 650 Spectrophotometer). This information was used to accurately calculate contrast when designing stimuli.

Analysis

For each participant, first-order regression analyses isolated fMRI activity related to specific task conditions, generating maps of beta coefficients. These analyses were restricted to the occipital lobe, based on the a priori assumption that deficits in schizophrenia to these particular tasks occur in early visual processing areas. These beta maps were used as input for higher-order group analyses and averages. All *p* values were corrected for multiple comparisons using AlphaSim, such that only clusters of 48 voxels or more were considered significant. For each task, three measures were assessed. Volume of activation in milliliters was obtained for each individual based on beta maps for each condition thresholded at $p = .001$. Strength of activation was measured as the proportion of total variance explained by each condition obtained by squaring the beta values and calculating the mean squared beta value over occipital cortex for values surviving $p = .001$.

Data from the isolated-check scans included activity related to each DOM (2, 4, 8, 16, and 32%) separately for M-biased and P-biased conditions. Measures of activation volume and strength were used as dependent variables in two separate three-way ANOVAs with group as a between-subjects factor and DOM and bias condition as within-subjects factors. In addition, location and direction of activation were determined by group averages of beta coefficient maps thresholded at $p = .001$. These were displayed on a flattened anatomical map of the occipital cortex.

Contrast sensitivity scans included four task conditions: 0.5 and 4 cycles per degree for near threshold contrast and for high contrast conditions separately. Because this task showed stimuli on the left or right visual field, first-order regression analysis yielded separate beta maps for left vs. right hemispheric activation for each of the four task conditions. Volume of activation and strength of activation were obtained for each task condition as described above, for combined left-stimuli and right-stimuli beta maps.

4. Results

Psychophysical Contrast Sensitivity

A main effect of group ($F(1,56) = 11.769$, $p < .005$) showed that patients had lower contrast sensitivity than healthy controls to both the 0.5 c/deg and 4 c/deg spatial frequency conditions (Figure 3). Further, a two-way Group x Condition interaction ($F(1,56) = 4.632$, $p < .05$) indicated that this deficit in contrast sensitivity was greater for the higher spatial frequency as compared to the low spatial frequency condition. This may be due to the fact that the high spatial frequency condition produced higher contrast sensitivity across groups ($F(1,56) = 46.529$), $p < .001$), thus showing that patient deficits relative to controls were greater when controls were able to detect lower contrasts.

Steady-State Visual Evoked Potentials

Signal-to-noise ratios (SNR) of the evoked potential response were used as the dependent measure. The three-way ANOVA with group as a between-subjects factor and condition (M- vs. P-biased) and DOM as within-subjects factors showed that patients had significantly lower SNRs than did healthy controls ($F(1,392) = 10.682$, $p < .005$). A significant three-way interaction for Group x Condition x DOM ($F(6,392) = 7.001$, $p < .001$) indicated greater deficits for patients in the M-biased compared to the P-biased condition (Figure 4).

For controls, the M-biased condition generated an initial steep rise in response indicative of strong contrast gain. There was a plateau at 16% DOM, indicative of shunting inhibition at the higher contrasts (Zemon and Gordon, 2006). A significant two-way Group x DOM interaction ($F(6,196) = 11.772$, $p < .005$) for this condition indicated that patients had lower

SNRs than did controls at every DOM where signal was greater than noise (SNR > 1) (Figure 4). Further, patients had decreased initial gain (i.e., decreased slope from 4 to 16% DOM) ($t(28) = 2.587$, $p < .05$) and lower plateau (i.e., mean SNR for 16 and 32% DOM) ($t(28) = 3.335$, $p < .005$) compared to controls. For both controls and patients, the P-biased condition generated a steadily rising response function with no plateau. For the P-biased condition, the group by DOM interaction was not significant ($F(6,196) = 1.944$, $p > .07$), but there was a significant main effect of group ($F(1,196) = 4.348$, $p < .05$). However, no group differences were found for any DOM where the signal was greater than the noise. Initial gain ($t(28) = 1.091$, $p > .28$) and plateau ($t(28) = 1.815$, $p > .08$) measures did not significantly differ between groups.

Functional Magnetic Resonance Imaging (fMRI): Contrast Sensitivity Task

Contrast sensitivity tasks were performed during fMRI scanning at 0.5 and 4 c/deg, at near threshold levels for each observer and at a fixed 71% contrast. Five controls were outliers with near threshold contrast levels above 50% and one patient was an outlier with an error in blood oxygenation level dependent (BOLD) signal acquisition, and they were removed from all analyses. Group differences were not found in behavioral contrast sensitivity. For 0.5 c/deg, both controls and patients had contrast sensitivities close to 1% contrast (M ± SD percent contrast: Controls: 2.07 ± 0.85; Patients: 2.60 ± 2.17), but participants had a larger range of thresholds to the 4 c/deg condition (M ± SD percent contrast: Controls: 9.25 ± 12.68; Patients: 12.53 ± 13.89). Across groups, higher contrast sensitivities were obtained for 0.5 than for 4 c/deg ($t(26) = 3.745$, $p < .005$) (data not plotted). This result is opposite to that obtained with the other psychophysical contrast sensitivity procedure performed using a VENUS system. This is likely due to the fact that the display used in the fMRI scanner was limited to 256 gray levels, such that the smallest contrast steps possible were approximately 1%. The VENUS system's display contained 4096 gray levels, which enabled far greater precision in measurement of thresholds.

For volume of activation, no interactions were found, but a main effect of group indicated greater occipital recruitment for controls than for patients ($F(1,88) = 17.583$, $p < .001$). This difference was significant for the 0.5 c/deg condition at both near threshold contrast and at high contrast, but not for 4 c/deg condition at either contrast level (Figure 5A). For strength of activation, no interactions or main effects were found, indicating equivalent activation strength for all task conditions and both groups (Figure 5B).

Functional Magnetic Resonance Imaging (fMRI): Isolated Check Task

Volume and strength of activation were assessed for each bias condition and DOM (Figure 6). In addition, location of activation is represented in group-averages displayed on flattened anatomical images of the occipital cortex, for each bias condition and DOM (Figure 7). For both volume and strength of activation measures, there was no significant main effect of group and no significant interactions containing group in a three-way ANOVA with group as a between subjects factor and condition (M- vs. P-biased) and DOM as within subjects factors. Across groups, there was a significant Condition x DOM interaction ($F(4,290) = 3.192$, $p < .05$) for activation volume. While both the M- and P-biased conditions showed a steep increase in volume of occipital activation from 2 to 8% DOM, and a decrease in activation volume from 8 to 16 and 32% DOM across groups (Figure 6A), the P-biased condition yielded an increase in activation volume from 16 to 32% DOM which the M-biased condition did not yield (Table 1).

For strength of activation, a main effect of DOM ($F(4,295) = 17.280$, $p < .001$) was found. The pattern of activation strength as DOM increased was strikingly different from the pattern of activation volume (Figure 6B). Activation strength remained low over the 2 to 8%

DOM range, and only increased at 16 and 32% DOM. Similarly to activation volume, activation strength showed an increase in activation from 16 to 32% DOM for the P-biased, but not the M-biased, condition (Table 1).

Group-averages displayed on flattened maps of occipital cortex ($p = .001$) showed differences in the location and direction of activation for different DOMs (Figure 7). For both bias conditions, the activation maps showed that the foveal representation was activated at all DOMs except 2%, where there was little activation. In addition, parafoveal areas showed positive activation (i.e. increased activation relative to rest) at 4 and 8% DOM, but negative activation (i.e. decreased activation relative to rest) at 16 and 32% DOM. For controls, this negative activation was most extensive at 16% DOM in the M-biased condition and at 32% in the P-biased condition. Schizophrenia patients showed less parafoveal negative activity, especially at 16% DOM in the M-biased condition, although these differences were not significant.

5. Discussion

This study investigated the cortical regions associated with gain control deficits in the visual system in schizophrenia. An ssVEP paradigm utilizing contrast stimuli (Butler et al., 2001, Butler et al., 2005, Zemon and Gordon, 2006, Butler et al., 2008a, Butler et al., 2009, Butler et al., 2012) and psychophysical contrast sensitivity tasks (Slaghuis, 1998, Kéri et al., 2002, Butler et al., 2005, Butler et al., 2009, Dias et al., 2011) have previously revealed such deficits, but no study has localized these processes in the visual cortex of controls or patients. The current study utilized similar stimuli as those used in these electrophysiological and behavioral tasks in an fMRI paradigm in order to elucidate the neural substrates involved in visual contrast processing in healthy controls and patients with schizophrenia.

Psychophysical Contrast Sensitivity

Psychophysical contrast sensitivity results indicated that schizophrenia patients had contrast sensitivity deficits to both the short-duration low spatial frequency and longer-duration high spatial frequency conditions, indicating that they were unable to detect low contrast stimuli that controls could for both conditions. The deficit was larger for high spatial frequency stimuli, though this was probably because this condition produced higher contrast sensitivities in general, and controls reached very low threshold contrasts (0.34%).

Steady-State Visual Evoked Potentials

Consistent with our previous findings, schizophrenia patients showed a selective deficit in the magnocellular- vs. the parvocellular-biased condition (Butler et al., 2001, Butler et al., 2005, Butler et al., 2009, Butler et al., 2012). For the magnocellular-biased condition, healthy controls showed a steep initial increase in response as contrast increased over the low contrast range, followed by a plateau in response when contrast reached 16%. Patients showed a less steep initial increase in response, indicative of reduced signal amplification to low contrasts, and a lower plateau, indicative of reduced level of maximal response. For the parvocellular-biased condition, both groups demonstrated a linear increase in response with a shallow slope over the full range of contrasts, with no group differences for responses out of the noise (SNR > 1). The shape of the curves is consistent with nonlinear gain in the magnocellular-biased condition and supports previous studies (Butler et al., 2001, Butler et al., 2005, Zemon and Gordon, 2006, Butler et al., 2007, Butler et al., 2008a, Green et al., 2009, Butler et al., 2012) that show schizophrenia is associated with deficits in initial contrast gain and in contrast gain control in the visual system.

Our previous ssVEP results (Butler et al., 2001, Butler et al., 2005, Butler et al., 2009) were obtained utilizing a VENUS system (Neuroscientific Corp., Farmingdale, NY) for stimulus presentation, VEP recording, and analysis, which is no longer manufactured. The current results were obtained utilizing a recently developed Neucodia system (VeriSci Corp., Raritan, NJ) which includes the feature of synchronized data collection, utilizes modern equipment, and provides ease of use. Thus, this deficit in contrast gain seen in the ssVEP paradigm is robust across assessment systems and cohorts of patients.

Functional Magnetic Resonance Imaging (fMRI): Contrast Sensitivity Task

In the fMRI paradigm, contrast sensitivity tasks were performed at low spatial frequency (0.5 c/deg) with short stimulus duration (32 ms) and at high spatial frequency (4 c/deg) with long stimulus duration (500 ms). Schizophrenia patients had lower volume of activation measures for low spatial frequency stimuli, at both threshold and high contrast (71%), but no significant differences were seen between groups for high spatial frequency stimuli at either threshold or high contrast. However, strength of activation measures were equivalent between groups and across all stimulus conditions. This indicates a selective deficit in processing low spatial frequency information for schizophrenia patients reflective of reduced volume of occipital activation, rather than reduced activation strength.

A recent study by Martinez and colleagues (Martinez et al., 2008) also found reduced volume of activation to low spatial frequency (0.2-1.4 c/deg) stimuli in schizophrenia at high (100%) and low (12%) contrast, in retinotopically defined V1 and V2. As in the current results, this study also did not find deficits to high spatial frequencies (3.5-4.9 c/deg) at either contrast level. The current results extend this selective deficit in activation volume for low spatial frequencies to even lower contrasts (1-2%). Martinez and colleagues presented stimuli centrally and had participants press a button when a central fixation cross dimmed. The current results show that this deficit is also present during the frequently used psychophysical contrast sensitivity task. An even more recent study by Martinez and colleagues (Martinez et al., 2012) found reduced fMRI activation to attended low spatial frequency (0.8 c/deg) compared to attended high spatial frequency (5 c/deg) gratings in schizophrenia patients. However, no group differences were found in areas known to be involved in feature-guided attention, suggesting that sensory processing of low spatial frequencies is impaired in schizophrenia independently of attentional deficits. The current study further supports this theory by showing deficits in activation volume to low spatial frequency in schizophrenia during equivalent task performance to controls. Additionally, Calderone and colleagues (Calderone et al., 2012) recently found deficits in a network of cortical areas including occipital cortex to low spatial frequency object stimuli (≈6 cycles per image) in schizophrenia. This indicates that low spatial frequency processing deficits are not limited to simple grating stimuli, but also occur to complex images. These previous findings and the current results indicate a robust deficit in fMRI activation to low spatial frequency in schizophrenia, across stimulus contrast and complexity. This deficit may additionally be related to contrast sensitivity deficits to low spatial frequencies, as previous findings have shown that reductions in contrast sensitivity were related to reduced occipital activation volume (Goodyear et al., 2000, Leguire et al., 2011).

Controls and patients did not differ in behavioral contrast sensitivity in the fMRI paradigm, likely due to technical limitations of the equipment (see Methods and Results). The lowest contrast possible in the fMRI task was 1%, while far lower contrasts (e.g., 0.34% for controls in the 4 c/deg condition) were reached in the psychophysical contrast sensitivity paradigm performed with more gray levels on specialized visual equipment (VENUS system).

For low spatial frequency, patient deficits in contrast sensitivity for the VENUS psychophysical paradigm may be related to deficits in fMRI activation volume, but for higher spatial frequency, contrast sensitivity deficits were observed in the VENUS psychophysical paradigm but no deficits in fMRI activation were found. There are two possible explanations for this discrepancy. For the 0.5 c/deg condition, threshold contrasts from the VENUS psychophysical paradigm (controls: 0.88%; patients: 1.22%) were close to the lowest contrast possible in the scanner (1%), and to thresholds obtained during fMRI scanning. However, for the 4 c/deg condition, threshold contrasts from the VENUS psychophysical paradigm (controls: 0.34%; patients: 0.57%) were well below 1%. Thus, fMRI activation to the low spatial frequency condition may reflect neural processes occurring during the VENUS psychophysical paradigm more accurately than fMRI activation to the higher spatial frequency condition. In addition, threshold contrasts were higher for the 4 c/deg condition than for the 0.5 c/deg condition in the fMRI paradigm, while this pattern was reversed for the VENUS paradigm. Thus, participants were viewing higher contrasts for the 4 c/deg condition in the fMRI paradigm than in the VENUS paradigm, but were viewing similar threshold contrasts for the 0.5 c/deg condition in both paradigms. An alternative explanation is that for the higher spatial frequency, fMRI results indicate that patients were able to recruit the same volume of occipital cortex with the same strength of activation, but the VENUS psychophysical results indicate that they were unable to utilize this activation to amplify responses to low contrasts. In this scenario, the deficit in activation volume in the 0.5 c/deg condition indicates a general deficit in processing low spatial frequencies, rather than a deficit specific to detection of low contrasts.

Controls did not show differences in activation volume or strength between spatial frequencies. Equivalent activation for lower and higher spatial frequencies at high contrast may relate to the perceptual phenomenon of "contrast constancy." At high contrast, spatial frequencies are perceived at their correct contrast, despite greater sensitivity of the visual system to mid-range rather than very low or high spatial frequencies (Georgeson and Sullivan, 1975). This may be due to contrast gain in the visual cortex increasing responses to very low and very high spatial frequencies (Boynton, 2005). Reduced activation to low spatial frequency in schizophrenia patients may thus indicate a failure of this contrast gain mechanism.

Neither controls nor patients showed differences in activation volume or strength between threshold and high contrast for either spatial frequency. This is in contrast to the isolated check paradigm, which showed dramatic changes in these measures as contrast increased. This difference may be due to the fact that the contrast sensitivity paradigm contained only low and high contrasts, without an intermediate range. In addition, isolated check stimuli were passively viewed, while the contrast sensitivity task required responses based on stimulus location. Equivalent activation at threshold and high contrast may indicate that the active detection of a stimulus in this task recruits a specific volume and strength of occipital activation regardless of stimulus contrast.

Functional Magnetic Resonance Imaging: Isolated-Check Task

Similar stimuli to those used in the ssVEP paradigm were shown in the fMRI task in order to localize the ssVEP response to specific visual cortical areas. Across groups and for both magnocellular- and parvocellular-biased stimuli, a general pattern emerged in which increasingly greater volumes of occipital cortex were recruited as contrast increased through the low contrast range, while higher contrasts showed reduced volume of activation (Figure 6A). Conversely, strength of activation remained low over the low contrast range, and increased dramatically at higher contrasts (Figure 6B). These fMRI results conflict with the ssVEP results, since they show similar patterns for magnocellular- and parvocellular-biased conditions, as well as for controls and patients. Likewise, the lack of increase in fMRI activation strength over the low contrast region conflicts with previous single-cell work, which has shown increases in the firing rates of individual cells as contrast increases (Kaplan and Shapley, 1986, Shapley, 1990). However, an important difference between magnocellular- and parvocellular-biased fMRI responses emerged for the two highest contrast modulations. For the magnocellular condition, in which the ssVEP response plateaus at 16% DOM, fMRI volume and strength of activation also plateaued at 16% DOM. However, for the parvocellular condition, which shows no plateau in ssVEP response, volume and strength of activation both increased from 16 to 32% DOM.

Group averages displayed on flattened maps of occipital cortex revealed that for the low contrast range, both foveal and parafoveal representations showed positive BOLD activity, while at high contrasts parafoveal activity was negative, but foveal activity remained positive (Figure 7). These group averages showed the greatest negative parafoveal activity at 16% DOM in the magnocellular condition, but at 32% in the parvocellular condition. The plateau in the ssVEP contrast response function for magnocellular-biased stimuli that occurs at 16% DOM is thought to be due to shunting inhibition (Zemon and Gordon, 2006, García-Quispe et al., 2009), and the negative fMRI signal at 16% contrast may reflect inhibitory processes. Indeed, negative BOLD activity coupled to positive BOLD activity has been observed in several visual fMRI studies (Harel et al., 2002, Shmuel et al., 2002), and negative BOLD activity has been linked specifically to active neuronal inhibition (Smith et al., 2004, Devor et al., 2007, Wade and Rowland, 2010).

For instance, a recent study by Wade and Rowland (Wade and Rowland, 2010) investigated negative BOLD activity in parafoveal representations and found that it occurred in response to foveal stimulation at high luminance contrast (90%). Our results are consistent with this and further showed that parafoveal negativity occurred at higher contrast modulations (16 and 32% DOM), but not at low contrast modulations (8% DOM and below). In addition, Wade and Rowland found significantly greater negativity in parafoveal areas in response to foveally presented magnocellular-biased luminance contrast stimuli than parvocellular-biased isoluminant chromatic contrast stimuli, concluding that this negativity was linked to magnocellular pathway function. Thus, the current results showing strong negative parafoveal activation at 16% DOM in the magnocellular-biased condition are consistent with the findings of Wade and Rowland (Wade and Rowland, 2010). These findings, together with the plateau in ssVEP response as well as fMRI activation volume and strength, suggest that fMRI activity at 16% DOM in the magnocellular-biased condition may be related to shunting inhibition observed in the ssVEP contrast response function. Further, schizophrenia patients had a non-significant reduction in this negative activity at 16% DOM, which may possibly relate to reduced shunting inhibition.

For the parvocellular-biased condition, 32% DOM, rather than 16% DOM, showed the most negative parafoveal activation. The ssVEP contrast response function for parvocellular-biased stimuli, as well as fMRI measures of activation volume and strength, continued to increase from 16 to 32% DOM. This negative activation, which may underlie response inhibition in the magnocellular condition, seems paradoxical given that the response continues to rise. Though speculative, this may indicate inhibition preventing the parvocellular response from rising too high at this contrast modulation, thus allowing a continued shallow linear increase in response over the whole contrast range. However, further work is necessary to investigate this possibility.

Healthy controls and schizophrenia patients did not differ significantly in volume or strength of activation for any condition in the fMRI paradigm, but had lower ssVEP responses in the magnocellular-biased condition. This indicates a dissociation between these two measures, and suggests that patients may recruit the same occipital areas with the same amount of metabolic energy as controls, but are not able to utilize these areas for optimal gain control.

Several studies have demonstrated correspondence between visual evoked potential (VEP) measures and fMRI BOLD measures, while others have shown them to be independent of each other. Whittingstall and colleagues (Whittingstall et al., 2007, Whittingstall et al., 2008) used contrast reversing checkerboard stimuli to show that source localization of a negative VEP deflection corresponded to positive BOLD activity, and a positive VEP deflection corresponded to a lesser extent to negative BOLD activity. Yesilyurt and colleagues (Yesilyurt et al., 2010) recently found a similar pattern using ultrashort duration stimuli (0.1 to 5 ms) in which an early negative VEP deflection was related to BOLD response, but a slightly later positive deflection was not. However, the relationship between the negative deflection and BOLD activity did not hold for very small deflections, indicating that VEP and fMRI may co-vary under certain circumstances but also reflect different brain processes. Indeed, VEP response adaptation to repetitive stimuli has been shown to be unrelated to BOLD activity (Janz et al., 2001), and insulin has recently been found to reduce BOLD activity while leaving VEP responses intact (Seaquist et al., 2007). Di Russo and colleagues (Di Russo et al., 2007) recently demonstrated that ssVEP responses to pattern-reversal stimuli were related to only some areas of occipital fMRI activation to the same stimuli, while other occipital fMRI activity did not contribute to the ssVEP response. Thus, VEP and ssVEP measures co-vary with fMRI activity only under certain conditions, and may only relate to part of the total fMRI activity elicited by a particular stimulus.

The current fMRI results for 16 and 32% DOM in the magnocellular-biased condition are suggestive of a link between fMRI BOLD signal and shunting inhibition as observed in the ssVEP contrast response function. However, the overall pattern of similar BOLD responses for magnocellular- and parvocellular-biased conditions across groups suggests that the neural processes measured by ssVEPs are divergent from the broader class of processes measured by fMRI, and that patient deficits to these particular stimuli occur at the neural level measured by ssVEP.

Summary and Conclusions

Within the domain of perception, gain control (ie. optimization of neural responses based on immediate context) has been identified as a potentially useful construct for the development of clinical trials aimed at improving cognition in schizophrenia. This study examined the cortical underpinnings of two tasks that utilize gain control and have previously been used to demonstrate deficits in early-stage visual perception in schizophrenia.

A psychophysical contrast sensitivity task showed deficits in schizophrenia patients for detecting very low contrast stimuli for both low and high spatial frequencies. For both controls and patients, a contrast sensitivity fMRI paradigm showed that during this psychophysical task, patients had deficits in occipital activation volume to low spatial frequency stimuli at both threshold and high contrast. However, patients had no deficits to high spatial frequency stimuli at either contrast. This may be due to limitations of the fMRI paradigm, or it may again show equivalent volume and strength of occipital activation to controls, but an inability to use these resources for optimal stimulus detection as reflected in the psychophysical contrast sensitivity data. The deficit in activation volume to low spatial frequencies seems robust in schizophrenia across contrast levels, and may also be related to contrast sensitivity deficits at low spatial frequencies.

An ssVEP paradigm was utilized in which stimuli were biased toward the magnocellular or parvocellular pathway based on contrast. The current study replicated previous results showing nonlinear initial gain (steep slope for low contrasts) and contrast gain control (plateau at high contrast) in the magnocellular-biased contrast response function for healthy controls, and a preferential deficit in these mechanisms for schizophrenia patients. Controls and patients showed similar patterns of fMRI activation to these stimuli with increased occipital activation volume but low activation strength for the low contrast region of the contrast response function involved in initial gain (i.e., signal amplification). Conversely, at higher contrasts, activation volume decreased while activation strength was high. For the magnocellular-biased condition, controls showed strong negative parafoveal activation at the contrast where responses reached a plateau, consistent with pharmacological (Borg-Graham et al., 1998) and fMRI (Wade and Rowland, 2010) studies indicating that neuronal inhibition may underlie this plateau. This negative activation was not significantly lower for patients, but it was less apparent. The fMRI responses in general did not differ significantly between groups, indicating that patients were capable of recruiting the same volume of occipital cortex with the same activation strength as controls, but may be unable to use these resources for optimal gain and contrast gain control as reflected in ssVEP response curves.

Together, the current results indicate that contrast gain and contrast gain control deficits in schizophrenia may not be due to a lack of cortical recruitment, but rather a failure to utilize the recruited areas to amplify responses. Additionally, schizophrenia seems to be associated with a deficit in occipital recruitment to low, but not high, spatial frequencies across contrast levels, which may also reflect a deficit in cortical gain control.

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7. Figure Captions

Figure 1. Contrast sensitivity task used in the fMRI paradigm. Participants indicated whether stimuli appeared on the left or right side of the screen. A. Low spatial frequency condition: stimuli were presented at 0.5 c/deg for approximately 32 ms. B. High spatial frequency condition: stimuli were presented at 4 c/deg for approximately 500 ms.

Figure 2. Sinusoidal modulation of isolated check stimuli used in the ssVEP and fMRI paradigms. Stimuli were sinusoidally modulated at ~12 Hz, such that each cycle through contrast levels shown in A and B occurred ~12 times per second. A. Magnocellular-biased condition: pedestal around which contrast was modulated equaled the depth of modulation, resulting in appearance/disappearance stimuli. B. Parvocellular-biased condition: pedestal around which contrast was modulated equaled 48%, so that contrast remained high during modulation.

Figure 3. Psychophysical contrast sensitivities obtained with the VENUS system, displayed on a log base 10 scale. Error bars show standard error. $^*p < .05$, $^{**}p < .01$.

Figure 4. Contrast response functions for the ssVEP paradigm. Error bars show standard error. $^*p < .05$.

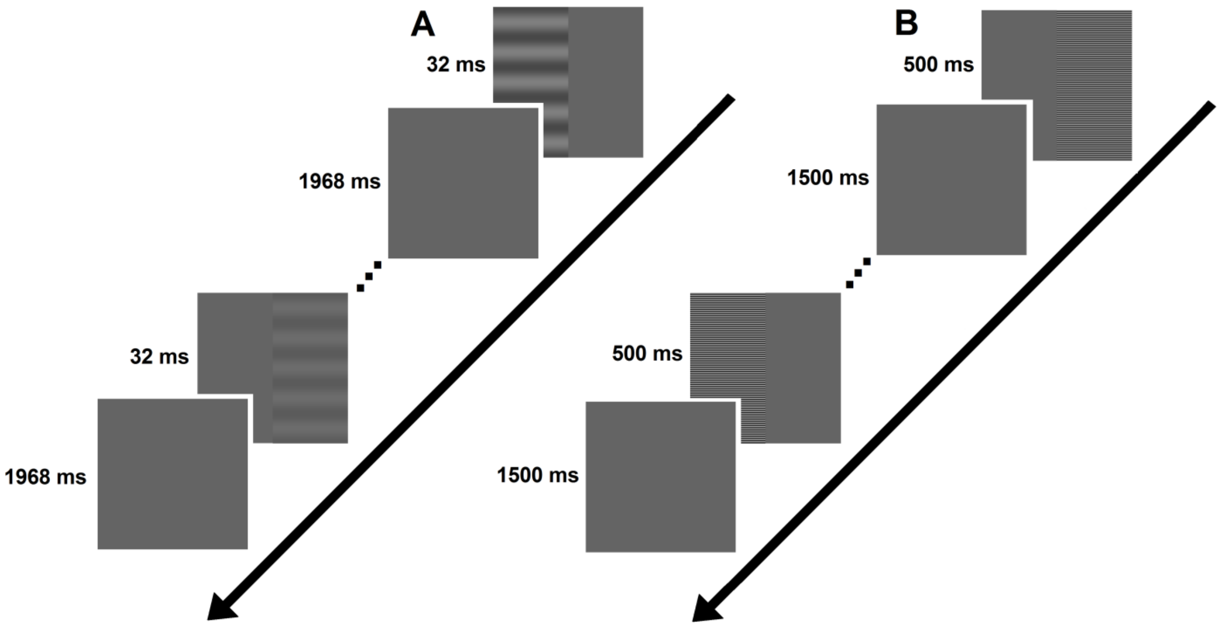
Figure 5. fMRI measures obtained during the contrast sensitivity task for 0.5 and 4 c/deg at either near threshold contrast or at high contrast. A. Volume of activation measured in milliliters. B. Strength of activation measured as first-order regression betas squared (percent of total variance). Error bars show standard error. $^*p < .05$.

Figure 6. fMRI measures for isolated check stimuli calculated for occipital cortex. A. Volume of activation measured in microliters. B. Strength of activation measured as first-order regression beta squared (variance). Error bars show standard error.

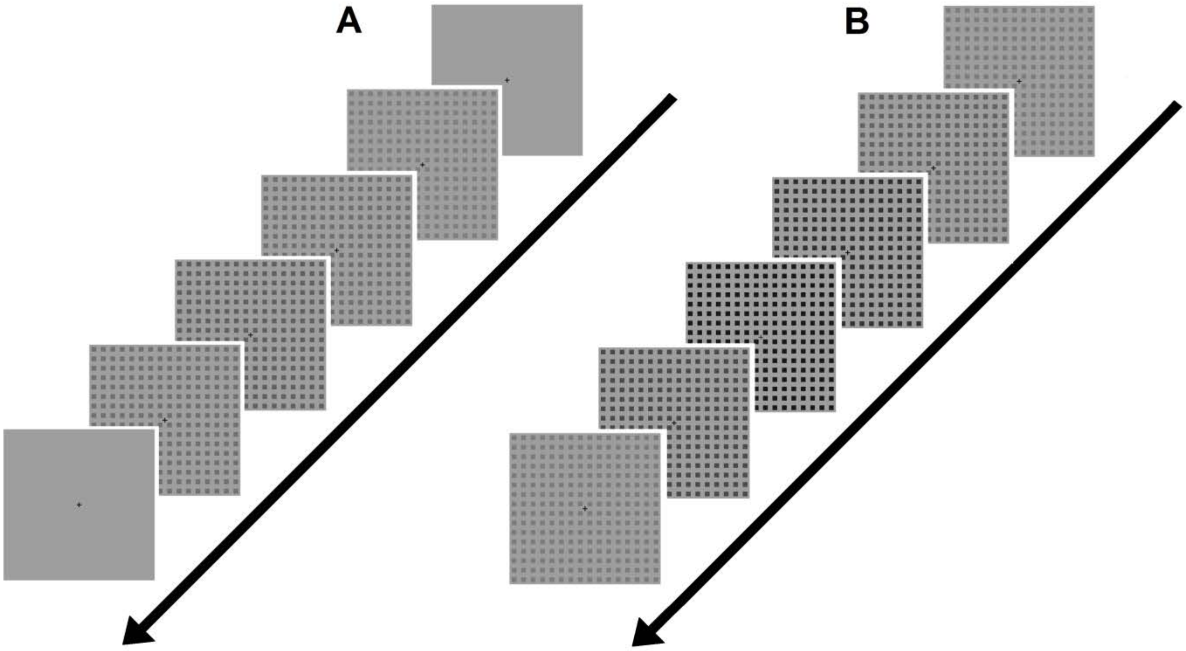
Figure 7. Flattened anatomical maps of occipital cortex showing direction and location of fMRI activation to isolated check stimuli. Each map shows a group-average of first-order regression beta values thresholded at $p = .001$. No differences between hemispheres were found for any condition at $p = .001$, and thus right hemisphere maps are shown here as representative of all occipital activation.

8. Figures

<u>Figure 1:</u>
Functional magnetic resonance imaging contrast sensitivity stimuli:



<u>Figure 2:</u>
Isolated check stimuli:



<u>Figure 3:</u>
Psychophysical contrast sensitivity:

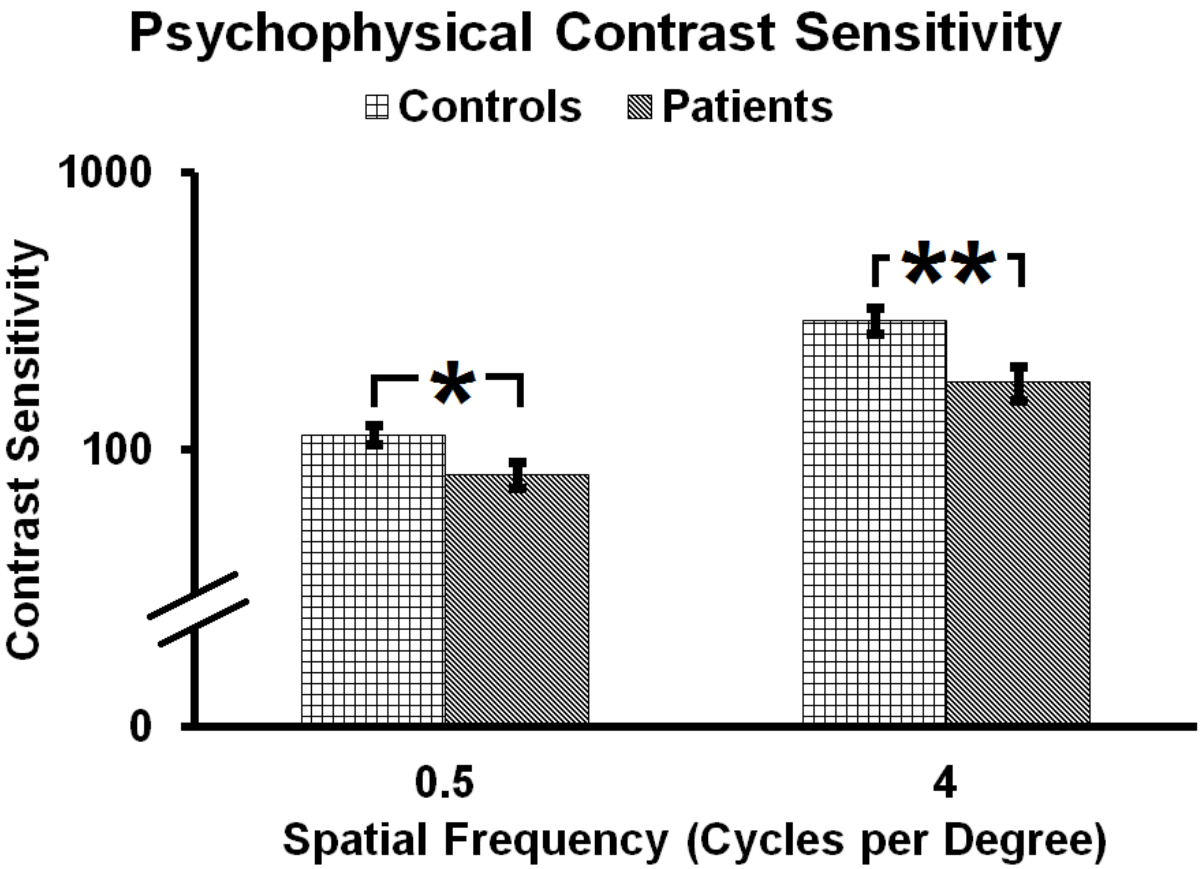


Figure 4:

Contrast response functions:

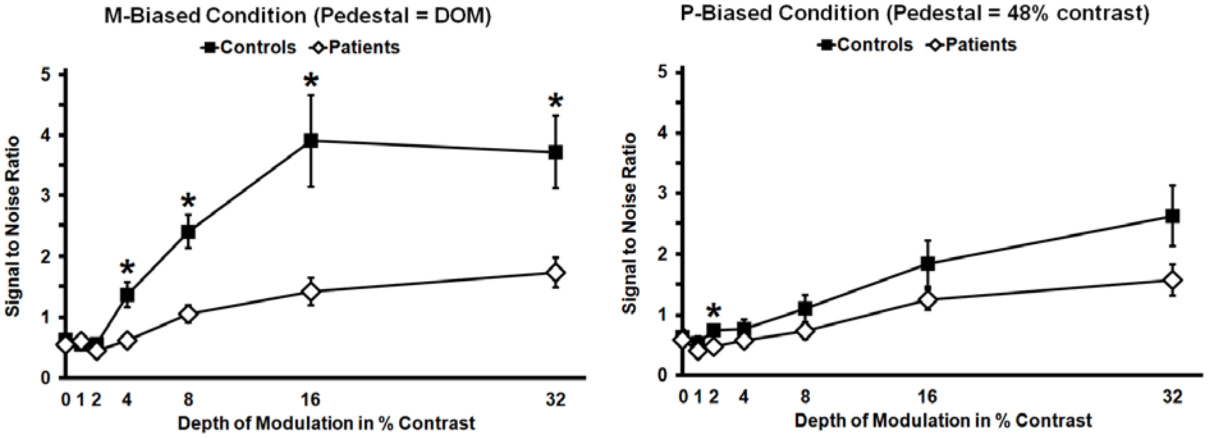


Figure 5:
fMRI activations for contrast sensitivity task:

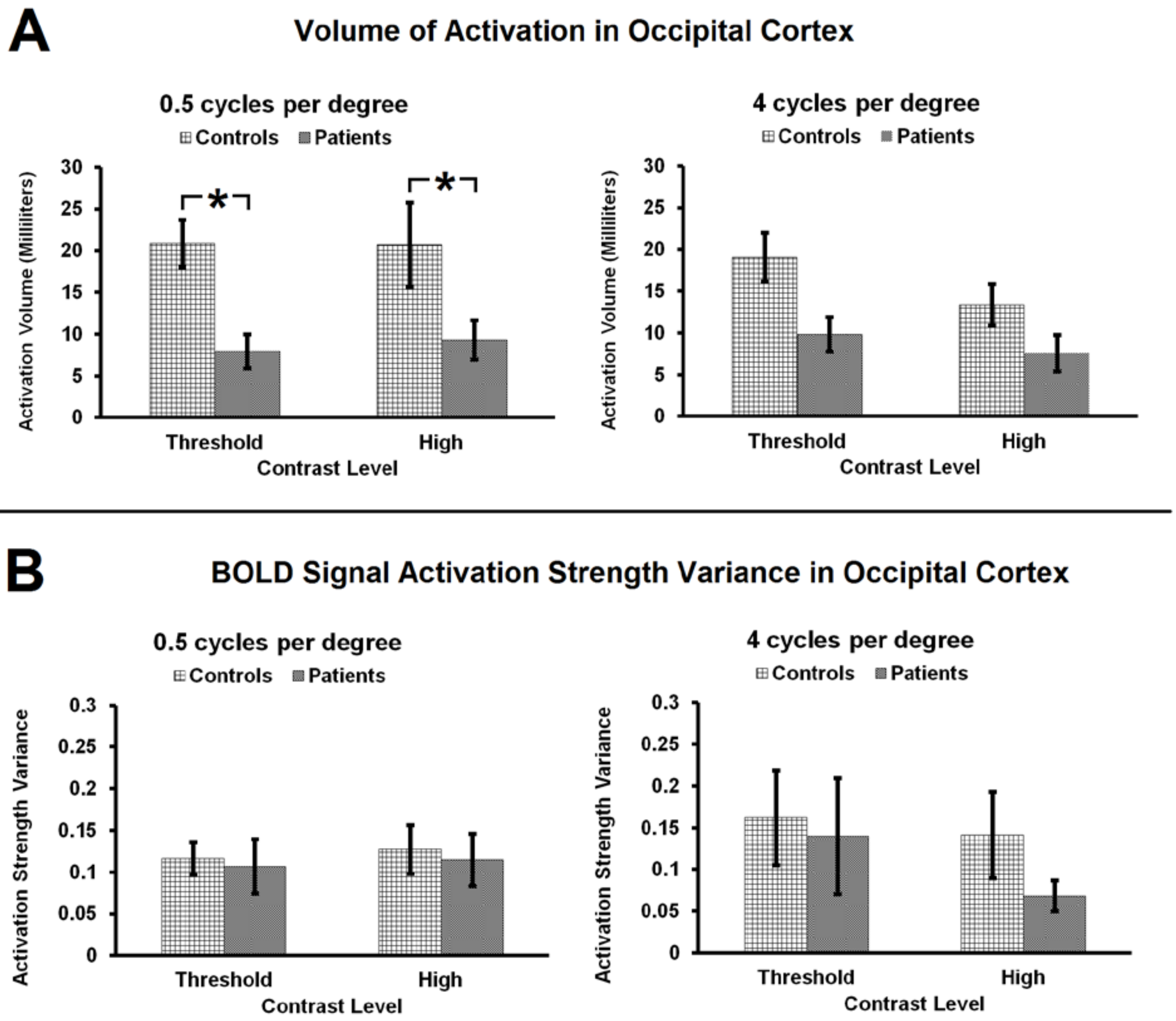


Figure 6:

fMRI activations for isolated check task:

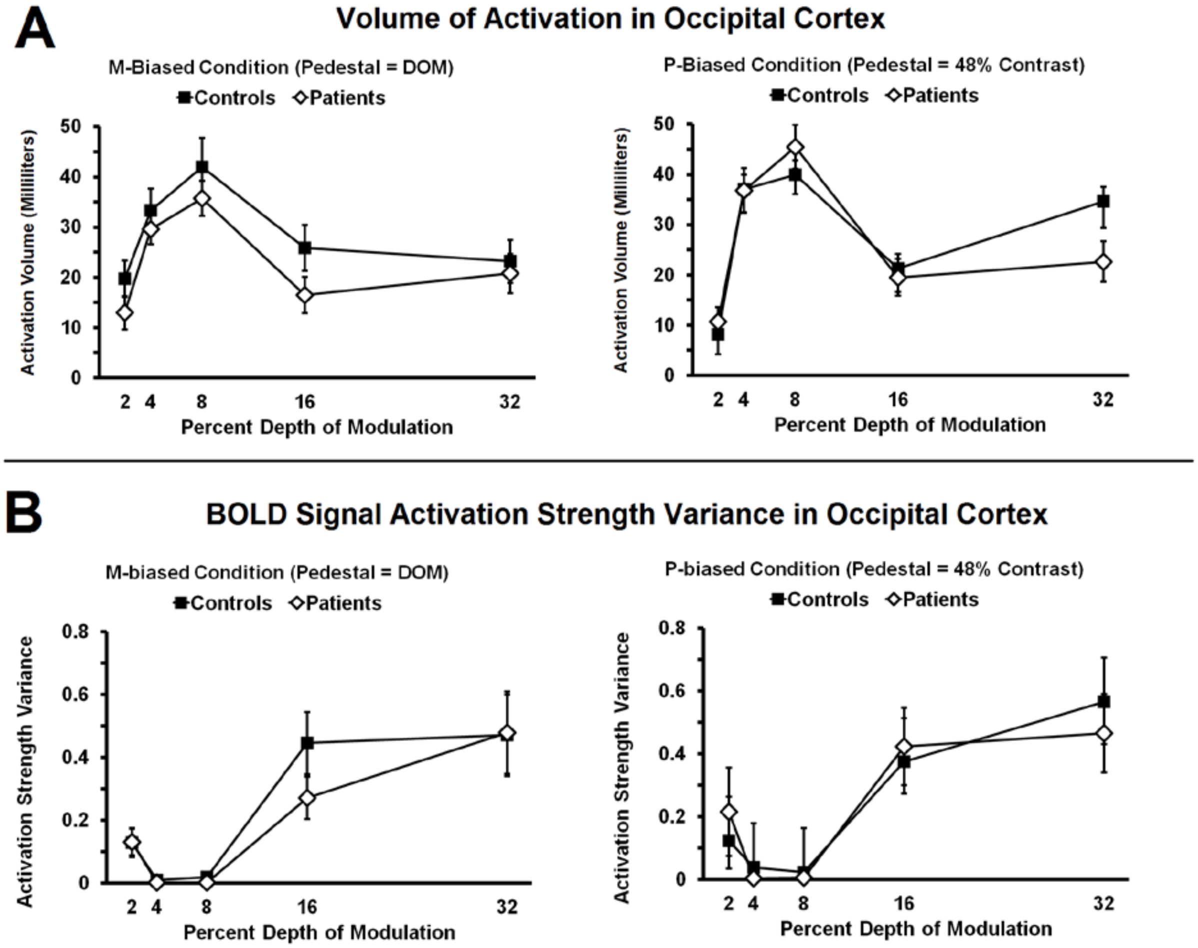
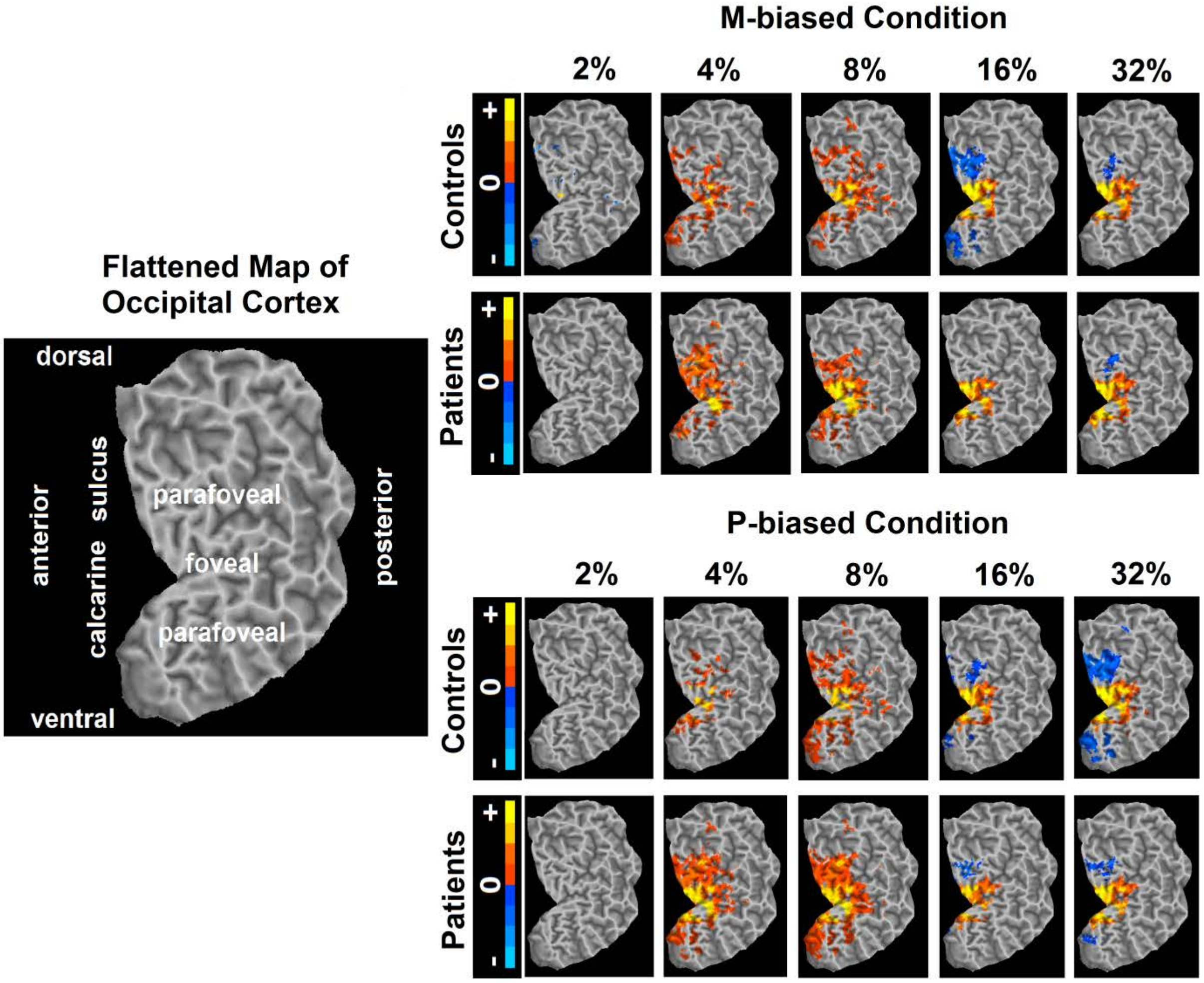


Figure 7:
fMRI activation maps for isolated check task:



9. Tables

Table 1:

fMRI Isolated check task: Differences in occipital activation volume and activation strength across groups as depth of modulation increases in the M-biased and P-biased conditions.

		Volume of Activation		Activation Strength	
Condition	Depth of Modulation	*t*(29)	*p*	*t*(29)	*p*
M-biased	2% vs. 4%	-4.033	<0.001*	4.028	<0.001*
M-biased	4% vs. 8%	-3.135	<0.005*	-1.653	0.109
M-biased	8% vs. 16%	5.639	<0.001*	-5.862	<0.001*
M-biased	16% vs. 32%	-0.393	0.697	-1.751	0.091
P-biased	2% vs. 4%	-6.603	<0.001*	1.798	0.083
P-biased	4% vs. 8%	-2.217	<0.050*	0.854	0.400
P-biased	8% vs. 16%	8.050	<0.001*	-4.868	<0.001*
P-biased	16% vs. 32%	-3.611	<0.005*	-2.396	<0.050*

CHAPTER 4

Contributions of low and high spatial frequency processing to impaired object recognition circuitry in schizophrenia

1. Abstract

Patients with schizophrenia exhibit cognitive and sensory impairment, and object recognition deficits have been linked to sensory deficits. The “frame and fill” model of object recognition posits that low spatial frequency (LSF) information rapidly reaches the prefrontal cortex (PFC) and creates a general shape of an object that feeds back to the ventral temporal cortex to assist object recognition. Visual dysfunction findings in schizophrenia suggest a preferential loss of LSF information. This study used functional magnetic resonance imaging (fMRI) and resting state functional connectivity (RSFC) to investigate the contribution of visual deficits to impaired object “framing” circuitry in schizophrenia. Participants were shown object stimuli that were intact or contained only LSF or high spatial frequency (HSF) information. For controls, fMRI revealed preferential activation to LSF information in precuneus, superior temporal, and medial and dorsolateral PFC areas, whereas patients showed a preference for HSF information or no preference. RSFC revealed a lack of connectivity between early visual areas and PFC for patients. These results demonstrate impaired processing of LSF information during object recognition in schizophrenia, with patients instead displaying increased processing of HSF information. This is consistent with findings of a preference for local over global visual information in schizophrenia.

2. Introduction

Cognitive dysfunction in schizophrenia is well documented (Carter et al., 2008) and is related to functional outcome (Green, 2006). A growing literature including steady-state and transient event-related potential, psychophysical, and functional magnetic resonance imaging (fMRI) studies provides evidence that sensory impairment is also a core feature of schizophrenia (Slaghuis, 1998, Foxe et al., 2001, Braus et al., 2002, Ardekani et al., 2003, Brenner et al., 2003, Butler et al., 2005, Kim et al., 2005, Schechter et al., 2005, Butler et al., 2006, Yeap et al., 2006, Butler et al., 2008a, Martinez et al., 2008, Silverstein et al., 2010b, Chen, 2011), and this impairment may propagate to higher cognitive processes such as motion processing (Kim et al., 2006), perceptual grouping and organization (Kurylo et al., 2007, Silverstein and Keane, 2011), reading (Revheim et al., 2006), and emotion recognition (Leitman et al., 2005, Turetsky et al., 2007, Butler et al., 2009, Leitman et al., 2011). Further, recent findings indicate that the bottom-up propagation of deficits from sensory to higher level processes in schizophrenia occur even when top-down processes are intact (Dias et al., 2011). However, the specific contributions of visual deficits to higher cognitive dysfunction have yet to be fully elucidated. The present study utilized functional magnetic resonance imaging (fMRI) to investigate object recognition in schizophrenia, a task which links visual input to higher cognitive functioning.

Object recognition occurs in the ventral temporal cortex (VTC) (Hubel and Wiesel, 1962, Tanaka, 1993, Pasupathy and Connor, 1999, Vogels et al., 2001) and depends on converging visual processing input. The VTC receives input from the magnocellular and parvocellular subcortical visual pathways (Kaplan and Shapley, 1982, 1986, Wurtz and Kandel, 2000). The magnocellular pathway responds rapidly and is biased toward responding to low spatial frequency (LSF) (i.e., low resolution) information, which it preferentially relays to cortical dorsal stream areas (Ungerleider and Mishkin, 1982, Shapley, 1990, Merigan and Maunsell, 1993). The dorsal stream, in turn, projects to the prefrontal cortex (Wise et al., 1997, Endo et al., 1999, Petrides and Pandya, 1999, Saron et al., 2001). One theory of object processing is that a general shape of an object stimulus is activated in the PFC, and this “frame” of the object is fed back to the VTC (Ullman, 1995, Bar, 2003, Bar et al., 2006, Kveraga et al., 2007, Sehatpour et al., 2010). The parvocellular pathway, on the other hand, responds more slowly and is biased toward responding to high spatial frequency (HSF) (i.e., fine detail) information, which it preferentially relays to cortical ventral stream areas including the VTC (Ungerleider and Mishkin, 1982, Shapley, 1990, Merigan and Maunsell, 1993). The VTC thus receives both dorsal and ventral stream inputs, which interact during object recognition. Due to the different speeds of the two pathways, the input from the PFC arrives in the VTC in time to provide a “frame” of an object which is then “filled” by fine detail information arriving later from the parvocellular pathway (Ullman, 1995, Schmolesky et al., 1998, Schroeder et al., 1998b, Lamme and Roelfsema, 2000, Bar, 2003, Bar et al., 2006, Kveraga et al., 2007, Sehatpour et al., 2010, Tapia and Breitmeyer, 2011). Under the “frame and fill” model, object recognition is achieved by gradually integrating fine details of an object into a coherent whole in the VTC (Tanaka, 1993, 1996, Bar et al., 2001, Grill-Spector et al., 2001, Malach et al., 2002, Brincat and Connor, 2006), and the PFC frame facilitates this process by constraining it to a limited number of possible objects (Bar, 2003, Bar et al., 2006, Kveraga et al., 2007).

Other recent findings support the idea that low resolution global information is processed prior to fine detail information in object recognition (Chen, 2005, Conci et al., 2011, de la Rosa et al., 2011). However, it is unclear which cortical areas process this information. Some evidence indicates that global information is represented as early as primary visual cortex and transmitted directly to the VTC (Altmann et al., 2003, Kourtzi et al., 2003, Ban et al., 2006, Mannion et al., 2010), while other findings suggest that primary visual cortex represents only fine detail information, and only higher areas process global information (Kourtzi and Huberle, 2005, Swettenham et al., 2010). The “frame and fill” model suggests that the VTC receives global information from higher areas such as the PFC and fine detail information from primary visual cortex. Indeed, the laminar profile of the earliest responses of VTC neurons in the macaque monkey was consistent with initial input from the dorsal stream and/or higher cortical areas, rather than with initial afferent input from occipital visual areas (Chen et al., 2007). In addition, connections between the frontal cortex and temporal cortex in the macaque were found to be crucial for object recognition (Parker and Gaffan, 1998).

Bar and colleagues have studied visual pathway contributions to human object recognition utilizing MEG and fMRI. They found that stimuli biased toward the magnocellular pathway by using low spatial frequency or low contrast increased PFC activity, whereas stimuli biased toward the parvocellular pathway by using high spatial frequency or isoluminant chromatic contrast produced less PFC activity and more ventral stream activity (Bar et al., 2006, Kveraga et al., 2007). In addition, PFC activity was related to a performance advantage for magnocellular-biased stimuli in an object recognition task (Kveraga et al., 2007). Effective connectivity analysis of MEG time courses revealed interactions between occipital visual areas and PFC, followed by later interactions between PFC and VTC. These interactions took place only for magnocellular biased and unbiased stimuli, and not for parvocellular biased stimuli (Bar et al., 2006). Taken together, these results suggest that during object recognition, the PFC rapidly receives low-resolution magnocellular pathway information via the dorsal stream, which in turn feeds back to the VTC. This feedback provides the frame of the object, which is then filled by the fine detail parvocellular pathway information.

Object recognition deficits have been found in schizophrenia with behavioral studies in which patients failed to integrate fine details into whole object representations (Doniger et al., 2002, Sehatpour et al., 2010). Early-stage visual deficits in schizophrenia preferentially involving the magnocellular pathway (Butler et al., 2001, Schechter et al., 2003, Butler et al., 2005, Kéri et al., 2005, Kim et al., 2005, Schechter et al., 2005, Butler et al., 2008a, Martinez et al., 2008, Butler et al., 2009, Green et al., 2009) suggest that the framing function of the PFC may be impaired, though parvocellular deficits (Slaghuis, 1998, Brittain et al., 2010) and increased magnocellular responses (Green et al., 1994, Kiss et al., 2010) have also been found. The preferential magnocellular deficit in schizophrenia is thought to arise as a result of impaired nonlinear gain (i.e., signal amplification) (Butler et al., 2005, Kim et al., 2005, Butler et al., 2008a, Green et al., 2009) mediated by N-Methyl-D-aspartate (NMDA) glutamate receptors as this mechanism is used by magnocellular neurons far more than by parvocellular neurons (Fox et al., 1990, Kwon et al., 1992, Daw et al., 1993, Zemon and Gordon, 2006, Lisman et al., 2008) and appears to be impaired in schizophrenia (Goff and Coyle, 2001, Javitt, 2004, Krystal et al., 2005, Javitt, 2009, Kantrowitz and Javitt, 2010b, a). Findings of parvocellular dysfunction may occur under conditions that drive that pathway to utilize this nonlinear gain mechanism normally favored by the magnocellular pathway (Butler et al., 2005). However, strong evidence in favor of a preferential magnocellular deficit in schizophrenia suggests a specific bottom-up deficit in the propagation of magnocellular-biased information to the dorsal stream and PFC during object recognition.

Evidence for this pattern of dysfunction has been found in studies of perceptual closure, a task in which participants are asked to recognize fragmented objects. For instance, impairments in perceptual closure, as well as impairments in event-related potential (ERP) components associated with perceptual closure and dorsal stream activity, were found in schizophrenia patients, while a ventral stream ERP component remained intact (Doniger et al., 2002). These ERP findings were recently replicated and, using fMRI an impaired network of dorsal stream, ventral stream, PFC, and hippocampal activity related to perceptual closure was found (Sehatpour et al., 2010). Path analysis suggested that dorsal stream deficits led to PFC deficits, which in turn led to ventral stream and hippocampal deficits. These studies support the findings of a dorsal stream-PFC-VTC circuit in object recognition, and its impairment in schizophrenia.

The current study sought to further clarify the link between early-stage visual deficits and impaired ability to frame objects in schizophrenia by utilizing the same fMRI object recognition paradigm as Bar and colleagues (Bar et al., 2006) and extending it to schizophrenia. This paradigm biases object stimuli toward the magnocellular or parvocellular pathway by filtering them to contain LSF or HSF information, respectively. Using ERP and fMRI, Martinez and colleagues (Martinez et al., 2011) recently demonstrated that schizophrenia patients have impaired activity in extrastriate visual areas in response to LSF, but not HSF, grating stimuli. This suggests that patients may display similar deficits to LSF object stimuli, and that these deficits may propagate to the PFC, resulting in impaired framing feedback to the VTC. In addition to this fMRI paradigm, this study also utilized resting state functional connectivity (RSFC) to examine the functional networks underlying object recognition in both schizophrenia patients and healthy control participants.

3. Methods

Participants

Twenty-four patients who met DSM-IV criteria for schizophrenia and 17 healthy volunteers participated. Patients were recruited through inpatient and outpatient 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 available clinical information. Controls were recruited through the Volunteer Recruitment Program at the Nathan Kline Institute. All participants provided informed consent and received cash compensation for their time. The study was approved by the Nathan Kline Institutional Review Board. 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 ophthalmological disorders, including glaucoma or cataracts, that might affect performance or if they met criteria for alcohol or substance dependence within the last 6 months or abuse within the last month. All participants had normal or corrected-to-normal visual acuity of 20/32 or better on the Logarithmic Visual Acuity Chart (Precision Vision). All patients were receiving antipsychotic medication at the time of testing, except for one patient who had refused to continue haloperidol decanoate. Chlorpromazine equivalents were calculated as previously described (Woods, 2003, 2005, 2011). All data reported below are mean ± standard deviation.

Groups did not differ significantly in age (patients: 37.39 ± 9.67; controls: 36.41 ± 7.65; p=0.73) or gender (patients: 19 males, 5 females; controls: 13 males, 4 females; p=0.83). Patients had significantly lower socioeconomic status (SES) as measured by the 4-factor Hollingshead Scale (patients: 23.67 ± 6.68; controls: 41.88 ± 10.13; $t(29)=-5.86$, $p<0.001$), although parental SES did not significantly differ between groups (patients: 32.82 ± 11.21; controls: 42.75 ± 14.19; p=0.06). Patients also had significantly reduced IQ (patients: 92.53 ±

7.33; controls: 98.56 ± 6.79; *t*(29)=-2.38, *p*=0.02) and education as measured by highest grade achieved (patients: 11.25 ± 1.77; controls: 14.06 ± 1.53; *t*(30)=-4.81, *p*<0.001). Patients were ill for an average of 14.22 ± 7.48 years, had an average Global Assessment of Functioning (GAF) score of 38.52 ± 11.05, and were receiving antipsychotic doses equivalent to an average of 938.41 ± 672.63 mg of chlorpromazine per day. Although demographic data for some variables were unavailable for some patients, the overall sample characteristics were similar to those in recent publications from our group (Dias et al., 2011, Martinez et al., 2011).

Functional Magnetic Resonance Imaging

Apparatus

A 3T Siemens TIM Trio magnetic resonance scanner at the Nathan Kline Institute was used for all functional and structural scans. Functional scans contained 34 axial slices, with TR=2000ms, TE=30ms, and voxel size=2.5x2.5x2.8mm, with a 0.7mm gap. High-resolution structural scans were performed with a 3-D magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence, having 192 sagital slices with TR=2500ms, TE=3.5ms, FA=8°, and voxel size =1x1x1mm. Slice time correction, motion correction, normalization to a value of 100, smoothing (8mm FWHM Gaussian kernel), skull stripping, deconvolution of relevant time series, and first order regression analyses were performed using AFNI (http://afni.nimh.nih.gov/; (Cox, 1996)). Functional and structural scans were coregistered and transformed into a common Talairach space using the Automatic Registration Toolbox (Ardekani et al., 2004, Klein et al., 2009).

Stimuli and Procedure

Grayscale images of ordinary objects and abstract sculptures were filtered to contain only LSF (≈6 cycles per image) or HSF (≈30 cycles per image) information, as reported by Bar and colleagues (Bar et al., 2006). All LSF, HSF, and unfiltered (Intact) images had an identical root mean square contrast of 50.26%, which is often reported for complex visual stimuli (Ojanpää and Näsänen, 2003). Two fMRI scanning blocks were performed, each consisting of 101 trials. In each block, 24 ordinary object images were each presented in Intact, LSF, and HSF form (Figure 1). Five abstract sculpture stimuli were also presented in each block (Intact:LSF:HSF ratio of 1:2:2, 2:1:2, or 2:2:1 randomly determined for each block). Abstract sculpture stimuli were purposely chosen to not resemble ordinary objects. In addition, 24 fixation trials were presented in each block to create "jitter" in the image time series to better sample the hemodynamic response function. Each trial consisted of 500 ms for image presentation, followed by 1500 ms of fixation, except for fixation trials which consisted solely of 2000 ms of fixation. Object image trials, sculpture image trials, and fixation trials were presented in a random order. In a forced choice task, participants indicated by button press whether the stimulus depicted an ordinary object or an abstract sculpture, with response time limited to 2000 ms after stimulus onset. Responses and reaction times were recorded.

Analysis

First order regression analyses for each participant isolated fMRI activity related to correct Intact, LSF, and HSF ordinary object trials, resulting in beta maps. These results were then used for higher order group analyses. A whole-brain mixed-effects two-way ANOVA with group and condition as factors was performed on the beta maps to examine differences in activity between stimulus conditions and between groups. Regions of interest (ROI) were determined based on the interaction of group and condition. Two a priori ROIs were calculated from the Talairach Tournoux atlas, for bilateral Brodmann area 17 (BA 17) and bilateral fusiform gyrus (FG). These areas represent basic visual processing and VTC areas, respectively. For each ROI, each participant's average beta value for each condition was calculated, and these were compared within and across groups.

Resting State Functional Connectivity

Apparatus

Scans were performed with the same scanner described above. Functional scans contained 34 axial slices, with TR=2000ms, TE=30ms, and voxel size=2.5x2.5x2.7mm with a 0.8mm skip. Preprocessing was conducted using the 1000 Functional Connectomes Project (Biswal et al., 2010) scripts, available at http://fcon_1000.projects.nitrc.org/indi/pro/nki.html. The MPRAGE was segmented using FSL's (http://www.fmrib.ox.ac.uk/fsl/) FAST software to get the masks for white matter and CSF. The white matter (WM) and cerebrospinal fluid (CSF) time series were then spatially averaged for their respective compartments. These time series, as well as those for the six motion parameters, were used as covariates of no interest in a general linear model (GLM), and were regressed from the native-space EPI time series.

Stimuli and Procedure

Participants were instructed to keep their eyes open and remain still and alert. 180 functional scans were performed, the first five of which were discarded prior to preprocessing.

Analysis

Seven seed regions were defined as the two a priori ROIs and five functionally derived ROIs defined above. For each participant, average time series data was extracted for each ROI and correlated with the time series of all other ROIs. These correlations were standardized using Fisher's r-to-z transformation. Correlation z-scores for each group were tested against zero in a one-sample t-test to determine which connections between ROIs were significant.

4. Results

Behavioral Results

A main effect of stimulus condition ($F(2,117)=22.832$, $p<0.001$) showed that reaction time was faster for Intact stimuli (controls: $M=694.29$, $SD=176.52$; patients: $M=730.77$, $SD=170.20$) than LSF stimuli (controls: $M=772.32$, $SD=190.38$; patients: $M=818.14$, $SD=177.57$) ($t(40)=-7.961$, $p<0.001$) and HSF stimuli (controls: $M=793.78$, $SD=238.37$; patients: $M=827.32$, $SD=187.94$) ($t(40)=-4.898$, $p<0.001$). A main effect of stimulus condition ($F(2,117)=29.598$, $p<0.001$) also revealed that accuracy was higher for Intact stimuli (controls: $M=76.34\%$, $SD=25.29\%$; patients: $M=81.23\%$, $SD=17.26\%$) than LSF stimuli (controls: $M=55.53\%$, $SD=28.51\%$; patients: $M=58.04\%$, $SD=21.82\%$) ($t(40)=6.493$, $p<0.001$) and HSF stimuli (controls: $M=52.82\%$, $SD=32.15\%$; patients: $M=54.86\%$, $SD=26.46\%$) ($t(40)=7.383$, $p<0.001$). However, no between group differences in reaction time or accuracy were found for any stimulus condition, and no interactions between group and condition were found. The lack of between group differences indicates that the task was not more difficult for patients or controls for any stimulus condition. Only correct trials were used in the fMRI analyses.

Functional Magnetic Resonance Imaging

A whole-brain mixed-effects two-way ANOVA revealed a significant interaction between group and condition in five regions ($F=4.09$, cluster size=48, corrected $p=0.001$). These regions were then defined as ROIs (Table 1), and post-hoc t-tests were performed on average beta coefficients within these ROIs. Similar t-tests were performed for average beta coefficients for the two a priori ROIs (Table 2).

A bilateral precuneus ROI (pCun) demonstrated an interaction in which controls had more activity for LSF than HSF stimuli ($t(16)=-2.313$, $p<0.05$), while patients had more activity for HSF than LSF ($t(23)=3.233$, $p<0.005$) and Intact stimuli ($t(23)=2.198$, $p<0.05$). Controls also had significantly greater activity than patients for LSF stimuli ($t(39)=-2.229$, $p<0.05$) (Figure 2A).

The right superior temporal gyrus ROI (STG) showed a similar interaction pattern to the pCun ROI. Controls had more activity for LSF than HSF ($t(16)=-2.311$, $p<0.05$) and Intact stimuli ($t(16)=-2.621$, $p<0.05$), while patients had less activity for LSF than HSF ($t(23)=3.570$, $p<0.005$) and Intact stimuli ($t(23)=2.748$, $p<0.05$) (Figure 2B)

The left caudate ROI (CD) again showed greater activity for LSF than HSF ($t(16)=-4.707$, $p<0.001$) and Intact stimuli ($t(16)=-2.506$, $p<0.05$) for controls, but no significant differences between conditions in patients (Figure 2C).

The left medial prefrontal ROI (MPFC) also showed greater activity for LSF than HSF stimuli ($t(16)=3.381$, $p<0.005$) for controls, and greater activity for HSF than Intact stimuli ($t(23)=-2.444$, $p<0.05$) for patients. In addition, patients had significantly greater activity than controls for the HSF condition ($t(39)=-2.188$, $p<0.05$) (Figure 2D).

The left dorsolateral prefrontal ROI (DLPFC) demonstrated differences in activity between conditions for controls, but not patients. For controls, activity for HSF stimuli differed significantly from activity for LSF ($t(16)=-3.632$, $p<0.005$) and Intact stimuli ($t(16)=-2.686$, $p<0.05$). In this case, HSF related activity was negative compared to fixation, while Intact and LSF related activity was positive (Figure 2E).

The a priori bilateral Brodmann area 17 ROI (BA 17) showed no differences between conditions for controls. Patients had significantly higher activity for Intact than LSF stimuli ($t(23)=2.517$, $p<0.05$) (Figure 3A). The a priori bilateral fusiform gyrus ROI (FG) also did not have differences between conditions for controls. Patients had significantly higher activity for

Intact than LSF ($t(23)=3.165$, $p<0.005$) and HSF stimuli ($t(23)=3.227$, $p<0.005$) (Figure 3B). There were no significant between group differences for A17 or FG.

Resting State Functional Connectivity

Seeds for the RSFC data were defined as the fMRI ROIs described above. Significant correlations between seeds ($p<0.05$) revealed differing functional networks between controls and patients (Figure 4). Controls had four correlations that patients lacked, which were BA 17 and DLPFC, BA 17 and MPFC, DLPFC and MPFC, and BA 17 and STG. Patients had three correlations that controls lacked, which were BA 17 and CD, pCun and CD, and BA 17 and pCun. These resting state correlations established functional networks for controls and patients.

5. Discussion

This study used an object recognition fMRI task that Bar and colleagues (Bar et al., 2006) had previously used to explore the theory that LSF information projecting to the PFC creates a low resolution “frame” of an object and that this information feeds back to the VTC to facilitate object recognition in normal individuals. Like the results of Bar and colleagues (Bar et al., 2006), the present fMRI results for healthy controls showed that the PFC responded differently for stimuli containing LSF information than for stimuli containing only HSF information. The present study extended the paradigm to schizophrenia patients. Whereas previous studies have shown impairments in perceptual closure involving impaired PFC activity in schizophrenia (Doniger et al., 2002, Sehatpour et al., 2010), the current study used LSF and HSF stimuli to examine the specific contributions of each type of information to object recognition in patients.

Functional Magnetic Resonance Imaging

Reaction time for controls and patients did not differ significantly for the object recognition task, indicating that patients were able to perform the task as quickly as controls for all stimulus conditions. This was perhaps not surprising given that the task involved only a small number of “catch” trials, and that these trials used abstract sculpture stimuli that were purposely chosen not to resemble ordinary objects. The lack of group differences in behavioral data indicated that patients were able to recognize the objects in this task normally, whereas differences in fMRI results indicated that they accomplished recognition using different patterns of cortical activation, possibly reflecting a different strategy. Recent findings indicate that even under conditions of approximately normal behavioral performance for visual tasks, schizophrenia patients may show impaired patterns of cortical activation (Spencer et al., 2003, Spencer et al., 2004, Silverstein et al., 2010b). The current results extend this idea to object recognition, with patients showing normal reaction times but abnormal patterns of activity over a widespread cortical network.

The two a priori ROIs examined were bilateral occipital area 17 and fusiform gyrus. In area 17, patients had decreased activation for LSF compared to Intact stimuli, whereas controls showed no difference in activation between the different types of stimuli. Previous research has found alterations in occipital cortex anatomy (Selemon et al., 1995, Dorph-Petersen et al., 2007) in post-mortem studies of schizophrenia patients as well as thinning of occipital cortex in an MRI study of unmedicated first-episode patients (Narr et al., 2005). Decreased fMRI activation has also been found in primary visual cortex to LSF, but not HSF, grating stimuli in schizophrenia patients compared to controls (Martinez et al., 2008). The current result of an impaired pattern of response within the schizophrenia group supports the idea that preferential magnocellular dysfunction in schizophrenia may result in a reduced occipital cortical response to LSF information.

The fusiform gyrus was chosen as an a priori VTC ROI due to its well documented involvement in object recognition (Gerlach et al., 2002, Simons et al., 2003, Hofer et al., 2007, Liu et al., 2008, Haist et al., 2010, Konen et al., 2011). Whereas the lateral occipital complex (LOC) is also well known to be involved in object recognition (Grill-Spector et al., 2001, Lerner et al., 2002, Sehatpour et al., 2010), definitions of LOC boundaries often include posterior parts of the fusiform gyrus (Grill-Spector et al., 1999, Malach et al., 2002). Bar and colleagues have repeatedly observed activity throughout the fusiform gyrus related to object recognition, particularly in studies of the “frame and fill” model (Bar et al., 2001, Bar et al., 2006, Kveraga et al., 2007), and thus the current study, which utilized one of their paradigms, also utilized this area as an a priori ROI. In this fusiform gyrus ROI, patients had decreased activation for LSF and HSF compared to Intact stimuli, whereas controls showed no difference in activation between stimulus types. Martinez and colleagues (Martinez et al., 2011) recently found decreased fMRI activation in fusiform gyrus to LSF, but not HSF, simple grating stimuli in schizophrenia patients compared to controls, while Silverstein and colleagues (Silverstein et al., 2010a) found increased fusiform activity to LSF and HSF filtered faces in schizophrenia. The current results, together with these other recent findings, suggest that the fusiform gyrus processes spatial frequencies abnormally in schizophrenia, and differently for various types of stimuli. The current results support findings of impaired transmission of LSF object information to the fusiform gyrus, and suggest that pure HSF processing of objects is also impaired in schizophrenia. Whereas the fusiform gyrus receives direct input from primary visual areas, this project also sought to study dorsal stream and PFC contributions to object recognition in schizophrenia.

The five functionally derived ROIs show which cortical areas process the spatial frequency of objects differently for controls than patients. The precuneus and superior temporal gyrus ROIs show similar patterns of response, with controls having increased activity for LSF over HSF stimuli, and patients having the opposite pattern. In addition, patients showed significantly decreased responses to LSF stimuli compared to controls in the precuneus. The caudate ROI shows the same pattern of increased activity for LSF over HSF stimuli in controls as the precuneus and superior temporal gyrus, but no differential activations for stimulus type in patients. These results suggest that patients with schizophrenia have a deficit in these three areas for processing LSF information. The pattern of deficits in the parietal and superior temporal areas in particular supports ERP and fMRI findings of dorsal stream deficits in schizophrenia (Doniger et al., 2002, Sehatpour et al., 2010, Dias et al., 2011, Martinez et al., 2011), which are preferentially seen to LSF information (Butler et al., 2007, Martinez et al., 2011). In addition, the observed pattern of increased HSF over LSF activation for patients fits with recent findings showing an increase as well as persistence in sensory ERP components in response to HSF over LSF gratings in schizophrenia (Martinez et al., 2011). In the presence of deficits in processing LSF information, the precuneus and superior temporal gyrus may compensate with more active processing of HSF information in schizophrenia. This is consistent with a recent fMRI study that showed greater activity in early visual areas for HSF rather than LSF face stimuli in schizophrenia patients but the opposite pattern in controls (Silverstein et al., 2010a). The current result of increased response to HSF stimuli may also be related to recent findings of greater interference of local on global processing for patients with schizophrenia but the opposite pattern in controls (Coleman et al., 2009, Kemner et al., 2009).

With regard to frontal activity, the MPFC ROI showed increased activity to LSF over HSF stimuli for controls, but increased activity to HSF over Intact stimuli for patients, and a significantly greater response to HSF stimuli for patients over controls. For controls, this shows that the MPFC strongly activates to LSF information found in LSF and Intact stimuli, but activates much less to pure HSF information. This is consistent with previous findings that the PFC uses LSF information to create a low resolution frame for an object stimulus (Bar et al., 2006, Chen et al., 2007, Kveraga et al., 2007, Sehatpour et al., 2010). For patients, this area has normal activity to LSF and Intact stimuli, but significantly more activity to HSF stimuli. Together with the findings in dorsal stream areas, this result suggests that HSF information is transmitted by the dorsal stream to the PFC in schizophrenia, possibly to compensate for deficits in LSF information. Patients may preferentially utilize HSF information, rather than LSF information, when constructing a frame for an object stimulus.

For controls, the DLPFC ROI shows a striking pattern of positive activity for Intact and LSF stimuli and negative activity for purely HSF stimuli. Using the same fMRI paradigm, Bar and colleagues (Bar et al., 2006) found small negative activations to Intact and LSF stimuli and a large negative activation to HSF stimuli in the orbitofrontal cortex, which they replicated with MEG. These previous findings, and the current results for both the DLPFC and MPFC frontal areas, illustrate the selectiveness of the PFC response to LSF information during object recognition. Both Intact and LSF stimuli contain LSF information, and have similar activations, whereas HSF stimuli that lack LSF information have significantly different activations. This is consistent with the PFC utilizing LSF information to rapidly create a frame for an object in controls. Patients, on the other hand, showed no differences in activation between stimulus conditions in the DLPFC, indicating that they are not preferentially processing any particular spatial frequency in this area. While patients may use the MPFC to attempt object framing with compensatory HSF information, the DLPFC may not be utilized for object recognition in schizophrenia.

These results extend and further clarify previous findings regarding object recognition in both healthy individuals and schizophrenia patients. This study used the same fMRI paradigm previously used by Bar and colleagues (Bar et al., 2006) to investigate the cortical areas involved in object recognition. This previous study used an a priori orbitofrontal ROI to represent PFC based on anatomical evidence that orbitofrontal cortex has connections with areas known to be involved in object recognition. The current study, however, defined two PFC ROIs based on the functional interaction of spatial frequency and group. Thus, the PFC regions analyzed here show where spatial frequency processing differs between healthy controls and schizophrenia patients, and this knowledge extends the previous findings of Bar et al. (Bar et al., 2006) by showing additional PFC regions involved in object recognition. Further, recent anatomical findings in humans have demonstrated relationships between primary visual cortex and both MPFC and DLPFC (Harvey et al., 2011, Song et al., 2011), as well as between dorsal stream parietal areas and DLPFC (Catani et al., 2002), suggesting direct involvement of these frontal regions in visual processing. White matter fiber tracts from DLPFC to the fusiform gyrus and inferior occipital cortex have also been described in humans (see (Catani et al., 2002) for review), indicating an anatomical substrate for the feedback of framing information from the DLPFC to the VTC.

A recent study of object recognition in schizophrenia using a perceptual closure task revealed a network involving dorsal stream areas and PFC that supported the frame and fill model and its impairment in schizophrenia (Sehatpour et al., 2010). That study provided evidence that early-stage visual dysfunction in schizophrenia propagates through the dorsal stream to the PFC, leading to dysregulation of ventral object recognition areas. This suggests that PFC involvement in object recognition is directly tied to early-stage visual processing as well as VTC object recognition function, supporting the framing function of the PFC. By using spatial frequency filtered stimuli, the current study expands this model of impaired framing in schizophrenia by specifically demonstrating deficits in LSF information processing and compensation with HSF information. As LSF and HSF information are preferentially transmitted by the magnocellular and parvocellular pathways respectively, this provides further support for the idea that preferential magnocellular deficits in schizophrenia underlie impaired object framing.

An alternative model of object recognition holds that the dorsal stream and PFC are not required to process global information. Previous findings have demonstrated that simple contour information in early visual areas is integrated in progressively anterior regions of the ventral stream to form general shape representations (Bar et al., 2001, Grill-Spector et al., 2001, Brincat and Connor, 2006, Bell et al., 2011), thus indicating that the ventral stream may carry general shape information independent of dorsal stream or PFC input. Feedback from the PFC or other areas may provide a prediction signal that would either be consistent or inconsistent with visual input emerging from the occipital and temporal regions (Dima et al., 2009, Friston and Kiebel, 2009, Silverstein et al., 2009). Under this model, the current findings of impaired PFC activity in schizophrenia may reflect a failure of ability to utilize predictions successfully. Further work is necessary to disentangle this hypothesis from the frame and fill hypothesis.

Resting State Functional Connectivity

In the RSFC analysis, controls had significant correlations between early visual area 17 and the two frontal areas, MPFC and DLPFC, while patients lacked this connectivity. For controls, MPFC and DLPFC were functionally connected, as might be expected from their mutual preference for LSF information in the fMRI results. Together, these results indicate that for controls, MPFC and DLPFC receive LSF information directly related to early visual processing in area 17, and work together to process this information. This pattern supports previous findings with effective connectivity (Bar et al., 2006, Sehatpour et al., 2010) and anatomical tracts (Catani et al., 2002, Song et al., 2011) that occipital visual and dorsal stream areas are connected to MPFC and DLPFC, and that these regions are in turn connected to the fusiform gyrus. This study extended these prior results by utilizing a separate resting state scan, together with functionally determined seed regions, to analyze functional connectivity in this object recognition circuit.

For patients, the PFC areas are functionally disconnected from each other and from area 17, and show either a preference for HSF information or no spatial frequency preference. Recent studies comparing patients with schizophrenia to controls have shown a lack of connectivity between prefrontal cortex and occipital visual areas during a visual attention task (Harvey et al., 2011), as well as reduced functional connectivity between DLPFC and both fusiform gyrus and primary occipital visual areas during a spatial working memory task (Kang et al., 2011). This study demonstrated that these areas lack functional connectivity even during the resting state, in the absence of a task.

The current functional connectivity results thus support the role of the PFC in the normal object recognition circuit, and the dysfunction of this PFC circuit in schizophrenia. In addition, both groups have correlations between MPFC and fusiform gyrus, as well as several indirect functional pathways between frontal areas and fusiform gyrus. This supports the feedback of

PFC framing information to the VTC, and echoes previous functional connectivity (Bar et al., 2006, Sehatpour et al., 2010) and anatomical (Catani et al., 2002) findings linking PFC and VTC.

Conclusions

Healthy controls demonstrated strong selectivity for LSF information in both dorsal stream areas and frontal areas, consistent with the framing function of the PFC during object recognition (Schmolesky et al., 1998, Schroeder et al., 1998b, Lamme and Roelfsema, 2000, Bar, 2003, Bar et al., 2006, Chen et al., 2007, Kveraga et al., 2007). The functional connections between PFC and VTC indicated that the low resolution frame derived in the PFC feeds back to object recognition processes in the VTC. Schizophrenia patients, however, activated less selectively to LSF information in basic visual, dorsal stream, frontal, and VTC areas. Instead, dorsal stream and MPFC ROIs showed a preference for HSF information, indicating that object framing in schizophrenia may rely on HSF information in the absence of strong LSF information. These results are consistent with findings that preferential magnocellular and dorsal stream deficits in schizophrenia lead to impaired framing feedback to the VTC during object recognition (Doniger et al., 2002, Sehatpour et al., 2010), and generally support the propagation of sensory deficits to higher cognitive functions in schizophrenia (Leitman et al., 2005, Kim et al., 2006, Revheim et al., 2006, Kurylo et al., 2007, Butler et al., 2009, Leitman et al., 2011). While top-down processing is certainly deficient in schizophrenia, future investigations of bottom-up dysfunction will further clarify the underlying causes of cognitive deficits in this disorder.

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7. Figure Captions

Figure 1. Object recognition task used during fMRI scanning. Ordinary object and abstract sculpture stimuli were shown in either their Intact state or filtered to contain only low spatial frequency (LSF) or high spatial frequency (HSF) information. A single 2000 ms stimulus trial consisted of stimulus presentation (500 ms) followed by fixation (1500 ms) (left side of Figure 1). In addition, there were 24 “fixation alone” trials consisting of 2000 ms of fixation that were randomly presented among stimulus trials (right side of Figure 1). Participants pressed buttons on stimulus trials to indicate whether the image depicted an ordinary object or an abstract sculpture.

Figure 2. ROIs showing an interaction between group and stimulus condition. For all ROIs, $F=4.09$, cluster size=48, corrected $p=0.001$. For all bar graphs, * $p<0.05$.

Figure 3. A priori ROIs defined by Talairach Tournoux atlas. For all bar graphs, * $p<0.05$.

Figure 4. RSFC correlations. Seed regions consisted of the five functional and two a priori fMRI ROIs applied to a resting state fMRI scan. pCun = bilateral precuneus, STG = right superior temporal gyrus, CD = left caudate, MPFC = left medial prefrontal, DLPFC = left dorsolateral prefrontal, BA 17 = bilateral Brodmann area 17, FG = bilateral fusiform gyrus.

8. Figures

Figure 1:
Object recognition task:

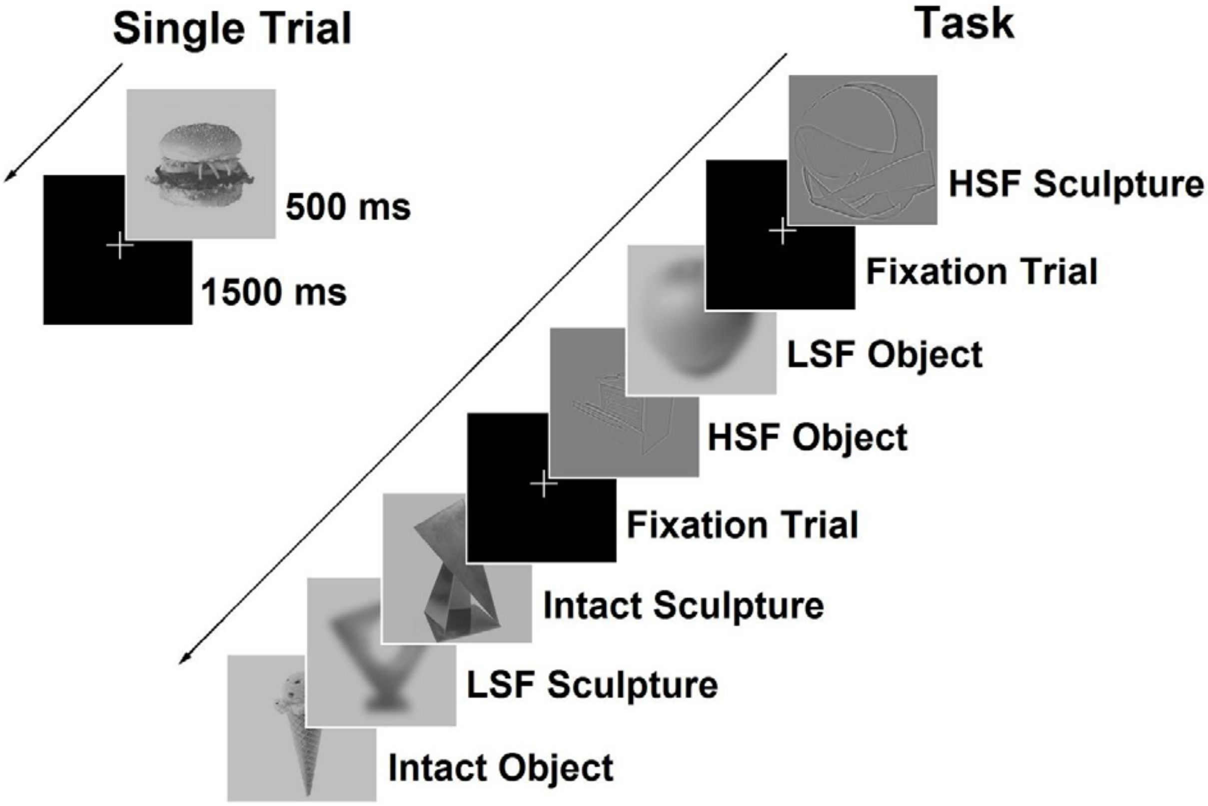


Figure 2:
fMRI activations in functionally derived regions of interest:

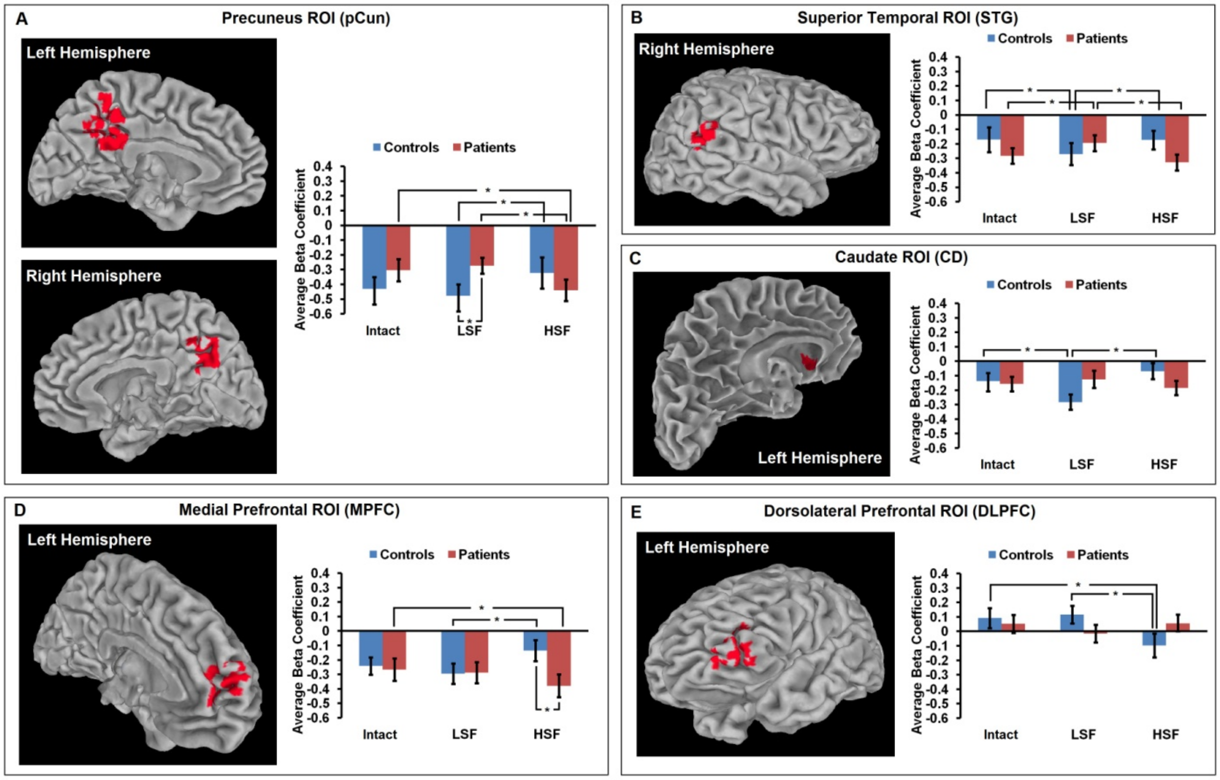
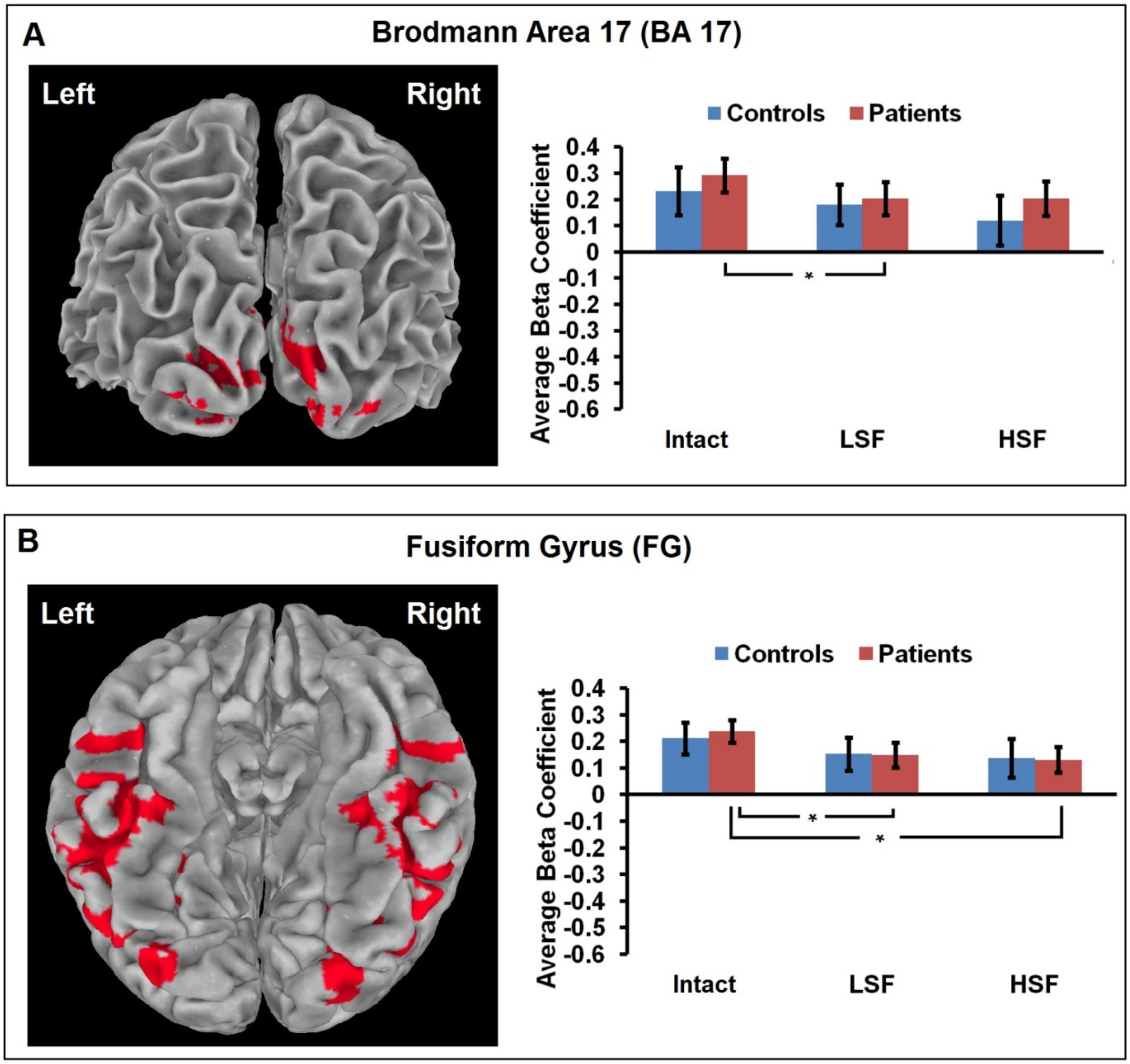
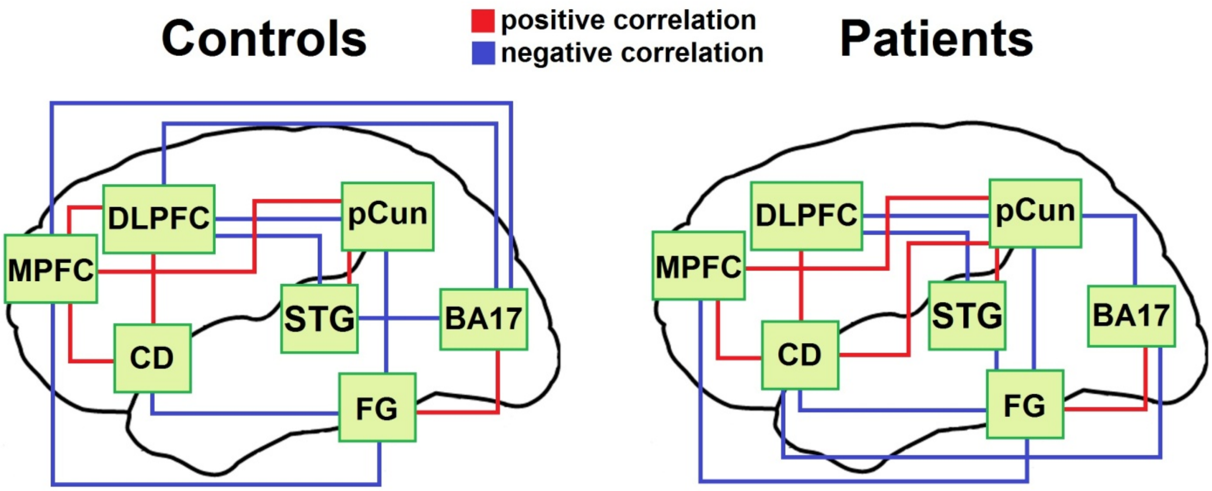


Figure 3:
fMRI activations in a priori regions of interest:



<u>Figure 4:</u>
Resting state functional connectivity:



9. Tables

Table 1:

Functional ROIs based on the group-by-condition interaction.

ROI	Brodmann Area	Center of Mass	Number of Voxels
pCun			
left	7, 31	6.9, 49.6, 36.6	178
right	7, 31	-6.8, 59.0, 30.3	76
STG (right)	40	-56.6, 46.7, 19.5	96
CD (left)	--	15.5, -16.2, -0.8	67
MPFC (left)	9	7.1, -47.9, 21.0	98
DLPFC (left)	46	41.7, -43.7, 5.6	88

Table 2:

A priori ROIs based on the Talairach Tournoux atlas.

ROI	Number of Voxels
BA 17	313
FG	
left	547
right	546

CHAPTER 5

Discussion

This dissertation sought to clarify the nature of early-stage visual deficits in schizophrenia and to investigate the relationship between these deficits and higher-order impairment as well as functional outcome. Evidence of gain control deficits in the visual system was found, which likely underlies findings of preferential magnocellular dysfunction in schizophrenia. An ssVEP paradigm revealed that some patients had a contrast gain deficit, while others had an additional contrast gain control deficit. All patients demonstrated a psychophysical deficit in detecting low contrasts across spatial frequencies and stimulus duration. fMRI revealed impaired occipital activation for low spatial frequencies, which are preferentially transmitted by the magnocellular pathway. Further, a network of cortical areas active during object recognition showed reduced processing of low spatial frequencies, with possible compensation by high spatial frequency information. Visual gain control deficits were linked to object recognition as well as other cognitive processes, which were shown to predict symptoms and functional status.

Experiment 1

Two established measures were used in this study to investigate visual gain control in a large sample of schizophrenia patients: an ssVEP paradigm using magnocellular- and parvocellular-biased stimuli, and psychophysical contrast sensitivity. Previous results were replicated, showing a preferential deficit in ssVEP response to the magnocellular-biased condition (Butler et al., 2001, Butler et al., 2005, Butler et al., 2008a). ssVEP contrast response curves for magnocellular-biased stimuli were also characterized using a nonlinear biophysical model (Zemon and Gordon, 2006). Individuals with a lack of response to low contrasts (low contrast deficit) and poor contrast gain control were found in both groups, though the percentage was twice as high in patients. When these individuals were removed from the analysis, patients still had deficits in contrast gain and speed of ssVEP response, though they had intact contrast gain control. When only individuals with low contrast deficits were considered, patients still had deficits in response speed compared to controls with low contrast deficits. Processing speed is impaired in schizophrenia (Kalkstein et al., 2010), and relates to functional outcome (Puig et al., 2012). The current results indicate that impaired contrast gain, rather than contrast gain control, may contribute to visual processing speed deficits, as all patients had slowed ssVEP responses, though only 25% had contrast gain control deficits. Though speed of response was impaired for all patients, these ssVEP results revealed two types of visual gain control impairment in schizophrenia: a deficit in responses to low contrast associated with poor contrast gain control (25% of patients), and a more common reduction in initial contrast gain with intact contrast gain control (75% of patients).

Patients with schizophrenia also showed contrast sensitivity deficits to a range of spatial frequencies (0.5 – 21 c/deg) shown for a short (32 ms) and longer (500 ms) duration, indicating a reduced ability to perceive very low contrast regardless of spatial frequency or timing characteristics. However, the size of the deficits were larger for short than longer duration stimuli containing low spatial frequencies, while deficits were larger for longer than short duration stimuli containing high spatial frequencies. These results agree with previous work showing selective deficits in schizophrenia for low spatial frequencies at 32 ms stimulus duration (Butler et al., 2005, Butler et al., 2009), as well as for higher spatial frequencies at 500 ms stimulus duration (Kéri et al., 2002). A loss of gain control as seen in the ssVEP paradigm may lead to a dysfunctional magnocellular response to low contrasts, which in turn impairs the ability of schizophrenia patients to detect very low contrast stimuli.

The ssVEP paradigm and psychophysical contrast sensitivity paradigm both aim to measure specific examples of the general gain control process, which optimizes neural responses based on context (Butler et al., 2008a, Butler et al., 2012). Barch and colleagues (Barch et al., 2012) recently investigated gain control impairment in the visual system in schizophrenia using a different task which predicts improved performance in the presence of gain control deficits. In the contrast-contrast task, healthy individuals perceive reduced contrast for a center stimulus if it is surrounded by a higher contrast stimulus (Chubb et al., 1989). This effect is due to inhibition of responses to the center stimulus by responses to the contextual high contrast surround (Zenger-Landolt and Heeger, 2003), and thus reflects gain control. Schizophrenia patients have recently shown improved performance in judging the true contrast of the center stimulus relative to controls (Dakin et al., 2005, Barch et al., 2012). This result importantly isolates gain control impairment from general impairment in performing the task, as patients show improved performance. However, when Barch and colleagues (Barch et al., 2012) eliminated participants showing poor attention from their analysis, improved task performance for patients was no longer significant. This result conflicts with the current finding of a preferential deficit in magnocellular-biased ssVEP response, as an attentional deficit would predict equally impaired responses to magnocellular- and parvocellular-biased stimuli. In addition, impaired gain control has also been found in the auditory system at the pre-attentive level. In the mismatch negativity task, an event-related potential response is elicited by presenting a deviant auditory stimulus among a series of standard stimuli (Green et al., 2009). This response depends on the context of the preceding standard stimuli, and thus reflects gain control in the auditory system. Reliable deficits in both the amplitude and latency of the mismatch negativity have been found in schizophrenia (Umbricht and Krljes, 2005, Javitt et al., 2008, Friedman et al., 2012). Importantly, this task reflects early, pre-attentive processes, and thus also demonstrates impaired gain control in sensory processes apart from general task performance deficits.

Relationships between the current results of impaired contrast gain in the visual system and higher cognitive functions as well as functional outcome were also assessed. Structural equation modeling has demonstrated links between early-stage visual processing and functional status in schizophrenia, with social perception (Sergi et al., 2006, Rassovsky et al., 2011) and negative symptoms (Rassovsky et al., 2011) found to mediate these links. Social perception includes emotion processing (Sergi and Green, 2003), and the current results show that emotion processing specifically also mediates a link between early-stage visual processing and functional status. Neuropsychological function, on the other hand, mediated a link between early-stage visual functioning and both functional status and symptoms. This indicates that deficits in neuropsychological function have wide-ranging consequences for both disease status and functional status, and that they are predicted by the visual gain control deficits observed in this study. Recent work by Gold and colleagues (Gold et al., 2012) demonstrated links between basic auditory processing impairment and auditory emotion recognition deficits in schizophrenia, and Leitman and colleagues (Leitman et al., 2010) found that both auditory emotion recognition and basic auditory perception were related to functional outcome. Together with the current findings in the visual system, these studies show that low-level sensory processing dysfunction in schizophrenia predicts higher cognitive functions as well as functional outcome.

Experiment 2

The ssVEP and psychophysical contrast sensitivity tasks from Experiment 1 were performed alone and during fMRI scanning in order to investigate neural correlates of these tasks. Psychophysical contrast sensitivity as well as contrast sensitivity performed in the fMRI utilized two stimulus conditions, based on the finding that short and longer duration stimuli produce peak contrast sensitivities at low and mid-range spatial frequencies, respectively (Tolhurst, 1975, Legge, 1978). Schizophrenia patients again showed deficits for 0.5 c/deg stimuli shown for 32 ms as well as 4 c/deg stimuli shown for 500 ms. Consistent with Experiment 1 and previous ssVEP findings, schizophrenia patients also showed a selective deficit in the magnocellular- vs. the parvocellular-biased condition, consistent with visual gain control deficits in schizophrenia (Butler et al., 2001, Butler et al., 2005, Butler et al., 2009, Butler et al., 2012).

In the fMRI contrast sensitivity task, patients had lower occipital volume of activation measures for low spatial frequency stimuli, at both near-threshold contrast and high contrast (71%), but no significant differences were seen between groups for high spatial frequency stimuli at either contrast level. However, strength of activation measures were equivalent between groups and across all stimulus conditions. This indicated a selective deficit in recruiting occipital cortex in response to low spatial frequency information for schizophrenia patients, rather than a loss of activation strength. This result is supported by the recent work of Martinez and colleagues (Martinez et al., 2008), which also found reduced occipital volume of activation to low spatial frequency (0.2-1.4 c/deg) stimuli in schizophrenia at high (100%) and low (12%) contrast. This study also did not find deficits to high spatial frequencies (3.5-4.9 c/deg) at either contrast level. The current results extend this selective deficit in activation volume for low spatial frequencies to even lower contrasts (1-2%), and uniquely demonstrate this deficit during performance of the psychophysical contrast sensitivity task. An even more recent study by Martinez and colleagues (Martinez et al., 2012) found reduced fMRI activation to attended low spatial frequency (0.8 c/deg) compared to attended high spatial frequency (5 c/deg) gratings in schizophrenia patients, with no differences in areas known to be involved in feature-guided attention. This importantly shows that sensory processing of low spatial frequencies is impaired in schizophrenia independently of attentional deficits. The current results further supported this by showing deficits in activation volume to low spatial frequency in schizophrenia during equivalent task performance to controls. These previous findings and the current results indicate a robust deficit in fMRI activation to low spatial frequency in schizophrenia independent of stimulus contrast. This deficit may additionally be related to psychophysical contrast sensitivity deficits to low spatial frequencies, as previous findings have shown that reductions in contrast sensitivity were related to reduced occipital activation volume (Goodyear et al., 2000, Leguire et al., 2011).

Controls did not show differences in activation volume or strength between spatial frequencies. Such equivalent activation for lower and higher spatial frequencies may relate to the perceptual phenomenon known as “contrast constancy.” At high contrast, spatial frequencies are perceived at their correct contrast, despite greater sensitivity of the visual system to mid-range rather than low or high spatial frequencies (Georgeson and Sullivan, 1975). This effect may be mediated by contrast gain in the visual cortex increasing responses in the context of very low and very high spatial frequencies (Boynton, 2005). Reduced activation to low spatial frequency in schizophrenia patients may thus indicate a failure of this contrast gain mechanism.

In the isolated-check fMRI task, similar stimuli to those used in the ssVEP paradigm were displayed. Across groups and for both magnocellular- and parvocellular-biased stimuli, increasingly greater volumes of occipital cortex were recruited as contrast increased through the low contrast range, while higher contrasts showed reduced volume of activation. Strength of activation, however, remained low over the low contrast range, and increased dramatically at higher contrasts. These fMRI results are in conflict with the ssVEP results as well as previous single-cell work, which indicated increased firing rates of individual cells with increasing contrast (Kaplan and Shapley, 1986, Shapley, 1990). However, for the magnocellular- but not the parvocellular-biased condition, fMRI volume and strength of activation plateaued at 16% DOM, similarly to the ssVEP response. Group average activation maps showed that for the low contrast range, both foveal and parafoveal representations had positive activation, while at high contrasts parafoveal activity was negative, but foveal activity remained positive. In addition, the greatest amount of negative parafoveal activity the magnocellular-biased condition was seen at 16% DOM. The plateau in the ssVEP response for this condition at 16% DOM is thought to be due to shunting inhibition (Zemon and Gordon, 2006, García-Quispe et al., 2009). Negative BOLD activity coupled to positive BOLD activity has been observed in several visual fMRI studies (Harel et al., 2002, Shmuel et al., 2002), and has been linked specifically to active neuronal inhibition (Smith et al., 2004, Devor et al., 2007, Wade and Rowland, 2010).

These results are consistent with a recent study by Wade and Rowland (Wade and Rowland, 2010) showing negative BOLD activity in parafoveal representations to high contrast (90%) foveal stimuli, and further showed that this activation pattern occurs at higher contrast modulations (16 and 32% DOM), but not at low contrast modulations (8% DOM and below). In addition, Wade and Rowland found this activation pattern specifically to magnocellular-biased stimuli. Thus, the current results showing strong negative parafoveal activation at 16% DOM in the magnocellular-biased condition are consistent with these findings, and suggest that this negative activity may be related to shunting inhibition observed in the ssVEP magnocellular-biased response.

A dissociation between fMRI and ssVEP was found, such that patients had deficits in the ssVEP paradigm but not in the fMRI paradigm. Thus, patients may recruit the same occipital areas with the same amount of metabolic energy as controls, but are not able to utilize these areas for optimal gain control. Several studies have demonstrated links between VEP measures and fMRI BOLD measures, while others have shown them to be independent of each other. Whittingstall and colleagues (Whittingstall et al., 2007, Whittingstall et al., 2008) showed that localization of a negative VEP deflection corresponded to positive BOLD activity, and localization of a positive VEP deflection corresponded to a lesser extent to negative BOLD activity. Yesilyurt and colleagues (Yesilyurt et al., 2010) also found an early negative VEP component that related to positive BOLD activity, but the relationship did not hold for very small deflections. VEP response adaptation has been found to be unrelated to BOLD activity (Janz et al., 2001), and insulin has recently been found to reduce BOLD activity while leaving VEP responses intact (Seaquist et al., 2007). Di Russo and colleagues (Di Russo et al., 2007) have demonstrated that ssVEP responses corresponded to some areas of occipital fMRI activation but not others. Thus, VEP and ssVEP measures co-vary with fMRI activity only under certain conditions, and may only relate to part of the total fMRI activity elicited by a particular stimulus. Overall, the current results indicate the deficits for processing low spatial frequencies are detectable with fMRI, but deficits in contrast gain and contrast gain control are better detected with ssVEP.

Experiment 3

This study used an object recognition fMRI task developed by Bar and colleagues (Bar et al., 2006) to investigate the frame and fill model in schizophrenia. Patients did not differ from controls in reaction time, indicating that they were able to recognize the objects in this task normally. However, differences in fMRI activation indicated that they accomplished recognition using an altered pattern of cortical activity. This result agrees with recent findings that even under conditions of approximately normal behavioral performance for visual tasks, schizophrenia patients may show impaired patterns of cortical activation (Spencer et al., 2003, Spencer et al., 2004, Silverstein et al., 2010b).

Patients showed decreased activation for low spatial frequency object stimuli compared to intact stimuli in primary visual cortex, whereas controls showed no differences. Patients also had decreased activation for both low and high spatial frequency object stimuli compared to intact stimuli, whereas controls showed no difference in activation between stimulus types. These results agree with recent work by Martinez and colleagues showing decreased fMRI activation in primary visual cortex (Martinez et al., 2008) and fusiform gyrus (Martinez et al., 2011) to low, but not high, spatial frequency grating stimuli in schizophrenia. Silverstein and colleagues (Silverstein et al., 2010a), however, found increased fusiform activity to LSF and HSF filtered faces in schizophrenia. Together, these findings suggest that the fusiform gyrus processes spatial frequencies abnormally in schizophrenia, and that there is a deficit in processing low spatial frequency information in primary visual cortex in schizophrenia.

Five functionally derived ROIs showed which cortical areas process the spatial frequency of objects differently for patients than controls. The precuneus and superior temporal gyrus ROIs showed similar patterns of response, with controls having increased activity for low over high spatial frequency stimuli, and patients having the opposite pattern. The caudate ROI also showed this same pattern for controls, but no differential activations for spatial frequencies in patients. These results suggest that patients with schizophrenia have a deficit in these three areas for processing low spatial frequency information, and may compensate for this with increased HSF information processing. This is consistent with a recent finding of an increase and persistence in sensory ERP components in response to high compared to low spatial frequency gratings (Martinez et al., 2011) and findings of increased activity in early visual areas for high compared to low spatial frequency face stimuli in schizophrenia (Silverstein et al., 2010a). The current findings in the parietal and superior temporal areas also support ERP and fMRI findings of dorsal stream deficits in schizophrenia (Doniger et al., 2002, Sehatpour et al., 2010, Dias et al., 2011, Martinez et al., 2011), which are preferentially seen for low spatial frequency information (Butler et al., 2007, Martinez et al., 2011).

The medial prefrontal (MPFC) ROI showed increased activity to low rather than high spatial frequency stimuli for controls, but increased activity to high spatial frequency over intact stimuli for patients, and a significantly greater response to high spatial frequency stimuli for patients over controls. Therefore, for controls, MPFC strongly activates to low spatial frequency information. This is consistent with previous findings in healthy individuals that the prefrontal cortex (PFC) uses low spatial frequency information to create a low resolution frame for an object stimulus (Bar et al., 2006, Chen et al., 2007, Kveraga et al., 2007, Sehatpour et al., 2010). For patients, this area showed no activation differences for low spatial frequency or intact stimuli compared to controls, but did show significantly more activity to high spatial frequency stimuli. Patients may therefore use high, rather than low, spatial frequency information when generating an initial frame for an object stimulus. For controls, the dorsolateral prefrontal (DLPFC) ROI showed a striking pattern of positive activity for intact and low spatial frequency stimuli and negative activity for high spatial frequency stimuli. This further illustrates the selectiveness of the PFC for low spatial frequency information during object processing in controls and supports the framing function of the PFC. Patients, on the other hand, had no activation differences for different spatial frequencies in the DLPFC, indicating that they are not preferentially processing any particular spatial frequency in this area. While patients may use the MPFC to attempt object framing with compensatory high spatial frequency information, the DLPFC may not be used for object recognition in schizophrenia.

This study used an fMRI object recognition task developed by Bar and colleagues (Bar et al., 2006), which they used to investigate an a priori orbitofrontal ROI. The current study defined two PFC ROIs based on the functional interaction of spatial frequency and group, thus showing additional PFC regions involved in object recognition. Indeed, recent anatomical findings in humans have linked primary visual cortex to both MPFC and DLPFC (Harvey et al., 2011, Song et al., 2011), and also linked dorsal stream parietal areas to DLPFC (Catani et al., 2002), suggesting direct involvement of these frontal regions in visual processing. White matter tracts from DLPFC to the fusiform gyrus and inferior occipital cortex have also been described in humans (see (Catani et al., 2002) for review), indicating an anatomical substrate for the feedback of framing information from the DLPFC to the VTC during object recognition.

The current results extend those of a recent study that revealed a cortical network involving dorsal stream areas and PFC for object recognition that supported the frame and fill model and its impairment in schizophrenia (Sehatpour et al., 2010). That study provided evidence that early-stage visual dysfunction in schizophrenia propagates through the dorsal stream to the PFC, leading to dysregulation of ventral object recognition areas. The current study expanded this model by using spatial frequency filtered stimuli to specifically demonstrate deficits in low spatial frequency information processing and compensation with high spatial frequency information. This also provides further support for the idea that preferential magnocellular deficits in schizophrenia underlie impairment in higher-level cognitive functions such as object framing.

This study also used resting state functional connectivity (RSFC) to show that controls had significant correlations between primary visual cortex and the two frontal areas, MPFC and DLPFC. For controls, MPFC and DLPFC were also correlated, indicating that MPFC and DLPFC receive low spatial frequency information directly related to early-stage visual processing, and work together to process this information. This pattern supports previous findings with effective connectivity (Bar et al., 2006, Sehatpour et al., 2010) and anatomical tracts (Catani et al., 2002, Song et al., 2011) that occipital visual and dorsal stream areas have connections with MPFC and DLPFC. For patients, the two PFC areas were functionally disconnected from each other and from primary visual cortex. Other recent studies have also shown a lack of connectivity between prefrontal cortex and occipital visual areas in schizophrenia during a visual attention task (Harvey et al., 2011) and a spatial working memory task (Kang et al., 2011). This study extended these findings by showing a lack of functional connectivity even during the resting state, in the absence of a task. Together, these fMRI and RSFC results support the role of the framing role of the PFC in the normal object recognition circuit, and the dysfunction of this PFC circuit in schizophrenia.

Conclusions

This dissertation found evidence in support of gain control deficits in schizophrenia, and showed that these may differ between individuals. An ssVEP task showed a preferential deficit to magnocellular-biased stimuli in two experiments. In addition, some patients had a lack of response to low contrast and poor contrast gain control, while others had intact contrast gain control but still showed reduced contrast gain. Patients in both of these categories had slower ssVEP responses than controls, indicating that contrast gain deficits may relate to processing speed impairment in schizophrenia. Contrast sensitivity measures from two experiments also showed a deficit for patients in detecting low contrasts for a range of spatial frequencies and stimulus durations. fMRI in two experiments showed a robust deficit in processing low spatial frequencies, which was found to propagate through a cortical network underlying object recognition. Finally, electrophysiological and psychophysical measures of early-stage visual dysfunction in schizophrenia were found to predict higher-level cognitive impairment in emotion processing and neuropsychological function, which in turn related to functional status and symptoms. In conclusion, early-stage visual deficits in schizophrenia reflect a loss of gain control in the visual system, which has consequences for higher-order processes and overall outcome.

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