FUNCTIONAL MAGNETIC RESONANCE IMAGING OF THE MAGNOCELLULAR VISUAL PATHWAY IN NONPSYCHOTIC RELATIVES OF PERSONS WITH SCHIZOPHRENIA

by

JEFFREY SCOTT BEDWELL

(Under the Direction of L. Stephen Miller)

ABSTRACT

Physiological research with monkeys and psychophysical research with humans has demonstrated the ability of diffuse red light to suppress activity in the magnocellular (M) visual pathway. In contrast, a previous psychophysical study found that a subset of nonpsychotic relatives of persons with schizophrenia showed the opposite effect, suggesting a novel biobehavioral marker for the disorder. Other research suggests that persons with schizophrenia have a dysfunctional M pathway under neutral (non-red) light conditions. However, it does not appear that these findings have been explored with physiological methods in nonpsychotic relatives, which would provide support for genetic contributions. The current study used physiological methodology to explore whether, as a group: 1) healthy adults show suppression of the M pathway in response to diffuse red light; 2) nonpsychotic relatives of persons with schizophrenia have a dysfunctional M pathway under neutral light conditions; and 3) nonpsychotic relatives of persons with schizophrenia have a differential M pathway response to red light.

Functional magnetic resonance imaging (fMRI) was used to investigate a group of 13 nonpsychotic relatives of persons with schizophrenia and 11 controls. Moving concentric rings were presented on both red and green backgrounds to stimulate the M pathway. The fMRI signal strength in bilateral cortical region V5 (MT) was measured as a marker of M pathway functioning.

Statistically significant results were limited to measures of fMRI signal in right hemisphere V5 relative to signal from bilateral V5, and suggested that: 1) the control group had reduced M pathway activity in response to diffuse red light; 2) the relative group had a hypoactive M pathway; and 3) a subset of the relatives had the opposite M pathway response to diffuse red light. The differential M pathway response to red light in the relatives remained a statistical trend after controlling for M pathway signal from the neutral (green) background condition. Results provide preliminary evidence that genetic risk for schizophrenia is related to a hypoactive M pathway and an independent differential response (increase in activity) of the M pathway to red light. These features may be more evident in the right hemisphere when examining cortical region V5.

INDEX WORDS: schizophrenia, relatives, magnocellular visual pathway, red light, V5

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CHAPTER 1

INTRODUCTION

Numerous studies examining persons with schizophrenia and their first-degree relatives have indicated abnormal functioning in visual processing (Holzman, 2000; Nuechterlein, Dawson, & Green, 1994; Schwartz, Tomlin, Evans, & Ross, 2001). Many psychophysical studies have specifically suggested that the visual pathway involved with processing motion and location – termed the magnocellular (M) pathway (Breitmeyer & Ganz, 1976; Livingstone & Hubel, 1987) – is dysfunctional in persons with genetic loading for schizophrenia (Cadenhead, Serper, & Braff, 1998; Chen, Nakayama, Levy, Matthysse, & Holzman, 1999; Chen, Palafox et al., 1999; O'Donnell et al., 1996; Schwartz, Satter, O'Neill, & Winstead, 1990; Schwartz et al., 2001; Stuve et al., 1997).

To the author's knowledge, only a few studies have used physiological methods, such as functional magnetic resonance imaging (fMRI; Braus, Weber-Fahr, Tost, Ruf, & Henn, 2002; O'Driscoll et al., 1999) and electroencephalography (Butler et al., 2001; Doniger, Foxe, Murray, Higgins, & Javitt, 2002; Foxe, Doniger, & Javitt, 2001), to specifically examine M pathway functioning in schizophrenia. Unfortunately, the study by O'Driscoll and colleagues did not statistically compare strength of activation in the M pathway in persons with schizophrenia and controls. The remaining three physiological studies reported reduced inferred neural signal in the M pathway in persons with schizophrenia. However, there does not appear to be any

published related studies in nonpsychotic first-degree relatives, which would help determine if such dysfunction is primarily related to genetic contributions of the illness.

Researchers using single-cell recording techniques in non-human primates have reported that a small proportion of neurons along the M pathway cease firing in response to the presentation of diffuse red light, which were termed "Type-IV" neurons (de Monasterio, 1978; Dreher, Fukada, & Rodieck, 1976; Kruger, 1977; Livingstone & Hubel, 1984; Wiesel & Hubel, 1966). Psychophysical research using diffuse red light has inferred a similar effect in humans (e.g, Breitmeyer & Breier, 1994; Brown & Koch, 2000). However, the author is not aware of any published physiological research substantiating the ability of red light to suppress M pathway activity in humans.

Consistent with this theory, the author has previously reported that a red background reduced accuracy (compared to a grey background) in healthy adults on a visual backward masking task that required location identification – a process reliant on M-system functioning (Bedwell, Brown, & Miller, 2003). While first-degree relatives of persons with schizophrenia demonstrated similar accuracy on this task with the grey background, they did not demonstrate a statistically significant change in accuracy with a red background (Bedwell et al., 2003), suggesting a novel biobehavioral marker of genetic risk for schizophrenia. However, the mechanism for this group difference could not be addressed with the psychophysical methodology used in that study.

The present study examined nonpsychotic first-degree relatives of persons with schizophrenia and healthy adults not related to any individual with known psychosis using fMRI to investigate baseline M pathway functioning and change in functioning in response to diffuse red light. Specifically, fMRI signal in visual cortical area V5 (also known as MT), a primary

center along the M pathway (Ahlfors et al., 1999; Hasnain, Fox, & Woldorff, 1998; Tootell, Reppas, Kwong et al., 1995; Watson et al., 1993), was measured in response to motion presented on a computer monitor with alternating green and red backgrounds. This dissertation is presented in a manuscript style, with particular individual chapters representing independent manuscripts that are written in the style required by particular peer-reviewed journals that they will be submitted to.

Study Goals

1) Investigated the hypothesized effect of red light in the suppression of M pathway activity in healthy adults. This was accomplished by examining the change in the magnitude and volume of fMRI signal in V5 between neutral (green) and red background conditions.
2) Determined whether nonpsychotic first-degree relatives of persons with schizophrenia display dysfunctional baseline activity in the M pathway compared to controls, as evidenced by the magnitude and volume of fMRI signal in V5 with the neutral (green) background condition.
3) Distinguished between two possible neurological explanations for the previous psychophysical study conducted by the author (Bedwell et al., 2003), which suggested a differential M pathway response to red light in persons at genetic risk for schizophrenia:
    - Persons genetically at-risk for schizophrenia have a dysfunctional baseline M pathway under neutral (non-red) light conditions – accounting for the apparent differential change to red light. This would be indicated by differential fMRI signal compared to controls from the neutral (green) background condition and

the absence of a differential fMRI signal change to red light after statistically adjusting for this baseline difference.

- Persons genetically at-risk for schizophrenia have a different physiological M pathway response in response to red light. This would be supported by finding a differential group fMRI signal response to red light (compared to controls), after controlling for group differences in V5 activity under the neutral (green) light condition.

References

Ahlfors, S. P., Simpson, G. V., Dale, A. M., Belliveau, J. W., Liu, A. K., Korvenoja, A., Virtanen, J., Huotilainen, M., Tootell, R. B., Aronen, H. J., & Ilmoniemi, R. J. (1999). Spatiotemporal activity of a cortical network for processing visual motion revealed by MEG and fMRI. *J Neurophysiol, 82*(5), 2545-2555.

Bedwell, J. S., Brown, J. M., & Miller, L. S. (2003). The magnocellular visual system and schizophrenia: what can the color red tell us? *Schizophrenia Research, 63*(3), 273-284.

Braus, D. F., Weber-Fahr, W., Tost, H., Ruf, M., & Henn, F. A. (2002). Sensory information processing in neuroleptic-naive first-episode schizophrenic patients: a functional magnetic resonance imaging study. *Arch Gen Psychiatry, 59*(8), 696-701.

Breitmeyer, B. G., & Breier, J. I. (1994). Effects of background color on reaction time to stimuli varying in size and contrast: inferences about human M channels. *Vision Res, 34*(8), 1039-1045.

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

Brown, J. M., & Koch, C. (2000). Influences of occlusion, color, and luminance on the perception of fragmented pictures. *Percept Mot Skills, 90*(3 Pt 1), 1033-1044.

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

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

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

Chen, Y., Palafox, G. P., Nakayama, K., Levy, D. L., Matthysse, S., & Holzman, P. S. (1999). Motion perception in schizophrenia. *Arch Gen Psychiatry, 56*(2), 149-154.

de Monasterio, F. M. (1978). Properties of concentrically organized X and Y ganglion cells of macaque retina. *J Neurophysiol, 41*(6), 1394-1417.

Doniger, G. M., Foxe, J. J., Murray, M. M., Higgins, B. A., & Javitt, D. C. (2002). Impaired visual object recognition and dorsal/ventral stream interaction in schizophrenia. *Arch Gen Psychiatry, 59*(11), 1011-1020.

Dreher, B., Fukada, Y., & Rodieck, R. W. (1976). Identification, classification and anatomical segregation of cells with X-like and Y-like properties in the lateral geniculate nucleus of old-world primates. *J Physiol, 258*(2), 433-452.

Foxe, J. J., Doniger, G. M., & Javitt, D. C. (2001). Early visual processing deficits in schizophrenia: impaired P1 generation revealed by high-density electrical mapping. *Neuroreport, 12*(17), 3815-3820.

Hasnain, M. K., Fox, P. T., & Woldorff, M. G. (1998). Intersubject variability of functional areas in the human visual cortex. *Hum Brain Mapp, 6*(4), 301-315.

Holzman, P. S. (2000). Eye movements and the search for the essence of schizophrenia [In Process Citation]. *Brain Res Brain Res Rev, 31*(2-3), 350-356.

Kruger, J. (1977). Stimulus dependent colour specificity of monkey lateral geniculate neurones. *Exp Brain Res, 30*(2-3), 297-311.

Livingstone, M. S., & Hubel, D. H. (1984). Anatomy and physiology of a color system in the primate visual cortex. *J Neurosci, 4*(1), 309-356.

Livingstone, M. S., & Hubel, D. H. (1987). Psychophysical evidence for separate channels for the perception of form, color, movement, and depth. *J Neurosci, 7*(11), 3416-3468.

Nuechterlein, K. H., Dawson, M. E., & Green, M. F. (1994). Information-processing abnormalities as neuropsychological vulnerability indicators for schizophrenia. *Acta Psychiatr Scand Suppl, 384*, 71-79.

O'Donnell, B. F., Swearer, J. M., Smith, L. T., Nestor, P. G., Shenton, M. E., & McCarley, R. W. (1996). Selective deficits in visual perception and recognition in schizophrenia [see comments]. *Am J Psychiatry, 153*(5), 687-692.

O'Driscoll, G. A., Benkelfat, C., Florencio, P. S., Wolff, A. L., Joober, R., Lal, S., & Evans, A. C. (1999). Neural correlates of eye tracking deficits in first-degree relatives of schizophrenic patients: a positron emission tomography study. *Arch Gen Psychiatry, 56*(12), 1127-1134.

Schwartz, B. D., Satter, E., O'Neill, P. T., & Winstead, D. K. (1990). Bilateral hemispheric processing deficits in schizophrenia. *Schizophr Res, 3*(2), 147-154.

Schwartz, B. D., Tomlin, H. R., Evans, W. J., & Ross, K. V. (2001). Neurophysiologic mechanisms of attention: a selective review of early information processing in schizophrenics. *Front Biosci, 6*, D120-134.

Stuve, T. A., Friedman, L., Jesberger, J. A., Gilmore, G. C., Strauss, M. E., & Meltzer, H. Y. (1997). The relationship between smooth pursuit performance, motion perception and sustained visual attention in patients with schizophrenia and normal controls. *Psychol Med, 27*(1), 143-152.

Tootell, R. B., Reppas, J. B., Kwong, K. K., Malach, R., Born, R. T., Brady, T. J., Rosen, B. R., & Belliveau, J. W. (1995). Functional analysis of human MT and related visual cortical areas using magnetic resonance imaging. *J Neurosci, 15*(4), 3215-3230.

Watson, J. D., Myers, R., Frackowiak, R. S., Hajnal, J. V., Woods, R. P., Mazziotta, J. C., Shipp, S., & Zeki, S. (1993). Area V5 of the human brain: evidence from a combined study using positron emission tomography and magnetic resonance imaging. *Cereb Cortex, 3*(2), 79-94.

Wiesel, T. N., & Hubel, D. H. (1966). Spatial and chromatic interactions in the lateral geniculate nucleus body of the rhesus monkey. *Journal of Neurophysiology, 29*, 1115-1156.

CHAPTER 2

LITATURE REVIEW

Visual Pathway Functioning in Schizophrenia

Researchers have long noticed abnormalities of visual system functioning in persons with schizophrenia. These abnormalities have included greater sensitivity to visual backward masking (Butler et al., 2003; Butler, Harkavy-Friedman, Amador, & Gorman, 1996; Green, Nuechterlein, Breitmeyer, & Mintz, 1999; Green, Nuechterlein, & Mintz, 1994a, 1994b; Rund, 1993; Saccuzzo, Cadenhead, & Braff, 1996), impaired motion perception (Brenner, Wilt, Lysaker, Koyfman, & O'Donnell, 2003; Chen, Nakayama, Levy, Matthysse, & Holzman, 1999; Chen, Palafox et al., 1999; Stuve et al., 1997), impaired spatial localization (Cadenhead, Serper, & Braff, 1998; O'Donnell et al., 1996), and impaired smooth-pursuit eye tracking (for review, see Holzman, 2000).

Recently, investigators have attempted to identify a mechanism that may account for these visual processing deficits in schizophrenia. Research on visual processing in healthy humans and monkeys has identified two unique but interactive physiological subsystems in the visual system (Breitmeyer & Ganz, 1976; Livingstone & Hubel, 1987). The “transient system” involves the magnocellular (M) subcortical visual pathway, which is primarily responsible for processing location information and motion. It is the relatively faster responding system with lower spatial resolution and greater contrast sensitivity. The “sustained system” involves the

parvocellular (P) subcortical visual pathway and is primarily responsible for processing detail and color. It is the relatively slower responding, higher spatial resolution system.

Previous research in persons with schizophrenia has suggested a dysfunctional M pathway. This hypothesis is supported by Schwartz and colleagues (1990; 2001), who reported that persons with schizophrenia had longer visual persistence to peripheral compared to foveal visual field stimulation, suggesting M pathway dysfunction. Other researchers found that persons with schizophrenia had difficulty in a visual spatial location task, but were not impaired on a task that required discrimination of visual stimuli with high spatial resolution (a P pathway function), lending further support for a visual processing deficit specific to the M pathway (Cadenhead et al., 1998; O'Donnell et al., 1996).

Similarly, several investigators have found that persons with schizophrenia display motion sensitivity impairment (Brenner et al., 2003; Chen, Nakayama et al., 1999; Chen, Palafox et al., 1999; Stuve et al., 1997), a phenomenon also seen in monkeys (Newsome & Pare, 1988; Wurtz, Yamasaki, Duffy, & Roy, 1990) and humans (Zihl, von Cramon, & Mai, 1983) with damage to the M pathway. Persons with schizophrenia have also shown deficits on smooth-pursuit eye tracking tasks (for review, see Holzman 2000). As the M pathway is required for proper control of eye movements (Page, King, Merigan, & Maunsell, 1994; Schiller & Lee, 1994), deficits on eye movement tasks may be secondary to a primary deficit specific to the M pathway.

Another type of measurement used to support the notion of an M pathway deficit is performance on tests of visual backward masking. In visual backward masking, a brief visual stimulus (target) is followed quickly by a second stimulus (mask). The interval between the offset of the target and the onset of the mask is referred to as the interstimulus interval (ISI).

While participants can usually identify the target presented without a mask, the addition of a mask makes identification of the target more difficult. Both target and mask are thought to elicit a fast M system response and a slower P system response. Target visibility is worse when the P response to the target is interrupted by the M response to the mask. In addition, specific backward masking conditions have been developed to emphasize the M or P system. For example, a condition that requires location identification will rely more on the M system, while conditions that use a clearly focused target and require target identification rely more on the P system (Green, Nuechterlein, & Breitmeyer, 1997).

Research using visual backward masking tasks have found that persons with schizophrenia tend to require a longer ISI than healthy controls in order to escape the interrupting influence of the mask (Braff & Saccuzzo, 1982; Green & Walker, 1986; Rund, 1993; Saccuzzo & Braff, 1986; Schwartz, Winstead, & Adinoff, 1983; Suslow & Arolt, 1998). This is particularly informative, as research with healthy individuals has found that an increase in the ISI of maximum masking is consistent with an increase in the response speed of the M system (Williams, Breitmeyer, Lovegrove, & Gutierrez, 1991). As persons with schizophrenia often require a prolonged ISI to escape the interrupting influence of the mask, this supports the notion of a hyperactive M system in persons with this disorder.

A recent report indicated that the visual backward masking deficit in schizophrenia appears to include a dysfunctional P pathway, in addition to a dysfunctional M pathway (Green, Nuechterlein, Breitmeyer, Tsuang, & Mintz, 2003). In addition, there is some evidence that persons with schizophrenia required longer display durations for detection of unmasked stimuli (Schechter, Butler, Silipo, Zemon, & Javitt, 2003), suggesting a P pathway deficit. However, as the M pathway is thought to be necessary for initial priming of P pathway processing (Schechter

et al., 2003; Schroeder, Mehta, & Givre, 1998), a weak M pathway may explain these apparent P pathway deficits and account for the greater masking effect (through a stronger ability of the mask to interrupt a weak P signal - due to deficient M pathway priming). Therefore, decreased accuracy on backward masking tasks can be accounted for by either a hyperactive M pathway (increasing the strength of the mask) or a hypoactive M pathway (weak priming of P pathway processing necessary for target identification).

Other investigators have provided evidence suggesting that schizophrenia is related to a hypoactive, rather than hyperactive, M pathway. Three studies used electroencephalography (EEG) to examine electric potentials on the scalp in persons with schizophrenia and found significantly reduced signal amplitude for visual-evoked potentials over the parietal cortical region of the M pathway (Butler et al., 2001; Doniger, Foxe, Murray, Higgins, & Javitt, 2002; Foxe, Doniger, & Javitt, 2001). These studies additionally support the notion that the dysfunction is specific to the M pathway, as visual-evoked potentials arising from cortical areas associated with the P pathway did not differ from controls. However, these studies inferred M pathway activation from a broad region of cortex that included areas adjacent to the M pathway; therefore, results need to be interpreted with caution.

Similarly, other investigators used functional magnetic resonance imaging (fMRI) to examine the M system in schizophrenia. Functional MRI commonly infers brain activity by measuring changes in the local concentration of deoxyhemoglobin, as oxygen supply increases locally to regions with an increased neuronal firing rate (Kwong et al., 1992). This technique is referred to as a BOLD contrast – blood oxygen-level dependent. Using this technique, investigators have found evidence of reduced BOLD activation in the inferior parietal lobe, where the M pathway transverses, in neuroleptic-naïve persons with first-episode schizophrenia

in response to a moving checkerboard visual stimulus – consistent with the notion of a hypoactive M pathway (Braus, Weber-Fahr, Tost, Ruf, & Henn, 2002). Thus, psychophysical research in persons with schizophrenia indicated a dysfunctional M pathway, but was not able to specify whether this dysfunction was due to a hypoactive or hyperactive M pathway. However, more recent physiological studies (e.g, fMRI, EEG) have consistently found evidence of a hypoactive M pathway in persons with schizophrenia.

Examining healthy first-degree relatives of persons with schizophrenia is advantageous because unique characteristics found in these individuals may offer insight into genetic expression in schizophrenia without the confounds of neuroleptic exposure, duration of hospitalization, or active symptom effects (Adler, Freedman, Ross, Olincy, & Waldo, 1999; Weinberger, 1999). First-degree relatives include biological parents, full-siblings, and children of a person with schizophrenia and share, on average, 50% of their genes with the affected relative. Several investigators have demonstrated reduced accuracy on backward masking tasks in healthy adult siblings of persons with schizophrenia (Green et al., 1997; Keri, Kelemen, Benedek, & Janka, 2001), supporting a genetic basis for the magnocellular deficit. In both of these studies, the authors found stronger effects in task conditions that emphasized the transient (magnocellular) channels. In contrast, Lieb and colleagues (1996) and Bedwell and colleagues (2003) did not find differential backward masking performance in samples of first-degree relatives of persons with schizophrenia. Thus, the reliability of increased sensitivity to backward masking in first-degree relatives is not clear. However, other investigators have found alternate markers of M pathway deficit in first-degree relatives including impairment in motion sensitivity (Chen, Nakayama et al., 1999) and eye tracking (Kathmann, Hochrein, Uwer, & Bondy, 2003;

Lencer, Trillenberg-Krecker, Schwinger, & Arolt, 2003), supporting a genetic influence on M pathway dysfunction in schizophrenia.

Determining whether M pathway dysfunction is related to genetic risk for schizophrenia has important clinical implications. For the past several decades, researchers have attempted to identify genes responsible for schizophrenia. Unfortunately, their efforts have been limited, likely due to insufficient statistical power in genetic linkage studies – as schizophrenia is hypothesized to be caused by multiple genes of small effect interacting in an unknown manner (Kidd, 1997; O'Rourke, Gottesman, Suarez, Rice, & Reich, 1982). The ability to identify which members of a family are "silently" carrying the genes for schizophrenia (e.g., carrying the genes without expressing the disorder) would greatly increase the statistical power in genetic linkage studies – making it more likely that the genes related to the disorder will be identified (Freedman, Adler, & Leonard, 1999). Once the responsible genes are identified, it would pave the way for the development of more effective treatment and prevention strategies targeted to individuals with the predisposing genes.

The notion of an early sensory processing deficit in schizophrenia may not be specific to the visual system, as research on early processing in other sensory systems in persons with schizophrenia have also noted dysfunction. Investigators using EEG with auditory stimuli have noted an early auditory processing deficit occurring within milliseconds of stimulus presentation in persons with schizophrenia and their nonpsychotic relatives (Clementz, Geyer, & Braff, 1998; Javitt, Shelley, & Ritter, 2000; Javitt, Shelley, Silipo, & Lieberman, 2000; Turetsky, Cannon, & Gur, 2000). Several studies have noted that persons with schizophrenia and their nonpsychotic relatives have impaired performance on tasks of odor discrimination and sensitivity (for review see Moberg & Turetsky, 2003). Additionally, there is evidence of impaired tactile discrimination

and prepulse inhibition in persons with schizophrenia and their relatives (Chang & Lenzenweger, 2001; Kumari et al., 2003). Prepulse inhibition refers to the ability of a weak stimulus, the prepulse, to inhibit the neural response to a strong stimulus that closely follows it in time (Kumari et al, 2003).

As the thalamus is a central brain region responsible for early sensory processing of all sensory modalities, this region has received particular focus in recent studies in schizophrenia. One study found that an auditory gating deficit found in schizophrenia could be replicated with single-unit recording in the reticular thalamic nucleus in rats exposed to D-amphetamine (which was reversed with haloperidol; Krause, Hoffmann, & Hajos, 2003). Auditory gating refers to the phenomenon of reduced amplitude of neural response (a positive signal occurring 50 ms after stimulus presentation – P50) to the second of two paired consecutive auditory stimuli (Krause et al, 2003). Two studies have found reduced right thalamic activity during visual stimulation in persons with schizophrenia (Braus et al., 2002; Heckers et al., 2000). In addition, numerous studies have found reduced thalamic volume (Danos et al., 2003; Gaser, Nenadic, Buchsbaum, Hazlett, & Buchsbaum, 2004; Highley, Walker, Crow, Esiri, & Harrison, 2003; Kemether et al., 2003) and abnormal thalamic shape (Hazlett et al., 1999) in persons with schizophrenia. Thus, abnormalities in the thalamus in schizophrenia may cause a variety of early sensory processing deficits, including M pathway dysfunction. The M pathway passes through the thalamus early in the visual processing stream, beginning at the lateral geniculate nucleus (LGN). Various thalamic nuclei influence information processing in the LGN, including inhibitory influences from the thalamic reticular nucleus (Uhlrich, Manning, & Feig, 2003). These inhibitory influences from the thalamic reticular nucleus are particularly interesting, as this is the thalamic nucleus found to be primarily involved with auditory gating deficits (see above). Therefore,

dysfunction from various nuclei in the thalamus, including the thalamic reticular nucleus, could potentially cause downstream effects in other visual areas and in behavioral performance on M pathway tasks in particular. However, there does not appear to be any research that directly examines the relation of M pathway functioning to thalamic structure or functioning in schizophrenia.

Functional Neuroanatomy of the Visual System. (Many details listed below have been well-established and thus do not include references. Much of this review has been adapted from a textbook chapter - Rains, 2002, pp. 93-127).

The neural anatomy of the M and P pathways has been extensively investigated in both monkeys and humans. The distinction between these pathways begins at the level of the retina, where the photoreceptors in the eye are distinguished into two classes – rods and cones. The rods are associated with the M pathway, while the cones are associated with the P pathway. The rods are most sensitive to light and are maximally activated in dim light conditions – such as at night, while the cones are responsible for most or all of vision at higher light levels – such as in daylight. Despite heavy reliance on cone-based vision during the day, when humans are most active, the human retina is comprised of 95% rods and only 5% cones. The majority of cones are concentrated in a small region in the center of the retina called the fovea, but are present in a relatively small number throughout the peripheral region. The rods are distributed more diffusely, but are absent in the center (radius = 0.6º) of the retina, while packed most densely around 20º from the center and gradually decreasing in density towards the periphery. In addition, rods are not sensitive to differences in color, while cones are highly color-sensitive and color–selective.

After light stimulates the photoreceptors, the information is communicated to ganglion cells in the retina, which further process the information. The photoreceptors outnumber the ganglion cells at a ratio of 120:1, indicating that much of the initial signal is filtered before leaving the retina. The ganglion cells are segmented into two major functional types – the P (parvocellular) ganglion cells and the M (magnocellular) ganglion cells. The P cells outnumber the M cells by a ratio of 9:1. The M ganglion cells have larger receptive fields, are more sensitive to low contrast, are insensitive to wavelength, and respond in transient bursts. The P ganglion cells have smaller receptive fields, respond with a sustained firing rate, and are sensitive to wavelength. As a result, the M ganglion cells are involved in the detection of large objects and the gross features of stimuli (such as motion and location), while the P ganglion cells are involved in the discrimination of detail and color. Notably, the two types of ganglion cells receive input from both rods and cones (but not necessarily equally), suggesting parallel processing and specialization of function occurring at the level of the retina.

The axons of the ganglion cells form the optic nerve, which leaves the retina of each eye and projects toward the back of the brain (see Figure 2.1). The fibers from the nasal side of each retina cross to the opposite (contralateral) side of the brain at a point called the optic chiasm. The fibers from the lateral side of each retina do not cross over and join the fibers from the nasal side of the opposite retina posterior to the optic chiasm. Posterior to the optic chiasm, the fiber bundles are called the optic tracts. Thus, each optic tract contains information from the contralateral hemispace.

The majority of axons in each optic tract synapse on the ipsilateral lateral geniculate nucleus (LGN). The LGN has six layers, with the most dorsal labeled as layer six. Each layer receives input from a particular eye's representation of the respective visual field and the cells

within each layer represent an orderly spatial representation of visual information from the corresponding visual hemispace. The layers of the LGN are also divided into the M and P pathways, as layers 1 and 2 receive their input from the M ganglion cells and layers 3-6 receive their input from the P ganglion cells, thereby preserving the parallel processing that began in the retina. The information at the level of the LGN is also influenced by other nuclei in the thalamus, including the thalamic reticular nucleus, which sends inhibitory signals to all layers of the LGN (Uhlrich et al., 2003).

The LGN then projects the visual information back to the primary visual cortex (V1), located medially in the posterior visual lobe (see Figure 2.1). This information is projected to V1 via four parallel tracks of axons – two from the M layers of the LGN and two from the P layers. Almost all of these axons terminate in layer IV-C of V1, where primary anatomical segregation of the M and P pathways is maintained, although evidence suggests a large degree of cross-talk between the pathways at this level (Ferrera, Nealey, & Maunsell, 1992). It appears that the majority of axons from the M layers of the LGN terminate in layer IV-Cα and the majority of axons from the P layers of the LGN terminate in layer IV-Cβ. Neurons in the M layer (IV-Cα) project to layer IV-B, while neurons in the P layer (IV-Cβ) project to areas called "blobs" and "interblobs" located in layers II and III Of V1. The functional specificity of the blobs and interblobs remains disputed, as some studies have found that the blobs contain a majority of color specific cells (Livingstone & Hubel, 1984; Tootell, Silverman, Hamilton, De Valois, & Switkes, 1988), while other findings do not support this claim (Ts'o, Frostig, Lieke, & Grinvald, 1990).

The neuroanatomy of the visual system begins to differ between monkeys and humans after the level of V1 processing (Clarke & Miklossy, 1990; Van Essen et al., 2001). Until more

recently, technology prevented the detailed study of functional neuroanatomy in humans, thus much more is known about the visual pathways in monkeys (Crick & Jones, 1993; Kaas, 1995; Tootell, Dale, Sereno, & Malach, 1996). In both humans and monkeys, it is known that the neurons of both the M and P pathways project from V1 to V2, which forms a ring around V1. Within V2, there are subareas called "thin stripes", "thick stripes", and "interstripes". In monkeys, it has been shown that neurons from the M pathway project from layer IV-B in V1 to the thick stripes of V2 and areas V3 and V5. Similarly, it has been shown in monkeys that neurons from the blobs of the P pathway project to the thin stripes of V2 and area V4, while neurons from the interblobs of the P pathway project to the interstripes of V2 and area V4. However, the functional segregation of the M and P pathways does not appear as clear in V2, as (in monkeys) some studies have found a majority of color selective cells in the 'thin' stripes (consistent with P pathway function) (Hubel & Livingstone, 1987; Tootell & Hamilton, 1989), while others have found these cells present to an equal degree in the thick stripes and interstripes (Gegenfurtner, Kiper, & Fenstemaker, 1996).

Area V4 has been particularly controversial, as even in monkeys, color-selectivity of neurons in V4 has been found to be present by some (Zeki, 1973, 1977, 1978, 1983), but not others (Schein, Marrocco, & de Monasterio, 1982). In humans, investigators used neuroimaging to detect the area of cortex responding to color and found a small color-selective region near the middle of the collateral sulcus (Lueck et al., 1989; McKeefry & Zeki, 1997; Zeki et al., 1991), which they named V4 – after the primate area. Similarly, neuropsychological data from brain-injured patients showed achromatopsia (lack of color vision) in patients with damage to the area around the collateral sulcus (Damasio, Yamada, Damasio, Corbett, & McKee, 1980; Pearlman, Birch, & Meadows, 1979), further suggesting color-selectivity in this region. However, these

groups did not use retinotopic mapping procedures to see whether this color-selectivity is really located in the same region as primate V4 relative to the other secondary visual areas.

Hadjikhani and colleagues (1998) used retinotopic mapping procedures to more precisely investigate the visual area of color-selectivity in humans using functional magnetic resonance imaging (fMRI). They too found a region near the middle of the collateral sulcus; however, retinotopic mapping indicated that this area is not in the same relative location as V4 in monkeys, but instead lies anterior to the most anterior boundary of the corresponding V4 area in humans (called V4-v). The research group labeled the color-selective region in humans – "V8", and found that the area corresponding to primate V4 in humans did not display evidence of color selectivity. As a result of this study, other groups now commonly refer to the color-selective area in humans as V8 (Burton et al., 2002; Nunn et al., 2002; Ramachandran & Hubbard, 2001).

Area V5 as a Marker of M Pathway Functioning

Investigation of the visual system of monkeys has identified an anatomically and physiologically distinctive region of cortex – termed V5 (also known as the middle temporal area (MT)), which responds selectively to motion, as determined by single cell recordings (Albright, 1984; Baker, Petersen, Newsome, & Allman, 1981; Born & Tootell, 1992; Felleman & Kaas, 1984; Malonek, Tootell, & Grinvald, 1994; Maunsell & Van Essen, 1983; Zeki, 1978) and contrast-enhanced fMRI (Vanduffel et al., 2001). In all non-human primates reported, V5 is a region in the posterior bank of the dorsal superior temporal sulcus, which is highly myelinated (Allman, Kaas, & Lane, 1973; Dubner & Zeki, 1971; Fiorani, Gattass, Rosa, & Sousa, 1989; Maunsell & van Essen, 1983).

A V5 homolog has been identified in humans using a variety of methods. Histological studies using myelin staining suggest an area V5 in adult humans (Clarke & Miklossy, 1990; Sereno & Allman, 1991), but vary on the precise location of this area. However, a more definitive study was conducted using more elaborate staining techniques and cortical flattening techniques, which clearly demonstrated that V5 was an oval area approximately 1.2 x 2.0 cm, located 5 – 6 cm anterior and dorsal to the foveal V1-V2 border (see Figure 2.2, Tootell & Taylor, 1995). One study compared single-neuron recordings in monkey V5 to fMRI measurements in humans and indicated a strong functional homology between human and macaque V5 (Rees, Friston, & Koch, 2000).

Neuropsychological testing of humans with brain damage to the region roughly corresponding to V5 in monkeys revealed relatively specific deficits in visual motion perception (Plant, Laxer, Barbaro, Schiffman, & Nakayama, 1993; Thurston, Leigh, Crawford, Thompson, & Kennard, 1988; Vaina, 1989; Zihl et al., 1983). Similarly, neuroimaging studies that examine neural activation due to moving as opposed to stationary stimuli confirmed an apparent V5 homolog in humans. Several different types of visual stimuli have been used to create motion in the human neuroimaging literature. Numerous investigators have used moving arrays of dots compared to stationary dots to display V5 activation using both positron emission tomography (PET; Dupont et al., 1997; Hasnain et al., 1998; Zeki et al., 1991) and fMRI (Beauchamp, Cox, & DeYoe, 1997; Braddick et al., 2001; ffytche, Howseman, Edwards, Sandeman, & Zeki, 2000; Kansaku et al., 2001; Rees et al., 2000; Tootell, Reppas, Kwong et al., 1995; Van Oostende, Sunaert, Van Hecke, Marchal, & Orban, 1997; Waddington & Youssef, 1996; Wang et al., 1999). Alternatively, others have used moving sinusoidal gratings (Heeger, Boynton, Demb, Seidemann, & Newsome, 1999; Singh, Smith, & Greenlee, 2000) or a moving checkerboard

(Watson et al., 1993) compared to a stationary target to isolate V5. One group of investigators was able to show V5 activation in response to real, imaginary, and apparent motion using fMRI (Goebel, Khorram-Sefat, Muckli, Hacker, & Singer, 1998).

Of particular relevance to this study, several investigators have used moving concentric rings to produce V5 activation with fMRI (Ahlfors et al., 1999; Culham et al., 1999; He, Cohen, & Hu, 1998; Tootell, Reppas, Dale et al., 1995). This technique was first used to demonstrate V5 activation to illusory motion, as continued expansion (or contraction) of the rings produced a temporary illusion of movement (labeled the "motion aftereffect") when a stationary target was presented immediately afterwards. Using this technique, several groups have demonstrated that V5 activates during the actual motion and then continues to activate during the stationary target for the length of the illusion (Culham et al., 1999; He et al., 1998; Tootell, Reppas, Dale et al., 1995). However, as a control task, these investigators used a period of movement where the rings alternated between contraction and expansion, which effectively eliminated the resulting impression of an illusion during the stationary phase and resulted in V5 activity that was restricted to the movement period and did not overlap the stationary period. Notably, several studies have indicated that V5 activation from optic flow stimuli (e.g., expanding/contracting concentric rings) is often located around 1 cm ventral (Morrone et al., 2000) or dorsal (Howard et al., 1996) to the location in V5 activated by translational movement (e.g., all dots moving in continuous direction), but still overlaps the broader V5 region defined by others. However, one group using radially expanding dots presented to only the ventral visual field did not find significant V5 activity using PET (de Jong, Shipp, Skidmore, Frackowiak, & Zeki, 1994).

A group of investigators later adopted this "control" version to isolate V5 activity (Ahlfors et al., 1999). During the movement period in this later study, expansion and contraction

of the concentric rings was alternated every three seconds to avoid the motion aftereffect. In addition, the investigators used a low contrast (~5%) between the rings and the background, as this has been previously shown to specifically enhance the response in V5 relative to areas V1 and V2 (Tootell, Reppas, Kwong et al., 1995). The study by Ahlfors and colleagues also used magnetoencephalography (MEG) in conjunction with fMRI to investigate the precise timing of neural firing in V5. MEG measures small magnetic fluctuations that result from neural activity on the level of milliseconds but provides relatively poor spatial resolution (Hamalainen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993), whereas fMRI relies on the hemodynamic response, resulting in response times that lag neural activity by several seconds, but with relatively good spatial resolution (Belliveau et al., 1991).

Both MEG and fMRI confirmed the activation of V5 in response to the moving concentric rings, which occurred at 130 ms after the start of motion and peaked at 170 ms, after the reversal of the direction of motion (Ahlfors et al., 1999). Similarly, a second group confirmed that the peak V5 response occurred around 170 ms, and elaborated to show that this response always followed the V1 response by 16-20 ms (Anderson, Holliday, Singh, & Harding, 1996). This timing was confirmed by a third independent group who found that V5 responded between 100 and 130 ms after the onsets of both rotating and stationary stimuli, suggesting that V5 responds to any transient changes in the environment (Uusitalo, Jousmaki, & Hari, 1997). Other investigators used MEG to confirm activation of V5 to moving stimuli (Adler et al., 1999; Anderson et al., 1996; Bundo et al., 2000; Patzwahl, Elbert, Zanker, & Altenmuller, 1996) and to apparent motion – the perception of realistic smooth movement when a stimulus is flashed in one place and then another (Kaneoke, Bundou, Koyama, Suzuki, & Kakigi, 1997; Uusitalo et al.,

1997). A recent MEG study reported that signal strength in V5 increased as the coherence of a field of moving dots increased (Nakamura et al., 2003).

Using MEG with moving stimuli, ffytche and colleagues (1995) found that when a stimulus moved quickly (22 degrees per second), the signal in V5 occurred before any signal appeared in V1, thereby indicating that the signal bypassed V1 on the way to V5. In contrast, this study found that when stimuli moved less than 6 degrees per second, the signal arrived in V1 prior to V5. The investigators concluded that motion processing evidences dynamic parallelism, as motion processing relied differentially on two apparently parallel pathways, depending on the speed of the stimulus.

Further evidence for an independent pathway that bypasses the traditional geniculostriate route stems from studies of two individuals who were missing all of the left primary visual cortical area V1. Fast (but not slow) motion stimuli presented to these individuals' blind hemifield activated a location consistent with V5, even in the absence of V1 – suggesting the presence of non-geniculostriate input to V5 involved with the processing of fast-moving stimuli (ffytche, Guy, & Zeki, 1996; Holliday, Anderson, & Harding, 1997). In addition, a recent study simulated a temporary primary visual cortex lesion in humans by presenting stimuli with strong V1 refractory effects and continued to find EEG and MEG evidence of V5 response to motion, consistent with a direct thalamic-V5 connection (Schoenfeld, Heinze, & Woldorff, 2002). At least one study could not find evidence of a non-geniculostriate input using MEG (Anderson et al., 1996), but the mathematical analysis of the evoked records in this study has been criticized (see ffytche et al, 1996) as not necessarily reflecting the true underlying physiology.

An alternative technology, transcranial magnetic stimulation (TMS), has been used to examine the V5 response to motion. TMS uses magnetic energy to transiently stimulate or

inactivate a restricted cortical region without causing a permanent change to the structure or functional capacity (Ilmoniemi et al., 1997). These studies have found that stimulating the region of the skull lying approximately above V5 can create temporary akinetopsia (motion imperception), thereby contributing converging evidence of the role of V5 in motion processing (Anand, Olson, & Hotson, 1998; Beckers & Homberg, 1992; Beckers & Zeki, 1995; d'Alfonso et al., 2002; Hotson, Braun, Herzberg, & Boman, 1994; Walsh, Ellison, Battelli, & Cowey, 1998). Some evidence exists using TMS that V5 activity occurs around 30 to 40 ms from stimulus (motion) onset and precedes V1 activity by around 30 ms, thereby contributing further evidence for a pathway to V5 that is independent of V1 (Beckers & Zeki, 1995).

Several studies suggest that V5 is also involved in the memory of the direction of visual motion, as TMS of V5 during interstimulus intervals eliminated the priming effect (reduction in reaction time) related to repetition of the same stimulus – without changing accuracy of motion direction detection (Campana, Cowey, & Walsh, 2002; Juan, Campana, & Walsh, 2004). The role of V5 in memory of direction of visual motion has been supported by others using alternative methodologies in primates (Bisley & Pasternak, 2000) and humans (Shulman et al., 1999).

Functional imaging and MEG studies have indicated that the location of V5 varies considerably from person to person. The first published imaging study that examined V5 used PET to investigate the location of V5 in 12 individuals and found that its position varied by as much as 27 mm in the left hemisphere and 18 mm in the right in regards to the pixel with the highest significance for blood flow change between a moving and stationary checkerboard pattern (Watson et al., 1993). This study noted that the 12 participants could be broken down into two subgroups based on average V5 location that limited the variation in V5 location to 13

mm. Using all 12 participants, the average Talairach coordinates (Talairach & Tournoux, 1988) from this study were -44, -70, 0 for left V5 and +40, -68, 0 for right V5. A different group of investigators examined the interindividual variability of V5 in 11 individuals using PET and found a standard deviation of 2.6, 4.2, and 4.1 (x, y, and z) Talairach coordinates for the left side and 4.7, 7.0, and 6.2 for the right side (Hasnain et al., 1998). These results differed from the Watson et al study, as the right V5 demonstrated the greatest variance as opposed to the left. However, the location of V5 in the Hasnain et al study was very similar to the Watson et al study, as Hasnain et al reported an average location of -39, -72, -1 for left V5 and 41, -65, 2 for right V5. Similarly, a MEG study reported that the apparent location of V5 varied over a few centimeters between participants (Patzwahl et al., 1996).

In terms of gyral and sulcal landmarks, the Watson et al study (1993) noted that in 16 of the 24 hemispheres (12 individuals with 2 hemispheres), V5 could be identified as the area at the junction of the ascending limb of the inferior temporal sulcus and the lateral occipital sulcus (see Figure 2.2). In the remainder of the hemispheres, the authors stated that this pattern was suggestive of where V5 appeared, but less clear-cut. The authors noted that the inferior temporal sulcus is a highly interrupted sulcus that is not always easily identified. Another group of investigators reported an inability to discern a consistent relationship between the location of V5 relative to the surrounding cortical gyri and noted that the gyri in this region are not very consistent (Tootell, Reppas, Kwong et al., 1995). A recent study demonstrated a high degree of overlap in the identification of V5 in healthy adults between high-resolution structural MRI patterns of cortical lamination and fMRI activation of V5 in response to motion – demonstrating for the first time that V5 can be identified using high-resolution structural MRI (Walters et al., 2003).

Other imaging studies have provided further evidence that the location of V5 varies greatly between individuals. One MEG study found that individuals could be classified into one of three types in terms of the brain location demonstrating the largest response to motion: temporo-occipital, occipital, or parietal (Bundo et al., 2000). The authors suggest that the temporo-occipital type corresponds to area V5, the occipital type may correspond to area V3-A, and the parietal type corresponds to the posterior end of the superior temporal sulcus (pSTS). The study reports that of 12 participants, seven displayed the temporo-occipital type, two had the occipital type, and three had the parietal type. Although both V3-A and pSTS have been shown to respond to moving stimuli in previous studies (Ahlfors et al., 1999; Cheng, Fujita, Kanno, Miura, & Tanaka, 1995; Tootell et al., 1997), the authors suggest the possibility that in some humans, V5 migrates to cortical regions other than the expected temporo-occipital area (Bundo et al., 2000). To support this suggestion, they note previous reports that histological localization of V5 could not be made in the expected region in some humans (Sereno & Allman, 1991; Tootell & Taylor, 1995).

The strength of activation in V5 due to motion compared to stationary stimuli using fMRI has been shown to vary widely over multiple scans, with movement-to-stationary ratios ranging from 2.2 to 16.1 – in sharp contrast to area V1, which varies much less, from 1 to 1.3 (Tootell, Reppas, Kwong et al., 1995). Similarly, Watson and colleagues reported that the strength of regional blood flow (using PET) differed in V5 in 12 healthy individuals from 2.6% to 11.5% (Watson et al., 1993). However, another group reported less variation using fMRI with five healthy participants, with a reported BOLD % change in V5 changing between 0.8% to 3.0% on the left and 0.9% to 2.7% on the right (Singh et al., 2000).

Inhibitory Effect of Red Light on M Pathway

In 1966, Torsten Wiesel and David Hubel were the first to report special types of neurons in ventral (M) layers of the lateral geniculate nucleus (LGN) in a rhesus monkey that they labeled "Type IV" cells (Wiesel & Hubel, 1966). The authors examined 10 Type IV cells and described the receptive field as being concentric in type, with an excitatory center and an inhibitory surround – similar to every other cell examined in the ventral layers. However, Type IV cells were unique in that diffuse red light completely suppressed the firing of the cell to large spots in the center of the field. The cessation of firing with red light was maintained the entire time the light was left on. White light appeared to act similarly with these cells, but the effect was not seen with short and medium wavelengths (violet through yellow). A few other cells were described that were similar to the cells mentioned above, but showed more specificity to inhibition with red light, as they did not show a notable effect with white light. The authors did not discuss variation in the proportion of Type IV cells between different monkeys, but noted that approximately 4% of all LGN cells examined were Type IV.

After the publication of the Wiesel and Hubel (1966) study, several other investigators confirmed the presence of Type IV LGN cells in monkeys. One group of investigators studied 41 ventral layer cells from monkey LGN and found that all inhibited firing when exposed to diffuse red light, regardless of whether they were on- or off-center cells (Kruger, 1977). This study noted that the inhibition was delayed by approximately 50 to 100 ms after the diffuse red light appeared. Consistent with this finding, another group of researchers identified Type IV cells in the ventral two layers of the LGN (Dreher, Fukada, & Rodieck, 1976). Similar to the Wiesel and Hubel (1966) study, 4% of all cells of the LGN were identified as Type IV. Dreher et al (1976) confirmed the inhibitory effect of diffuse red light on Type IV cells and further

described these cells as being magnocellular in nature, as only coarse gratings evoked responses, fast-moving stimuli evoked a strong response, and optic-chiasm latencies were short. Based on reported results, it can be estimated that approximately 29% (6/21) of the magnocellular-type neurons in the LGN are suppressed by diffuse red light. Similarly, Marrocco and colleagues (1982) examined the macaque LGN and found that 13% of the M layer cells were consistent with Type IV cells and usually had only red cone input to the surround. However, this group did not report the effect of red light on these cells.

One research group confirmed the presence of monkey retinal ganglion cells that, similar to Type IV cells of the LGN, inhibited firing when exposed to diffuse red light (de Monasterio, 1978). These retinal ganglion cells comprised 9% of all ganglion cells examined and in all cases, the surround mechanism received input from red cones. Long wavelength light (e.g., red) produced delayed inhibition of on-responses, similar to Type IV cells described by others in the LGN. Another group of investigators used single-cell recording in monkeys to demonstrate that the level of separation between the M system and P system begins at the retina, as retinal ganglion cells with high contrast sensitivity (M-type feature) project to the M layers (ventral) of the LGN, while those with low contrast sensitivity (P-type feature) project to the P layers of the LGN (Kaplan & Shapley, 1986). Thus, it may be at the level of the retinal ganglion cells that red light has its primary suppressive effect on the M pathway.

The suppressive effect of red light has also been observed in the primary visual cortex of primates (Livingstone & Hubel, 1984). This study found that 19 of 204 (9%) of non-oriented cells in the primary visual cortex were classified as Type IV cells. These were thought to be similar to Type IV cells of the LGN because they displayed a broad-band on-center, suppression of the initial on-burst by the surround, and maintained suppression of spontaneous firing by large

red spots. These cortical Type IV cells showed characteristic rhythmic, burst-like firing also seen in LGN Type IV cells.

Due to the invasive nature of the techniques used to measure these neuronal features in monkeys, similar examination has not been conducted in humans. The author is not aware of any published study that reported physiological data in the human visual system in response to diffuse red light. However, psychophysical studies have been published that are consistent with red light suppressing the M visual pathway in humans. Several studies have shown that performance on tasks is altered in a way that is consistent with a suppression of the M system in conditions with red light compared to light of other isoluminant colors. Many of these studies have reported a reduced metacontrast backward masking effect (Breitmeyer, May, & Heller, 1991; Breitmeyer & Williams, 1990; Edwards, Hogben, Clark, & Pratt, 1996; Pammer & Lovegrove, 2001; Williams et al., 1991), reduced stroboscopic motion detection, (Breitmeyer & Williams, 1990), reduced reading performance (Chase, Ashourzadeh, Kelly, Monfette, & Kinsey, 2003), reduced coordinate spatial processing accuracy (Hellige & Cumberland, 2001; Roth & Hellige, 1998), and reduced depth processing (Brown & Koch, 2000). However, one study did not find an effect for red light to decrease performance on an apparent motion detection task, as would be expected from a suppressed M system (Pammer & Lovegrove, 2001).

Breitmeyer and Breier (1994) examined participants' reaction time to the onset of spots of varying diameter when presented on a red, compared to green or blue, background. They systematically increased and decreased the luminance of the spot relative to the background. Results indicated slower reaction times to large spots (which favor the M pathway) with the red background (consistent with M pathway suppression), relative to the green or blue background, but only with the increasing luminance condition. The authors could not definitively determine

the reason that this phenomenon was not seen in the decreasing luminance condition, but hypothesized that this may be due to specialization in Type-IV cells for detection of luminance increments.

Weisstein and Brannan (1991) conducted a study using the presentation of a bipartite field comprised of horizontal gratings divided in the middle. A 1 c/deg sinewave grating was presented to one side of the bipartite field and a 1.4 c/deg sinewave grating was presented to the remaining field. Diffuse red light was applied to one side of the field and diffuse green light to the other, in a counterbalanced manner. The red grating consistently appeared to be the figure and the green grating as the ground, regardless of which spatial frequency the red light appeared on. Previous research has demonstrated that a sine wave grating of higher spatial frequency (compared to an adjacent grating) will appear to float in front of the lower spatial frequency grating (Weisstein & Wong, 1986), as the lower spatial frequency grating is more relevant to the M system and information processed by the M system is more likely to be perceived as the ground. Therefore, the results of this study support the idea that red light is suppressing the M system, as the red light was never perceived as the ground – even when present on the lower spatial frequency grating.

One study reported a visual defect in a single male participant, which was described as a potent inhibitory response to only long-wavelength (red) stimuli (Hendricks, Holliday, & Ruddock, 1981). This inhibition was reported to spread for up to 12 degrees from the area of stimulation and suppressed his ability to detect other high contrast stimuli. However, this individual was not color-blind, as he was able to accurately fuse red and green random dot stereogram pairs, indicating that the inhibition likely arises centrally in the visual system. This

visual defect is intriguing, as it may relate to an excess of Type IV cells in this individual and is consistent with the notion of red light suppressing on-center cells.

A study by Bedwell and colleagues (2003) found that a diffuse red background impaired the ability of healthy control participants to locate stimuli in a backward masking paradigm (compared to a gray background). As the ability to locate in space is reliant on the M pathway, this result is consistent with the ability of red light to suppress the M system. The study also examined nonpsychotic first-degree relatives of persons with schizophrenia and found that as a group, they did not change performance significantly in response to the red background. This effect appeared to be driven by a subset of relatives who showed the opposite effect (increase in accuracy) in response to red light. The indication that only a subset of the relatives showed a differential effect of red light is consistent with the notion that only a subset of relatives are expected to have any particular susceptibility gene (and related biobehavioral trait), given that they share only 50% of their genes with an affected proband (Weinberger, 1999). To the author's knowledge, there are no other published studies that examined the effect of red light on M pathway functioning in persons with schizophrenia or their nonpsychotic relatives. This may represent a novel biobehavioral marker for genes related to schizophrenia. However, the mechanism for this effect is not clear based on the psychophysical methods in this previous study, which prompted the rationale for conducting the current physiological study.

Hypotheses

The author hypothesized the following points, which directly relate to the specific aims previously mentioned:

1) In the control group, the magnitude and volume of fMRI signal in bilateral V5 region will be reduced with a red background compared to a green background in all individuals.

2) As a group, relatives of persons with schizophrenia will show reduced magnitude and volume of fMRI signal in bilateral V5 with a green background.

3) As a group, the relatives will show no evidence for a consistent reduction in fMRI signal in bilateral V5 in response to a red (compared to green) background, compared to the control group. It is hypothesized that, similar to the earlier behavioral study, this effect will appear to be driven by a subset of relatives who show an increase in bilateral fMRI signal in response to the red background.

References

Adler, L. E., Freedman, R., Ross, R. G., Olincy, A., & Waldo, M. C. (1999). Elementary phenotypes in the neurobiological and genetic study of schizophrenia. *Biol Psychiatry, 46*(1), 8-18.

Ahlfors, S. P., Simpson, G. V., Dale, A. M., Belliveau, J. W., Liu, A. K., Korvenoja, A., Virtanen, J., Huotilainen, M., Tootell, R. B., Aronen, H. J., & Ilmoniemi, R. J. (1999). Spatiotemporal activity of a cortical network for processing visual motion revealed by MEG and fMRI. *J Neurophysiol, 82*(5), 2545-2555.

Albright, T. D. (1984). Direction and orientation selectivity of neurons in visual area MT of the macaque. *J Neurophysiol, 52*(6), 1106-1130.

Allman, J. M., Kaas, J. H., & Lane, R. H. (1973). The middle temporal visual area(MT)in the bushbaby, Galago senegalensis. *Brain Res, 57*(1), 197-202.

Anand, S., Olson, J. D., & Hotson, J. R. (1998). Tracing the timing of human analysis of motion and chromatic signals from occipital to temporo-parieto-occipital cortex: A trancranial magnetic study. *Vision Res, 38*, 2619-2627.

Anderson, S. J., Holliday, I. E., Singh, K. D., & Harding, G. F. (1996). Localization and functional analysis of human cortical area V5 using magneto-encephalography. *Proc R Soc Lond B Biol Sci, 263*(1369), 423-431.

Baker, J. F., Petersen, S. E., Newsome, W. T., & Allman, J. M. (1981). Visual response properties of neurons in four extrastriate visual areas of the owl monkey (Aotus trivirgatus): a quantitative comparison of medial, dorsomedial, dorsolateral, and middle temporal areas. *J Neurophysiol, 45*(3), 397-416.

Beauchamp, M. S., Cox, R. W., & DeYoe, E. A. (1997). Graded effects of spatial and featural attention on human area MT and associated motion processing areas. *J Neurophysiol, 78*(1), 516-520.

Beckers, G., & Homberg, V. (1992). Cerebral visual motion blindness: transitory akinetopsia induced by transcranial magnetic stimulation of human area V5. *Proc R Soc Lond B Biol Sci, 249*(1325), 173-178.

Beckers, G., & Zeki, S. (1995). The consequences of inactivating areas V1 and V5 on visual motion perception. *Brain, 118*(Pt 1), 49-60.

Bedwell, J. S., Brown, J. M., & Miller, L. S. (2003). The magnocellular visual system and schizophrenia: what can the color red tell us? *Schizophrenia Research, 63*(3), 273-284.

Belliveau, J. W., Kennedy, D. N., Jr., McKinstry, R. C., Buchbinder, B. R., Weisskoff, R. M., Cohen, M. S., Vevea, J. M., Brady, T. J., & Rosen, B. R. (1991). Functional mapping of the human visual cortex by magnetic resonance imaging. *Science, 254*(5032), 716-719.

Bisley, J. W., & Pasternak, T. (2000). The multiple roles of visual cortical areas MT/MST in remembering the direction of visual motion. *Cereb Cortex, 10*(11), 1053-1065.

Born, R. T., & Tootell, R. B. (1992). Segregation of global and local motion processing in primate middle temporal visual area. *Nature, 357*(6378), 497-499.

Braddick, O. J., O'Brien, J. M., Wattam-Bell, J., Atkinson, J., Hartley, T., & Turner, R. (2001). Brain areas sensitive to coherent visual motion. *Perception, 30*(1), 61-72.

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

Braus, D. F., Weber-Fahr, W., Tost, H., Ruf, M., & Henn, F. A. (2002). Sensory information processing in neuroleptic-naive first-episode schizophrenic patients: a functional magnetic resonance imaging study. *Arch Gen Psychiatry, 59*(8), 696-701.

Breitmeyer, B. G., & Breier, J. I. (1994). Effects of background color on reaction time to stimuli varying in size and contrast: inferences about human M channels. *Vision Res, 34*(8), 1039-1045.

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

Breitmeyer, B. G., May, J. G., & Heller, S. S. (1991). Metacontrast reveals asymmetries at red-green isoluminance. *J. Opt. Soc. Am. A, 8*(8), 1324-1329.

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

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

Brown, J. M., & Koch, C. (2000). Influences of occlusion, color, and luminance on the perception of fragmented pictures. *Percept Mot Skills, 90*(3 Pt 1), 1033-1044.

Bundo, M., Kaneoke, Y., Inao, S., Yoshida, J., Nakamura, A., & Kakigi, R. (2000). Human visual motion areas determined individually by magnetoencephalography and 3D magnetic resonance imaging. *Hum Brain Mapp, 11*(1), 33-45.

Burton, H., Snyder, A. Z., Conturo, T. E., Akbudak, E., Ollinger, J. M., & Raichle, M. E. (2002). Adaptive changes in early and late blind: a fMRI study of Braille reading. *J Neurophysiol, 87*(1), 589-607.

Butler, P. D., DeSanti, L. A., Maddox, J., Harkavy-Friedman, J. M., Amador, X. F., Goetz, R. R., Javitt, D. C., & Gorman, J. M. (2003). Visual backward-masking deficits in schizophrenia: relationship to visual pathway function and symptomatology. *Schizophr Res, 59*(2-3), 199-209.

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

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

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

Campana, G., Cowey, A., & Walsh, V. (2002). Priming of Motion Direction and Area V5/MT: a Test of Perceptual Memory. *Cereb Cortex, 12*(6), 663-669.

Chang, B. P., & Lenzenweger, M. F. (2001). Somatosensory processing in the biological relatives of schizophrenia patients: a signal detection analysis of two-point discrimination. *J Abnorm Psychol, 110*(3), 433-442.

Chase, C., Ashourzadeh, A., Kelly, C., Monfette, S., & Kinsey, K. (2003). Can the magnocellular pathway read? Evidence from studies of color. *Vision Res, 43*(10), 1211-1222.

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

Chen, Y., Palafox, G. P., Nakayama, K., Levy, D. L., Matthysse, S., & Holzman, P. S. (1999). Motion perception in schizophrenia. *Arch Gen Psychiatry, 56*(2), 149-154.

Cheng, K., Fujita, H., Kanno, I., Miura, S., & Tanaka, K. (1995). Human cortical regions activated by wide-field visual motion: an H2(15)O PET study. *J Neurophysiol, 74*(1), 413-427.

Clarke, S., & Miklossy, J. (1990). Occipital cortex in man: organization of callosal connections, related myelo- and cytoarchitecture, and putative boundaries of functional visual areas. *J Comp Neurol, 298*(2), 188-214.

Clementz, B. A., Geyer, M. A., & Braff, D. L. (1998). Poor P50 suppression among schizophrenia patients and their first-degree biological relatives. *Am J Psychiatry, 155*(12), 1691-1694.

Crick, F., & Jones, E. (1993). Backwardness of human neuroanatomy. *Nature, 361*(6408), 109-110.

Culham, J. C., Dukelow, S. P., Vilis, T., Hassard, F. A., Gati, J. S., Menon, R. S., & Goodale, M. A. (1999). Recovery of fMRI activation in motion area MT following storage of the motion aftereffect. *J Neurophysiol, 81*(1), 388-393.

d'Alfonso, A. A., van, H. J., Schutter, D. J., Caffe, A. R., Postma, A., & de, H. E. (2002). Spatial and temporal characteristics of visual motion perception involving V5 visual cortex. *Neurol Res, 24*(3), 266-270.

Damasio, A., Yamada, T., Damasio, H., Corbett, J., & McKee, J. (1980). Central achromatopsia: behavioral, anatomic, and physiologic aspects. *Neurology, 30*(10), 1064-1071.

Danos, P., Baumann, B., Kramer, A., Bernstein, H. G., Stauch, R., Krell, D., Falkai, P., & Bogerts, B. (2003). Volumes of association thalamic nuclei in schizophrenia: a postmortem study. *Schizophr Res, 60*(2-3), 141-155.

de Jong, B. M., Shipp, S., Skidmore, B., Frackowiak, R. S., & Zeki, S. (1994). The cerebral activity related to the visual perception of forward motion in depth. *Brain, 117*(Pt 5), 1039-1054.

de Monasterio, F. M. (1978). Properties of concentrically organized X and Y ganglion cells of macaque retina. *J Neurophysiol, 41*(6), 1394-1417.

Doniger, G. M., Foxe, J. J., Murray, M. M., Higgins, B. A., & Javitt, D. C. (2002). Impaired visual object recognition and dorsal/ventral stream interaction in schizophrenia. *Arch Gen Psychiatry, 59*(11), 1011-1020.

Dreher, B., Fukada, Y., & Rodieck, R. W. (1976). Identification, classification and anatomical segregation of cells with X-like and Y-like properties in the lateral geniculate nucleus of old-world primates. *J Physiol, 258*(2), 433-452.

Dubner, R., & Zeki, S. M. (1971). Response properties and receptive fields of cells in an anatomically defined region of the superior temporal sulcus in the monkey. *Brain Res, 35*(2), 528-532.

Dupont, P., De Bruyn, B., Vandenberghe, R., Rosier, A. M., Michiels, J., Marchal, G., Mortelmans, L., & Orban, G. A. (1997). The kinetic occipital region in human visual cortex. *Cereb Cortex, 7*(3), 283-292.

Edwards, V. T., Hogben, J. H., Clark, C. D., & Pratt, C. (1996). Effects of a red background on magnocellular functioning in average and specifically disabled readers. *Vision Res, 36*(7), 1037-1045.

Felleman, D. J., & Kaas, J. H. (1984). Receptive-field properties of neurons in middle temporal visual area (MT) of owl monkeys. *J Neurophysiol, 52*(3), 488-513.

Ferrera, V. P., Nealey, T. A., & Maunsell, J. H. (1992). Mixed parvocellular and magnocellular geniculate signals in visual area V4. *Nature, 358*(6389), 756-761.

ffytche, D. H., Guy, C. N., & Zeki, S. (1995). The parallel visual motion inputs into areas V1 and V5 of human cerebral cortex. *Brain, 118*(Pt 6), 1375-1394.

ffytche, D. H., Guy, C. N., & Zeki, S. (1996). Motion specific responses from a blind hemifield. *Brain, 119*(Pt 6), 1971-1982.

ffytche, D. H., Howseman, A., Edwards, R., Sandeman, D. R., & Zeki, S. (2000). Human area V5 and motion in the ipsilateral visual field. *Eur J Neurosci, 12*(8), 3015-3025.

Fiorani, M., Jr., Gattass, R., Rosa, M. G., & Sousa, A. P. (1989). Visual area MT in the Cebus monkey: location, visuotopic organization, and variability. *J Comp Neurol, 287*(1), 98-118.

Foxe, J. J., Doniger, G. M., & Javitt, D. C. (2001). Early visual processing deficits in schizophrenia: impaired P1 generation revealed by high-density electrical mapping. *Neuroreport, 12*(17), 3815-3820.

Freedman, R., Adler, L. E., & Leonard, S. (1999). Alternative phenotypes for the complex genetics of schizophrenia. *Biol Psychiatry, 45*(5), 551-558.

Gaser, C., Nenadic, I., Buchsbaum, B. R., Hazlett, E. A., & Buchsbaum, M. S. (2004). Ventricular enlargement in schizophrenia related to volume reduction of the thalamus, striatum, and superior temporal cortex. *Am J Psychiatry, 161*(1), 154-156.

Gegenfurtner, K. R., Kiper, D. C., & Fenstemaker, S. B. (1996). Processing of color, form, and motion in macaque area V2. *Vis Neurosci, 13*(1), 161-172.

Goebel, R., Khorram-Sefat, D., Muckli, L., Hacker, H., & Singer, W. (1998). The constructive nature of vision: direct evidence from functional magnetic resonance imaging studies of apparent motion and motion imagery. *Eur J Neurosci, 10*(5), 1563-1573.

Green, M., & Walker, E. (1986). Symptom correlates of vulnerability to backward masking in schizophrenia. *Am J Psychiatry, 143*(2), 181-186.

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

Green, M. F., Nuechterlein, K. H., Breitmeyer, B., & Mintz, J. (1999). Backward masking in unmedicated schizophrenic patients in psychotic remission: possible reflection of aberrant cortical oscillation. *Am J Psychiatry, 156*(9), 1367-1373.

Green, M. F., Nuechterlein, K. H., Breitmeyer, B., Tsuang, J., & Mintz, J. (2003). Forward and backward visual masking in schizophrenia: influence of age. *Psychol Med, 33*(5), 887-895.

Green, M. F., Nuechterlein, K. H., & Mintz, J. (1994a). Backward masking in schizophrenia and mania. I. Specifying a mechanism. *Arch Gen Psychiatry, 51*(12), 939-944.

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

Hadjikhani, N., Liu, A. K., Dale, A. M., Cavanagh, P., & Tootell, R. B. (1998). Retinotopy and color sensitivity in human visual cortical area V8. *Nat Neurosci, 1*(3), 235-241.

Hamalainen, M., Hari, R., Ilmoniemi, R. J., Knuutila, J., & Lounasmaa, O. (1993). Magnetoencephalography - theory, instrumentation, and applications to noninvasive studies of the working human brain. *Rev. Mod. Phys., 65*, 413-497.

Hasnain, M. K., Fox, P. T., & Woldorff, M. G. (1998). Intersubject variability of functional areas in the human visual cortex. *Hum Brain Mapp, 6*(4), 301-315.

Hazlett, E. A., Buchsbaum, M. S., Byne, W., Wei, T. C., Spiegel-Cohen, J., Geneve, C., Kinderlehrer, R., Haznedar, M. M., Shihabuddin, L., & Siever, L. J. (1999). Three-dimensional analysis with MRI and PET of the size, shape, and function of the thalamus in the schizophrenia spectrum. *Am J Psychiatry, 156*(8), 1190-1199.

He, S., Cohen, E. R., & Hu, X. (1998). Close correlation between activity in brain area MT/V5 and the perception of a visual motion aftereffect. *Curr Biol, 8*(22), 1215-1218.

Heckers, S., Curran, T., Goff, D., Rauch, S. L., Fischman, A. J., Alpert, N. M., & Schacter, D. L. (2000). Abnormalities in the thalamus and prefrontal cortex during episodic object recognition in schizophrenia. *Biol Psychiatry, 48*(7), 651-657.

Heeger, D. J., Boynton, G. M., Demb, J. B., Seidemann, E., & Newsome, W. T. (1999). Motion opponency in visual cortex. *J Neurosci, 19*(16), 7162-7174.

Hellige, J. B., & Cumberland, N. (2001). Categorical and coordinate spatial processing: more on contributions of the transient/magnocellular visual system. *Brain Cogn, 45*(2), 155-163.

Hendricks, I. M., Holliday, I. E., & Ruddock, K. H. (1981). A new class of visual defect. Spreading inhibition elicited by chromatic light stimuli. *Brain, 104*(Pt 4), 813-840.

Highley, J. R., Walker, M. A., Crow, T. J., Esiri, M. M., & Harrison, P. J. (2003). Low medial and lateral right pulvinar volumes in schizophrenia: a postmortem study. *Am J Psychiatry, 160*(6), 1177-1179.

Holliday, I. E., Anderson, S. J., & Harding, G. F. (1997). Magnetoencephalographic evidence for non-geniculostriate visual input to human cortical area V5. *Neuropsychologia, 35*(8), 1139-1146.

Holzman, P. S. (2000). Eye movements and the search for the essence of schizophrenia [In Process Citation]. *Brain Res Brain Res Rev, 31*(2-3), 350-356.

Hotson, J., Braun, D., Herzberg, W., & Boman, D. (1994). Transcranial magnetic stimulation of extrastriate cortex degrades human motion direction discrimination. *Vision Res, 34*(16), 2115-2123.

Howard, R. J., Brammer, M., Wright, I., Woodruff, P. W., Bullmore, E. T., & Zeki, S. (1996). A direct demonstration of functional specialization within motion-related visual and auditory cortex of the human brain. *Curr Biol, 6*(8), 1015-1019.

Hubel, D. H., & Livingstone, M. S. (1987). Segregation of form, color, and stereopsis in primate area 18. *J Neurosci, 7*(11), 3378-3415.

Ilmoniemi, R. J., Virtanen, J., Ruohonen, J., Karhu, J., Aronen, H. J., Naatanen, R., & Katila, T. (1997). Neuronal responses to magnetic stimulation reveal cortical reactivity and connectivity. *Neuroreport, 8*(16), 3537-3540.

Javitt, D. C., Shelley, A., & Ritter, W. (2000). Associated deficits in mismatch negativity generation and tone matching in schizophrenia. *Clin Neurophysiol, 111*(10), 1733-1737.

Javitt, D. C., Shelley, A. M., Silipo, G., & Lieberman, J. A. (2000). Deficits in auditory and visual context-dependent processing in schizophrenia: defining the pattern. *Arch Gen Psychiatry, 57*(12), 1131-1137.

Juan, C. H., Campana, G., & Walsh, V. (2004). Cortical interactions in vision and awareness: hierarchies in reverse. *Prog Brain Res, 144*, 117-130.

Kaas, J. H. (1995). Human visual cortex. Progress and puzzles. *Curr Biol, 5*(10), 1126-1128.

Kaneoke, Y., Bundou, M., Koyama, S., Suzuki, H., & Kakigi, R. (1997). Human cortical area responding to stimuli in apparent motion. *Neuroreport, 8*(3), 677-682.

Kansaku, K., Hashimoto, K., Muraki, S., Miura, K., Takahashi, T., & Kawano, K. (2001). Retinotopic hemodynamic activation of the human V5/MT area during optokinetic responses. *Neuroreport, 12*(18), 3891-3895.

Kaplan, E., & Shapley, R. M. (1986). The primate retina contains two types of ganglion cells, with high and low contrast sensitivity. *Proc Natl Acad Sci U S A, 83*(8), 2755-2757.

Kathmann, N., Hochrein, A., Uwer, R., & Bondy, B. (2003). Deficits in gain of smooth pursuit eye movements in schizophrenia and affective disorder patients and their unaffected relatives. *Am J Psychiatry, 160*(4), 696-702.

Kemether, E. M., Buchsbaum, M. S., Byne, W., Hazlett, E. A., Haznedar, M., Brickman, A. M., Platholi, J., & Bloom, R. (2003). Magnetic resonance imaging of mediodorsal, pulvinar, and centromedian nuclei of the thalamus in patients with schizophrenia. *Arch Gen Psychiatry, 60*(10), 983-991.

Keri, S., Kelemen, O., Benedek, G., & Janka, Z. (2001). Different trait markers for schizophrenia and bipolar disorder: a neurocognitive approach. *Psychol Med, 31*(5), 915-922.

Kidd, K. K. (1997). Can we find genes for schizophrenia? *Am J Med Genet, 74*(1), 104-111.

Krause, M., Hoffmann, W. E., & Hajos, M. (2003). Auditory sensory gating in hippocampus and reticular thalamic neurons in anesthetized rats. *Biol Psychiatry, 53*(3), 244-253.

Kruger, J. (1977). Stimulus dependent colour specificity of monkey lateral geniculate neurones. *Exp Brain Res, 30*(2-3), 297-311.

Kumari, V., Gray, J. A., Geyer, M. A., ffytche, D., Soni, W., Mitterschiffthaler, M. T., Vythelingum, G. N., Simmons, A., Williams, S. C., & Sharma, T. (2003). Neural correlates of tactile prepulse inhibition: a functional MRI study in normal and schizophrenic subjects. *Psychiatry Res, 122*(2), 99-113.

Kwong, K. K., Belliveau, J. W., Chesler, D. A., Goldberg, I. E., Weisskoff, R. M., Poncelet, B. P., Kennedy, D. N., Hoppel, B. E., Cohen, M. S., Turner, R., & et al. (1992). Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proc Natl Acad Sci U S A, 89*(12), 5675-5679.

Lencer, R., Trillenberg-Krecker, K., Schwinger, E., & Arolt, V. (2003). Schizophrenia spectrum disorders and eye tracking dysfunction in singleton and multiplex schizophrenia families. *Schizophr Res, 60*(1), 33-45.

Lieb, K., Denz, E., Hess, R., Schuttler, R., Kornhuber, H. H., & Schreiber, H. (1996). Preattentive information processing as measured by backward masking and texton detection tasks in adolescents at high genetic risk for schizophrenia. *Schizophr Res, 21*(3), 171-182.

Livingstone, M. S., & Hubel, D. H. (1984). Anatomy and physiology of a color system in the primate visual cortex. *J Neurosci, 4*(1), 309-356.

Livingstone, M. S., & Hubel, D. H. (1987). Psychophysical evidence for separate channels for the perception of form, color, movement, and depth. *J Neurosci, 7*(11), 3416-3468.

Lueck, C. J., Zeki, S., Friston, K. J., Deiber, M. P., Cope, P., Cunningham, V. J., Lammertsma, A. A., Kennard, C., & Frackowiak, R. S. (1989). The colour centre in the cerebral cortex of man. *Nature, 340*(6232), 386-389.

Malonek, D., Tootell, R. B., & Grinvald, A. (1994). Optical imaging reveals the functional architecture of neurons processing shape and motion in owl monkey area MT. *Proc R Soc Lond B Biol Sci, 258*(1352), 109-119.

Marrocco, R. T., McClurkin, J. W., & Young, R. A. (1982). Spatial summation and conduction latency classification of cells of the lateral geniculate nucleus of macaques. *J Neurosci, 2*(9), 1275-1291.

Maunsell, J. H., & van Essen, D. C. (1983). The connections of the middle temporal visual area (MT) and their relationship to a cortical hierarchy in the macaque monkey. *J Neurosci, 3*(12), 2563-2586.

Maunsell, J. H., & Van Essen, D. C. (1983). Functional properties of neurons in middle temporal visual area of the macaque monkey. II. Binocular interactions and sensitivity to binocular disparity. *J Neurophysiol, 49*(5), 1148-1167.

McKeefry, D. J., & Zeki, S. (1997). The position and topography of the human colour centre as revealed by functional magnetic resonance imaging. *Brain, 120*(Pt 12), 2229-2242.

Moberg, P. J., & Turetsky, B. I. (2003). Scent of a disorder: olfactory functioning in schizophrenia. *Curr Psychiatry Rep, 5*(4), 311-319.

Morrone, M. C., Tosetti, M., Montanaro, D., Fiorentini, A., Cioni, G., & Burr, D. C. (2000). A cortical area that responds specifically to optic flow, revealed by fMRI. *Nat Neurosci, 3*(12), 1322-1328.

Nakamura, H., Kashii, S., Nagamine, T., Matsui, Y., Hashimoto, T., Honda, Y., & Shibasaki, H. (2003). Human V5 demonstrated by magnetoencephalography using random dot kinematograms of different coherence levels. *Neurosci Res, 46*(4), 423-433.

Newsome, W. T., & Pare, E. B. (1988). A selective impairment of motion perception following lesions of the middle temporal visual area (MT). *J Neurosci, 8*(6), 2201-2211.

Nunn, J. A., Gregory, L. J., Brammer, M., Williams, S. C., Parslow, D. M., Morgan, M. J., Morris, R. G., Bullmore, E. T., Baron-Cohen, S., & Gray, J. A. (2002). Functional magnetic resonance imaging of synesthesia: activation of V4/V8 by spoken words. *Nat Neurosci, 5*(4), 371-375.

O'Donnell, B. F., Swearer, J. M., Smith, L. T., Nestor, P. G., Shenton, M. E., & McCarley, R. W. (1996). Selective deficits in visual perception and recognition in schizophrenia [see comments]. *Am J Psychiatry, 153*(5), 687-692.

O'Rourke, D. H., Gottesman, II, Suarez, B. K., Rice, J., & Reich, T. (1982). Refutation of the general single-locus model for the etiology of schizophrenia. *Am J Hum Genet, 34*(4), 630-649.

Page, W. K., King, W. M., Merigan, W., & Maunsell, J. (1994). Magnocellular or parvocellular lesions in the lateral geniculate nucleus of monkeys cause minor deficits of smooth pursuit eye movements. *Vision Res, 34*(2), 223-239.

Pammer, K., & Lovegrove, W. (2001). The influence of color on transient system activity: implications for dyslexia research. *Percept Psychophys, 63*(3), 490-500.

Patzwahl, D. R., Elbert, T., Zanker, J. M., & Altenmuller, E. O. (1996). The cortical representation of object motion in man is interindividually variable. *Neuroreport, 7*(2), 469-472.

Pearlman, A. L., Birch, J., & Meadows, J. C. (1979). Cerebral color blindness: an acquired defect in hue discrimination. *Ann Neurol, 5*(3), 253-261.

Plant, G. T., Laxer, K. D., Barbaro, N. M., Schiffman, J. S., & Nakayama, K. (1993). Impaired visual motion perception in the contralateral hemifield following unilateral posterior cerebral lesions in humans. *Brain, 116*(Pt 6), 1303-1335.

Rains, G. D. (2002). *Principles of Human Neuropsychology*. Boston: McGraw Hill.

Ramachandran, V. S., & Hubbard, E. M. (2001). Psychophysical investigations into the neural basis of synaesthesia. *Proc R Soc Lond B Biol Sci, 268*(1470), 979-983.

Rees, G., Friston, K., & Koch, C. (2000). A direct quantitative relationship between the functional properties of human and macaque V5. *Nat Neurosci, 3*(7), 716-723.

Roth, E. C., & Hellige, J. B. (1998). Spatial processing and hemispheric asymmetry. Contributions of the transient/magnocellular visual system. *J Cogn Neurosci, 10*(4), 472-484.

Rund, B. R. (1993). Backward-masking performance in chronic and nonchronic schizophrenics, affectively disturbed patients, and normal control subjects. *J Abnorm Psychol, 102*(1), 74-81.

Saccuzzo, D. P., & Braff, D. L. (1986). Information-processing abnormalities: trait- and state-dependent components. *Schizophr Bull, 12*(3), 447-459.

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

Schechter, I., Butler, P. D., Silipo, G., Zemon, V., & Javitt, D. C. (2003). Magnocellular and parvocellular contributions to backward masking dysfunction in schizophrenia. *Schizophr Res, 64*(2-3), 91-101.

Schein, S. J., Marrocco, R. T., & de Monasterio, F. M. (1982). Is there a high concentration of color-selective cells in area V4 of monkey visual cortex? *J Neurophysiol, 47*(2), 193-213.

Schiller, P. H., & Lee, K. (1994). The effects of lateral geniculate nucleus, area V4, and middle temporal (MT) lesions on visually guided eye movements. *Vis Neurosci, 11*(2), 229-241.

Schoenfeld, M. A., Heinze, H. J., & Woldorff, M. G. (2002). Unmasking motion-processing activity in human brain area V5/MT+ mediated by pathways that bypass primary visual cortex. *Neuroimage, 17*(2), 769-779.

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

Schwartz, B. D., Satter, E., O'Neill, P. T., & Winstead, D. K. (1990). Bilateral hemispheric processing deficits in schizophrenia. *Schizophr Res, 3*(2), 147-154.

Schwartz, B. D., Tomlin, H. R., Evans, W. J., & Ross, K. V. (2001). Neurophysiologic mechanisms of attention: a selective review of early information processing in schizophrenics. *Front Biosci, 6*, D120-134.

Schwartz, B. D., Winstead, D. K., & Adinoff, B. (1983). Temporal integration deficit in visual information processing by chronic schizophrenics. *Biol Psychiatry, 18*(11), 1311-1320.

Sereno, M. I., & Allman, J. M. (1991). Cortical visual areas in mammals. In A. G. Leventhal (Ed.), *The neural basis of visual function.* London: Macmillan.

Shulman, G. L., Ollinger, J. M., Akbudak, E., Conturo, T. E., Snyder, A. Z., Petersen, S. E., & Corbetta, M. (1999). Areas involved in encoding and applying directional expectations to moving objects. *J Neurosci, 19*(21), 9480-9496.

Singh, K. D., Smith, A. T., & Greenlee, M. W. (2000). Spatiotemporal frequency and direction sensitivities of human visual areas measured using fMRI. *Neuroimage, 12*(5), 550-564.

Stuve, T. A., Friedman, L., Jesberger, J. A., Gilmore, G. C., Strauss, M. E., & Meltzer, H. Y. (1997). The relationship between smooth pursuit performance, motion perception and sustained visual attention in patients with schizophrenia and normal controls. *Psychol Med, 27*(1), 143-152.

Suslow, T., & Arolt, V. (1998). Backward masking in schizophrenia: time course of visual processing deficits during task performance. *Schizophr Res, 33*(1-2), 79-86.

Talairach, J., & Tournoux, P. (1988). *Co-planar stereotaxic atlas of the human brain.* Stuttgart: Georg Thieme Verlag.

Thurston, S. E., Leigh, R. J., Crawford, T., Thompson, A., & Kennard, C. (1988). Two distinct deficits of visual tracking caused by unilateral lesions of cerebral cortex in humans. *Ann Neurol, 23*(3), 266-273.

Tootell, R. B., Dale, A. M., Sereno, M. I., & Malach, R. (1996). New images from human visual cortex. *Trends Neurosci, 19*(11), 481-489.

Tootell, R. B., & Hamilton, S. L. (1989). Functional anatomy of the second visual area (V2) in the macaque. *J Neurosci, 9*(8), 2620-2644.

Tootell, R. B., Mendola, J. D., Hadjikhani, N. K., Ledden, P. J., Liu, A. K., Reppas, J. B., Sereno, M. I., & Dale, A. M. (1997). Functional analysis of V3A and related areas in human visual cortex. *J Neurosci, 17*(18), 7060-7078.

Tootell, R. B., Reppas, J. B., Dale, A. M., Look, R. B., Sereno, M. I., Malach, R., Brady, T. J., & Rosen, B. R. (1995). Visual motion aftereffect in human cortical area MT revealed by functional magnetic resonance imaging. *Nature, 375*(6527), 139-141.

Tootell, R. B., Reppas, J. B., Kwong, K. K., Malach, R., Born, R. T., Brady, T. J., Rosen, B. R., & Belliveau, J. W. (1995). Functional analysis of human MT and related visual cortical areas using magnetic resonance imaging. *J Neurosci, 15*(4), 3215-3230.

Tootell, R. B., Silverman, M. S., Hamilton, S. L., De Valois, R. L., & Switkes, E. (1988). Functional anatomy of macaque striate cortex. III. Color. *J Neurosci, 8*(5), 1569-1593.

Tootell, R. B., & Taylor, J. B. (1995). Anatomical evidence for MT and additional cortical visual areas in humans. *Cereb Cortex, 5*(1), 39-55.

Ts'o, D. Y., Frostig, R. D., Lieke, E. E., & Grinvald, A. (1990). Functional organization of primate visual cortex revealed by high resolution optical imaging. *Science, 249*(4967), 417-420.

Turetsky, B. I., Cannon, T. D., & Gur, R. E. (2000). P300 subcomponent abnormalities in schizophrenia: III. Deficits In unaffected siblings of schizophrenic probands. *Biol Psychiatry, 47*(5), 380-390.

Uhlrich, D. J., Manning, K. A., & Feig, S. L. (2003). Laminar and cellular targets of individual thalamic reticular nucleus axons in the lateral geniculate nucleus in the prosimian primate Galago. *J Comp Neurol, 458*(2), 128-143.

Uusitalo, M. A., Jousmaki, V., & Hari, R. (1997). Activation trace lifetime of human cortical responses evoked by apparent visual motion. *Neurosci Lett, 224*(1), 45-48.

Vaina, L. M. (1989). Selective impairment of visual motion interpretation following lesions of the right occipito-parietal area in humans. *Biol Cybern, 61*(5), 347-359.

Van Essen, D. C., Lewis, J. W., Drury, H. A., Hadjikhani, N., Tootell, R. B., Bakircioglu, M., & Miller, M. I. (2001). Mapping visual cortex in monkeys and humans using surface-based atlases. *Vision Res, 41*(10-11), 1359-1378.

Van Oostende, S., Sunaert, S., Van Hecke, P., Marchal, G., & Orban, G. A. (1997). The kinetic occipital (KO) region in man: an fMRI study. *Cereb Cortex, 7*(7), 690-701.

Vanduffel, W., Fize, D., Mandeville, J. B., Nelissen, K., Van Hecke, P., Rosen, B. R., Tootell, R. B., & Orban, G. A. (2001). Visual motion processing investigated using contrast agent-enhanced fMRI in awake behaving monkeys. *Neuron, 32*(4), 565-577.

Waddington, J. L., & Youssef, H. A. (1996). Cognitive dysfunction in chronic schizophrenia followed prospectively over 10 years and its longitudinal relationship to the emergence of tardive dyskinesia. *Psychol Med, 26*(4), 681-688.

Walsh, V., Ellison, A., Battelli, L., & Cowey, A. (1998). Task-specific impairments and enhancements induced by magnetic stimulation of human visual area V5. *Proc R Soc Lond B Biol Sci, 265*(1395), 537-543.

Walters, N. B., Egan, G. F., Kril, J. J., Kean, M., Waley, P., Jenkinson, M., & Watson, J. D. (2003). In vivo identification of human cortical areas using high-resolution MRI: an approach to cerebral structure-function correlation. *Proc Natl Acad Sci U S A, 100*(5), 2981-2986. Epub 2003 Feb 2924.

Wang, J., Zhou, T., Qiu, M., Du, A., Cai, K., Wang, Z., Zhou, C., Meng, M., Zhuo, Y., Fan, S., & Chen, L. (1999). Relationship between ventral stream for object vision and dorsal stream for spatial vision: an fMRI + ERP study. *Hum Brain Mapp, 8*(4), 170-181.

Watson, J. D., Myers, R., Frackowiak, R. S., Hajnal, J. V., Woods, R. P., Mazziotta, J. C., Shipp, S., & Zeki, S. (1993). Area V5 of the human brain: evidence from a combined study using positron emission tomography and magnetic resonance imaging. *Cereb Cortex, 3*(2), 79-94.

Weinberger, D. R. (1999). Schizophrenia: new phenes and new genes [editorial]. *Biol Psychiatry, 46*(1), 3-7.

Weisstein, N., & Brannan, J. R. (1991). A low spatial frequency, red sine wave grating will float in front of gratings with the same or similar spatial frequency but other chromaticities: M and P interactions in figure-ground perception. *Investigative Ophthalmology and Visual Science, 32*((supp.)), 1274.

Weisstein, N., & Wong, E. (1986). Figure-ground organization and the spatial and temporal responses of the visual system. In E. C. Schwab & H. C. Nusbaum (Eds.), *Pattern Recognition by Humans and Machines* (Vol. 2, pp. 31-61): Academic Press.

Wiesel, T. N., & Hubel, D. H. (1966). Spatial and chromatic interactions in the lateral geniculate nucleus body of the rhesus monkey. *Journal of Neurophysiology, 29*, 1115-1156.

Williams, M. C., Breitmeyer, B. G., Lovegrove, W. J., & Gutierrez, C. (1991). Metacontrast with masks varying in spatial frequency and wavelength. *Vision Res, 31*(11), 2017-2023.

Wurtz, R. H., Yamasaki, D. S., Duffy, C. J., & Roy, J. P. (1990). Functional specialization for visual motion processing in primate cerebral cortex. *Cold Spring Harb Symp Quant Biol, 55*, 717-727.

Zeki, S. (1983). The distribution of wavelength and orientation selective cells in different areas of monkey visual cortex. *Proc R Soc Lond B Biol Sci, 217*(1209), 449-470.

Zeki, S., Watson, J. D., Lueck, C. J., Friston, K. J., Kennard, C., & Frackowiak, R. S. (1991). A direct demonstration of functional specialization in human visual cortex. *J Neurosci, 11*(3), 641-649.

Zeki, S. M. (1973). Colour coding in rhesus monkey prestriate cortex. *Brain Res, 53*(2), 422-427.

Zeki, S. M. (1977). Colour coding in the superior temporal sulcus of rhesus monkey visual cortex. *Proc R Soc Lond B Biol Sci, 197*(1127), 195-223.

Zeki, S. M. (1978). Uniformity and diversity of structure and function in rhesus monkey prestriate visual cortex. *J Physiol, 277*, 273-290.

Zihl, J., von Cramon, D., & Mai, N. (1983). Selective disturbance of movement vision after bilateral brain damage. *Brain, 106*(Pt 2), 313-340.

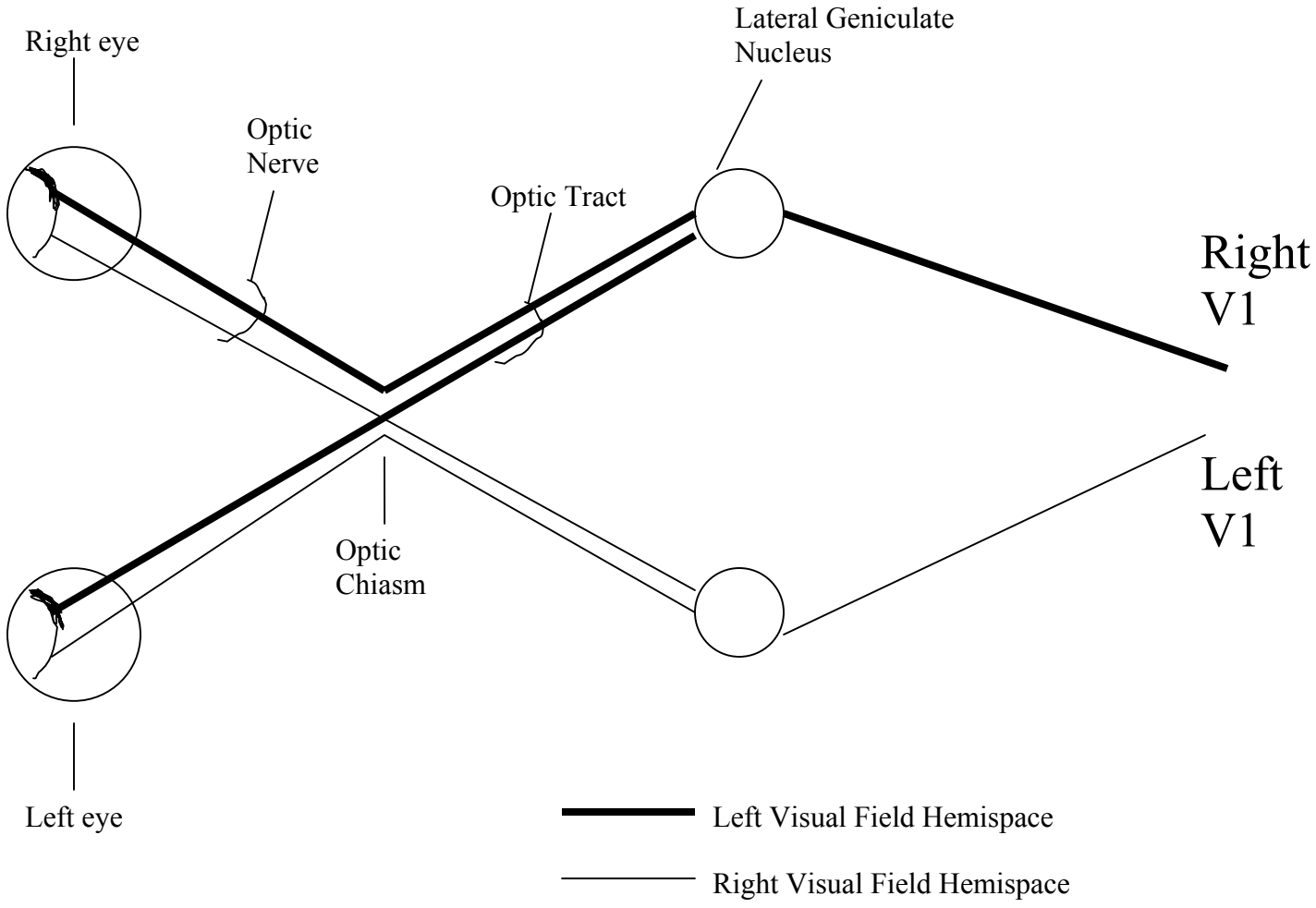

Figure 2.1. The Neural Pathways Related to Visual Field Hemispace

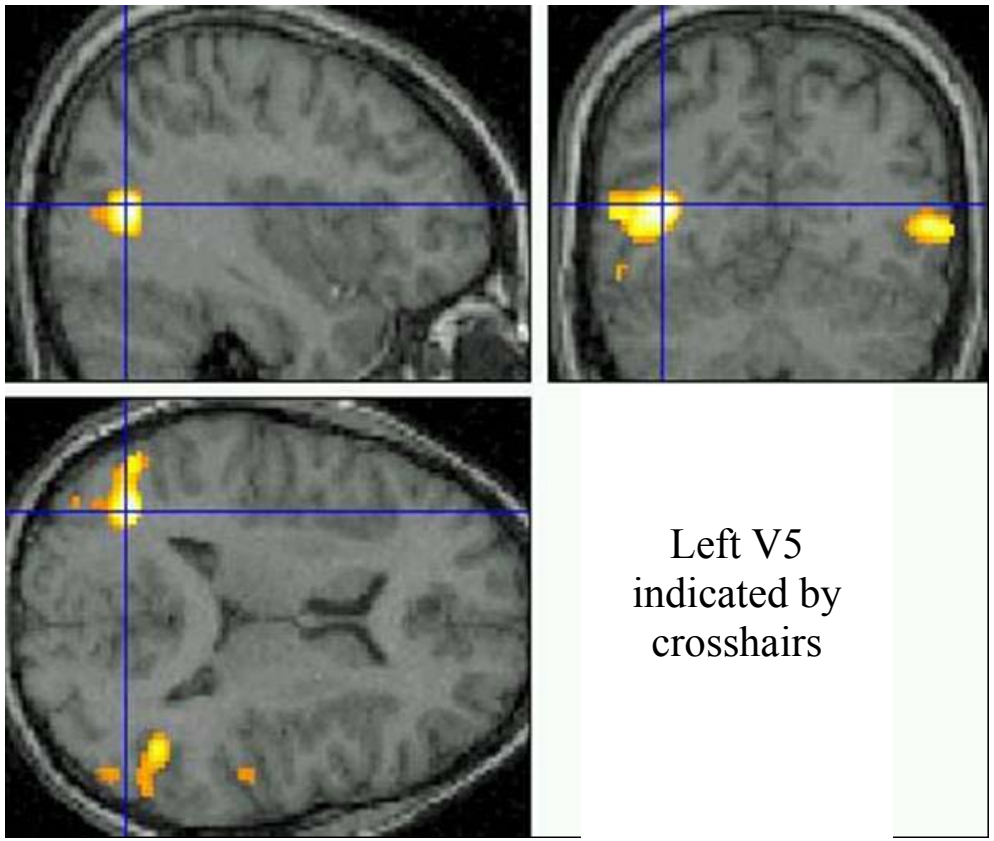

Figure 2.2. Location of V5 from Functional MRI in a Healthy Adult*

*From a control participant scanned in the current study

CHAPTER 3

PHYSIOLOGICAL EVIDENCE FOR A SUPPRESSIVE EFFECT OF RED LIGHT ON THE MAGNOCELLULAR VISUAL PATHWAY IN HEALTHY ADULTS [1]

[1] Bedwell, J.S., Miller, L.S., Brown, J.M., and Yanasak, N.E. To be submitted to *Neuroreport*.

Abstract

Previous single-cell recording research in non-human primates and psychophysical research in humans suggests that diffuse red light suppresses neural activity in the magnocellular (M) visual pathway. Functional magnetic resonance imaging (fMRI) was used to investigate the response of the M pathway in bilateral cortical region V5 (MT) to the presentation of diffuse red (relative to green) light in 11 healthy adults. A group analysis revealed a statistically-significant reduction in the fMRI signal in V5, in response to red light, which was only evident in the right hemisphere.

Introduction

Research on visual processing in humans and primates has identified two unique but interactive physiological subsystems in the visual system (Breitmeyer & Ganz, 1976; Livingstone & Hubel, 1987). The magnocellular (M) visual pathway is primarily responsible for processing location information and motion, while the parvocellular (P) visual pathway is primarily responsible for processing detail and color.

Investigation of the visual system of non-human primates has identified an anatomically and physiologically distinct region of cortex – termed V5 or MT (middle temporal area), which responds selectively to motion (an M pathway trait), as determined by single-cell recording (e.g, Albright, 1984; Baker, Petersen, Newsome, & Allman, 1981; Felleman & Kaas, 1984) and contrast-enhanced functional magnetic resonance imaging (fMRI; Vanduffel et al., 2001). Neuroimaging studies of human adults viewing moving, as opposed to stationary, stimuli provide converging evidence of a V5 homolog in humans (e.g., Ahlfors et al., 1999; Hasnain, Fox, & Woldorff, 1998; Tootell et al., 1995; Watson et al., 1993). A histological study in humans

demonstrated that the V5 region is an oval area approximately 1.2 x 2.0 cm, located 5 – 6 cm anterior and dorsal to the foveal V1-V2 border (Tootell & Taylor, 1995).

Early single-cell recording research with monkeys reported that a small portion of M pathway neurons showed tonic suppression of on-center responses when the monkey was exposed to diffuse red light. These neurons were labeled as "Type-IV" (Wiesel & Hubel, 1966) and have been reported in several locations along the M pathway, including the retinal ganglia (de Monasterio, 1978), lateral geniculate nucleus (Dreher, Fukada, & Rodieck, 1976; Kruger, 1977; Wiesel & Hubel, 1966), and striate cortex (Livingstone & Hubel, 1984). While no published physiological evidence of this phenomenon appears to exist in humans, research using psychophysical M pathway-biased tasks has inferred a similar effect in humans based on behavioral performance change in response to red light (Bedwell et al, 2003; Breitmeyer & Breier, 1994; Breitmeyer & Williams, 1990; Brown & Koch, 2000).

There is some psychophysical evidence that the right hemisphere is more involved with processing M pathway information, such as spatial relationships (Hellige, 1996; Kosslyn, Maljkovic, Hamilton, Horwitz, & Thompson, 1995; Roth & Hellige, 1998). Thus, any suppressive effect of red light may be more evident in the right hemisphere. However, recent visual half-field experiments have tested this hypothesis using psychophysical methods and concluded that red light suppressed the M pathway equally in both hemispheres (Hellige & Cumberland, 2001; Roth & Hellige, 1998). As it does not appear that any physiological research has been published examining the red light effect in humans, the question of hemispheric lateralization remains unclear.

The aims of the present study were to search for fMRI evidence for the effect of red light to suppress neural activity in cortical region V5 in humans and examine potential hemispheric

laterality differences of this effect. We hypothesized that bilateral V5 activation would be reduced with a red, compared to a green, background. It was hypothesized that this effect would be more robust in the right hemisphere.

Methods

Participants

Participants included 11 adults (mean age = 47.3 ± 12.3; range = 29 to 66; 64% female). Exclusionary criteria included: 1) past or present DSM-IV Axis I psychiatric diagnosis as determined through a SCID-I diagnostic interview (First, Spitzer, Gibbon, & Williams, 1998), with allowance for Specific Phobia; 2) current use of psychoactive medication; 3) corrected visual acuity less than 20/50; and 4) past or present history of a neurological disorder or insult. The full SCID-I diagnostic interview was completed in a previous study on the same participants, completed approximately one year prior to the current study (Bedwell et al, 2003). To assess possible changes in psychopathology over the past year, a diagnostic screen was created (see Appendix A), which was largely based on screening questions from the SCID-I. No significant change in psychopathology was noted for any participant. None of the participants met criteria for substance abuse within the past three months. All participants provided informed written consent.

Stimuli

A hardware and software package (Integrated Functional Imaging Systems, IFIS; Psychology Software Tools) was used to present the psychophysical task in the fMRI

environment. This system included a monitor placed above the head within the bore of the fMRI device for viewing visual stimuli (subtending a visual angle of 14.69º (h) x 19.22º (v))**.**

Participants were asked to maintain fixation on a small black cross located in the middle of the screen. Stimuli consisted of nine concentric black rings on either a red or green background (see Figure 3.1), with green serving as the neutral background color. The red and green backgrounds were matched for luminance (0.9 cd/m^2) using a Tektronix J17 digital photometer on the fMRI monitor. The largest ring subtended 13.09º of the visual angle, while the smallest ring subtended 1.86º. The rings were presented sequentially, creating the illusion of a single ring expanding or contracting. In this manner, the rings expanded for 3.6 sec at the rate of 5 Hz and then contracted for the same duration at the same rate. The expansion and contraction repeated three times for a total motion period of 21.6 sec. This was followed by all nine rings appearing simultaneously and remaining stationary (as in Figure 3.1) for 21.6 sec. The cycle of motion and stationary rings was repeated two times for a total block length of 86.4 sec. This block was presented multiple times over two separate, but consecutive, fMRI scanning runs, with different color backgrounds, with each run following one of two color-ordering schemes – Sequence #1: red, green, red, green; Sequence #2: green, red, green, red. The usage of a particular sequence for the first run and the remaining sequence for the subsequent run was counterbalanced between participants. Thus, the 86.4 sec. block was repeated a total of eight times, four times with each background.

Magnetic Resonance Imaging Parameters

MRI scans were acquired on a 1.5 Tesla Signa LX Horizon (General Electric, Milwaukee, WI) whole body magnetic resonance scanner configured with a GE head coil. For

fMRI imaging, a T_2-sensitive gradient recalled echo pulse sequence with spiral readout was used with the following parameters: TR = 1200 ms, TE = 40 ms, two interleaves, 77º flip angle, reconstructed matrix = 64 x 64 mm, FOV = 240 mm, slice thickness = 5 mm, zero gap. This sequence collects one of two k-space readouts for each slice of the image volume every 1.2 seconds, reading out the second interleave for every slice in the next 1.2 seconds. In this manner, a full image volume is collected in 2.4 seconds, and the signal in each slice is partially-sampled twice over this interval. Fifteen adjacent, non-oblique, axial planes of fMRI data were acquired in each image volume, broadly covering bilateral V5 regions. In each scanning run, 144 image volumes were collected at the rate of 2.4 seconds per volume. A T_1-sensitive series of 120 axial anatomical slices, covering the entire brain, were collected for subsequent spatial normalization of the fMRI images, which used the following parameters: TR = 10.8 ms, TE = 2.8 ms, one interleave, 20º flip angle, FOV = 240 mm, slice thickness = 1.3 mm, zero gap.

fMRI Data Analysis

The fMRI data were processed and analyzed using Statistical Parametric Mapping software (SPM2, Wellcome Department of Cognitive Neurology, London, UK). The SPM2 software used in this study contained in-house modifications (by N.Y.) for extracting parameters not available in the standard package (e.g, percent intensity change measure and measures averaged over a region of interest). Imaging data was pre-processed in the following manner for each participant: 1) images from the two runs, within each background color, were collapsed temporally into a single analysis (forming a continuous series of red background scans and a separate series of green background scans); 2) images were realigned to adjust for participant movement; 3) the anatomical image was spatially normalized to a T_1 template (from the

Montreal Neurological Institute; Evans et al, 1993) and resulting normalization parameters were used to transform fMRI images (resulting in 2 mm isotropic voxel size); 4) normalized fMRI images were spatially smoothed using an isotropic Gaussian kernel having a 15 mm full width at half maximum (based on the average anatomical size of V5 - Tootell and Taylor 1995); and 5) a model that defined temporal periods of moving and stationary stimuli within each color background was constructed.

Within this model, fMRI signal during moving stimuli was specified as an explicit variable, and signal during the stationary period was considered to be the baseline. A model contrast of moving vs. stationary was applied for all results in this study in order to determine brain areas more active during the period of moving stimuli than during stationary stimuli (e.g., V5). Temporal variation of the signal intensity was compared to the expected hemodynamic response functional time dependence and saved as a statistical map for each individual (within each color condition).

Area V5 was determined bilaterally on resulting statistical maps using the following two-step procedure: 1) statistically-significant voxels ($p < .05$, uncorrected for multiple comparisons) were identified within a sphere, with a radius of 18 mm, defined by a center with Talairach coordinates (Talairach & Tournoux, 1988) of x = ±40 (bilateral), y = -70, and z = 3 (average reported location of V5 from previous neuroimaging studies –Barton et al 1996; O'Driscoll et al 1999; Orban et al 1998; Tootell et al 1995; Watson et al 1993); and 2) the voxel of highest statistical significance was chosen and a new subset of statistically-significant ($p < .01$ [$t = 2.50$]; uncorrected) voxels within a sphere, with a radius of 10 mm, from this center was identified. These final two clusters of voxels (one for each side of the brain) were then considered "V5." The coordinates used to determine each 10 mm sphere from the green background condition

were used to determine the 10 mm spheres from the red background condition. Within each color condition, if a particular sphere contained no voxels that met the initial statistical threshold, the threshold was progressively lowered to $p < .05$ and, when necessary, $p < .20$. This progressive thresholding method was modeled after the method used in a V5 neuroimaging study by Watson and colleagues (1993), which allowed for detection of low levels of V5 activity in particular participants. This method resulted in a decrease in threshold (from $p < .01$) to $p < .05$ in one participant with the green background and in two participants with the red background (in each case - for only one of the bilateral V5 locations). The decrease in threshold to $p < .20$ was not necessary for any participant with the green background, but was used with one participant with the red background (for only one of the bilateral V5 locations).

For each defined V5 cluster, the cluster-averaged *t* score, cluster-averaged percent intensity change (PIC), and cluster volume (number of voxels meeting threshold of $p < .01$) were recorded. In this study, PIC is defined as the average fit signal magnitude within a cluster of voxels during the motion condition as compared to the magnitude during the stationary condition, normalized by the overall intensity of the brain volume scanned for expression in units of percent. These quantities were averaged across V5 bilaterally and also examined independently to assess proportional laterality effects. Proportional laterality for each measure was assessed by dividing the score from the right hemisphere by the sum of that measure from both hemispheres. This laterality parameter indicates what proportion of the bilaterally-summed signal resides in the right hemisphere, and hereafter this proportional laterality for a measure is referred to as the 'right hemispheric proportion' for that measure. The right hemispheric proportion for volume of activation did not follow a normal distribution and a paired Wilcoxon

Signed Ranks Test was used to examine change to red light. The remaining fMRI measures followed a normal distribution and paired *t*-tests were used to examine change to red light.

Results

The mean Talairach coordinates for V5 location with the green background were -37, -75, 5 (left) and 53, -72, 6 (right) - within the range reported by others (e.g., Hasnain et al., 1998; Watson et al., 1993). With the red background, change in location of the most significant voxel in V5 was largely insignificant, with the exception of a significant shift in the right hemisphere V5 *x*-coordinate to -2.09 ± 2.7 mm from that found with green background, $t(10) = 2.60$, $p = .03$. The reason for this lateral shift is unclear, but may reflect underlying spatial distribution of Type-IV M pathway neurons in right hemisphere V5.

Contrary to the hypothesis, group analyses of the change in bilaterally-averaged measures of V5 activity in response to red light were not statistically significant (see Table 3.1). However, group analyses of the right hemispheric proportion measures indicated a statistically significant reduction in the relative strength of the *t*-score in right hemisphere V5 in response to red light, with 9 participants showing a reduction in this measure and two showing a slight increase ($t = 2.74$, $p = .02$; see Table 3.1 and Figures 3.2 and 3.3). This right hemispheric proportion change appears to be driven unilaterally by a reduction in *t*-scores from right hemisphere V5 ($t = 1.88$, $p = .09$), as *t*-scores from left hemisphere V5 showed no indication of change in either direction ($t = 0.71$, $p = .49$). A similar statistically significant effect was present with the right hemispheric proportion for the PIC measure (see Table 3.1). However, the right hemispheric proportion for the volume measure did not show a statistically significant effect.

Discussion

Results provide physiological support for the ability of red light to suppress activity in a proportion of M pathway neurons in humans. This effect was seen in the majority of participants as a reduction in the strength of right (relative to bilateral) hemisphere V5 fMRI activation in response to red, as compared to green (neutral), light in the task background (see Figures 3.2 and 3.3). Reasons for this lateralized suppression effect in V5 in response to red light are unclear, but may relate to right hemisphere specialization for M pathway information (Hellige, 1996; Kosslyn et al., 1995; Roth & Hellige, 1998). Previous physiological studies that have documented the suppressive effect of red light on the M pathway in non-human primates did not address possible laterality differences, nor did they examine neurons in the V5 region. However, two psychophysical studies using visual half-field techniques suggested that the suppressive effect of red light was equivalent in both hemispheres (Hellige & Cumberland, 2001; Roth & Hellige, 1998). Thus, this lateralized effect may be unique to the V5 region of the M pathway. Future research using a variety of physiological methods to examine various locations along the M pathway will be needed to adequately address this finding.

The luminance of the colored backgrounds in the current study was relatively low, in the mesopic range, at 0.9 cd/m^2. It is possible that stronger luminance levels of red light would produce a stronger and more consistent suppressive effect on the M pathway across participants. The study is additionally limited by a relatively small sample size (N = 11). Thus, results should be considered preliminary.

The current study expands and validates previous psychophysical research in humans suggesting a suppressive effect of red light on the M pathway by providing physiological evidence of this effect. Thus, humans may have a population of neurons in the M pathway,

similar to Type-IV neurons reported in non-human primates, which have an inhibitory surround field that is selective for long-wavelength (red) light. Apparent differential M pathway response to red light has been useful in distinguishing individuals genetically at-risk for schizophrenia (Bedwell et al., 2003). Therefore, further understanding of this phenomenon in healthy individuals will contribute to the application of this technique in understanding a hypothesized M pathway disturbance in schizophrenia.

References:

Ahlfors, S. P., Simpson, G. V., Dale, A. M., Belliveau, J. W., Liu, A. K., Korvenoja, A., Virtanen, J., Huotilainen, M., Tootell, R. B., Aronen, H. J., & Ilmoniemi, R. J. (1999). Spatiotemporal activity of a cortical network for processing visual motion revealed by MEG and fMRI. *J Neurophysiol, 82*(5), 2545-2555.

Albright, T. D. (1984). Direction and orientation selectivity of neurons in visual area MT of the macaque. *J Neurophysiol, 52*(6), 1106-1130.

Baker, J. F., Petersen, S. E., Newsome, W. T., & Allman, J. M. (1981). Visual response properties of neurons in four extrastriate visual areas of the owl monkey (Aotus trivirgatus): a quantitative comparison of medial, dorsomedial, dorsolateral, and middle temporal areas. *J Neurophysiol, 45*(3), 397-416.

Barton, J. J., Simpson, T., Kiriakopoulos, E., Stewart, C., Crawley, A., Guthrie, B., Wood, M., & Mikulis, D. (1996). Functional MRI of lateral occipitotemporal cortex during pursuit and motion perception. *Ann Neurol, 40*(3), 387-398.

Bedwell, J. S., Brown, J. M., & Miller, L. S. (2003). The magnocellular visual system and schizophrenia: what can the color red tell us? *Schizophrenia Research, 63*(3), 273-284.

Breitmeyer, B. G., & Breier, J. I. (1994). Effects of background color on reaction time to stimuli varying in size and contrast: inferences about human M channels. *Vision Res, 34*(8), 1039-1045.

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

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

Brown, J. M., & Koch, C. (2000). Influences of occlusion, color, and luminance on the perception of fragmented pictures. *Percept Mot Skills, 90*(3 Pt 1), 1033-1044.

de Monasterio, F. M. (1978). Properties of concentrically organized X and Y ganglion cells of macaque retina. *J Neurophysiol, 41*(6), 1394-1417.

Dreher, B., Fukada, Y., & Rodieck, R. W. (1976). Identification, classification and anatomical segregation of cells with X-like and Y-like properties in the lateral geniculate nucleus of old-world primates. *J Physiol, 258*(2), 433-452.

Felleman, D. J., & Kaas, J. H. (1984). Receptive-field properties of neurons in middle temporal visual area (MT) of owl monkeys. *J Neurophysiol, 52*(3), 488-513.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (1998). *Structured Clinical Interview for DSM-IV Axis I Disorders - Non-patient Edition (SCID-I/NP Version 2.0)*. New York: Biometrics Research Department.

Hasnain, M. K., Fox, P. T., & Woldorff, M. G. (1998). Intersubject variability of functional areas in the human visual cortex. *Hum Brain Mapp, 6*(4), 301-315.

Hellige, J. B. (1996). Hemispheric asymmetry for visual information processing. *Acta Neurobiol Exp (Wars), 56*(1), 485-497.

Hellige, J. B., & Cumberland, N. (2001). Categorical and coordinate spatial processing: more on contributions of the transient/magnocellular visual system. *Brain Cogn, 45*(2), 155-163.

Kosslyn, S. M., Maljkovic, V., Hamilton, S. E., Horwitz, G., & Thompson, W. L. (1995). Two types of image generation: evidence for left and right hemisphere processes. *Neuropsychologia, 33*(11), 1485-1510.

Kruger, J. (1977). Stimulus dependent colour specificity of monkey lateral geniculate neurones. *Exp Brain Res, 30*(2-3), 297-311.

Livingstone, M. S., & Hubel, D. H. (1984). Anatomy and physiology of a color system in the primate visual cortex. *J Neurosci, 4*(1), 309-356.

Livingstone, M. S., & Hubel, D. H. (1987). Psychophysical evidence for separate channels for the perception of form, color, movement, and depth. *J Neurosci, 7*(11), 3416-3468.

O'Driscoll, G. A., Benkelfat, C., Florencio, P. S., Wolff, A. L., Joober, R., Lal, S., & Evans, A. C. (1999). Neural correlates of eye tracking deficits in first-degree relatives of schizophrenic patients: a positron emission tomography study. *Arch Gen Psychiatry, 56*(12), 1127-1134.

Orban, G. A., Dupont, P., De Bruyn, B., Vandenberghe, R., Rosier, A., & Mortelmans, L. (1998). Human brain activity related to speed discrimination tasks. *Exp Brain Res, 122*(1), 9-22.

Roth, E. C., & Hellige, J. B. (1998). Spatial processing and hemispheric asymmetry. Contributions of the transient/magnocellular visual system. *J Cogn Neurosci, 10*(4), 472-484.

Talairach, J., & Tournoux, P. (1988). *Co-planar stereotaxic atlas of the human brain.* Stuttgart: Georg Thieme Verlag.

Tootell, R. B., Reppas, J. B., Kwong, K. K., Malach, R., Born, R. T., Brady, T. J., Rosen, B. R., & Belliveau, J. W. (1995). Functional analysis of human MT and related visual cortical areas using magnetic resonance imaging. *J Neurosci, 15*(4), 3215-3230.

Tootell, R. B., & Taylor, J. B. (1995). Anatomical evidence for MT and additional cortical visual areas in humans. *Cereb Cortex, 5*(1), 39-55.

Vanduffel, W., Fize, D., Mandeville, J. B., Nelissen, K., Van Hecke, P., Rosen, B. R., Tootell, R. B., & Orban, G. A. (2001). Visual motion processing investigated using contrast agent-enhanced fMRI in awake behaving monkeys. *Neuron, 32*(4), 565-577.

Watson, J. D., Myers, R., Frackowiak, R. S., Hajnal, J. V., Woods, R. P., Mazziotta, J. C., Shipp, S., & Zeki, S. (1993). Area V5 of the human brain: evidence from a combined study using positron emission tomography and magnetic resonance imaging. *Cereb Cortex, 3*(2), 79-94.

Wiesel, T. N., & Hubel, D. H. (1966). Spatial and chromatic interactions in the lateral geniculate nucleus body of the rhesus monkey. *Journal of Neurophysiology, 29*, 1115-1156.

Table 3.1. Change in fMRI measures in response to red light.

Measure	**Green Background**	**Red Background**	**Statistic**	***p***
Bilateral *t* score	4.45 ± 1.45	3.98 ± 1.18	$t = 1.36$	0.20
Bilateral PIC[1] score	0.62 ± 0.18	0.61 ± 0.21	$t = 0.22$	0.83
Bilateral Volume[2]	720 ± 234	629 ± 326	$t = 0.95$	0.37
Right hemispheric proportion[3] for *t* score	48.7% ± 4.65	45.3% ± 5.02	$t = 2.74$	0.02 *
Right hemispheric proportion[3] for PIC	49.6% ± 6.72	45.9% ± 7.07	$t = 2.41$	0.04 *
Right hemispheric proportion[3] for volume	45.3% ± 18.7	42.6% ± 14.6	$Z = 0.36$	0.72

[1] PIC = Percent intensity change in fMRI signal

[2] Volume = Number of contiguous activated 2 x 2 x 2 mm voxels (size of voxels after normalization procedure)

[3] Right hemispheric proportion = value in right hemisphere divided by sum of values from both hemispheres

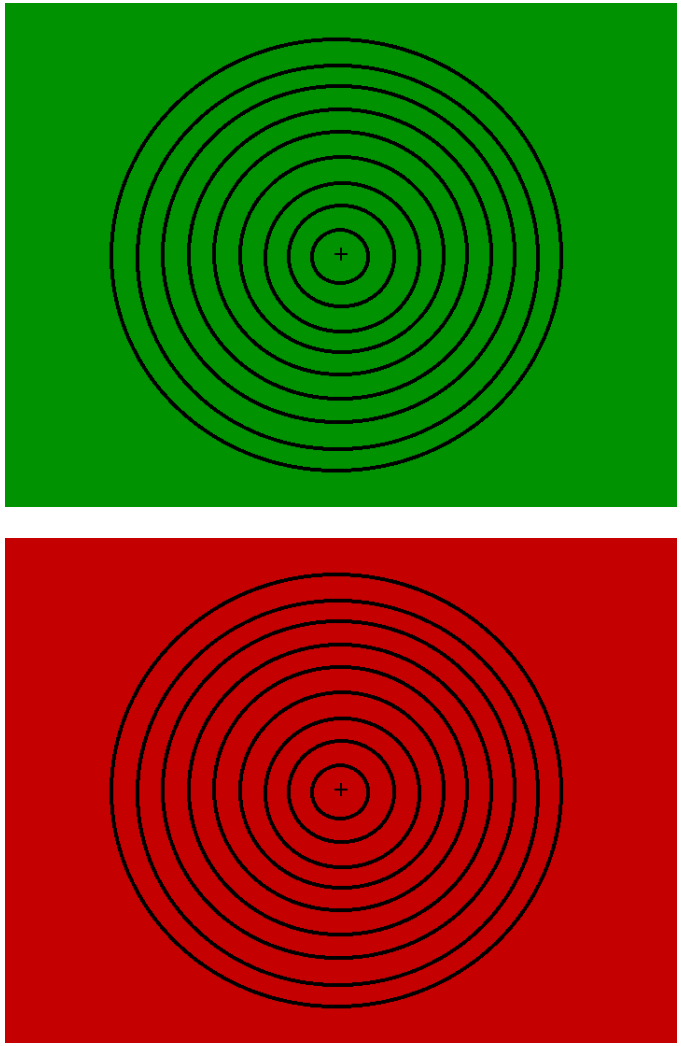

Figure 3.1. Example stationary stimulus on the green and red backgrounds.

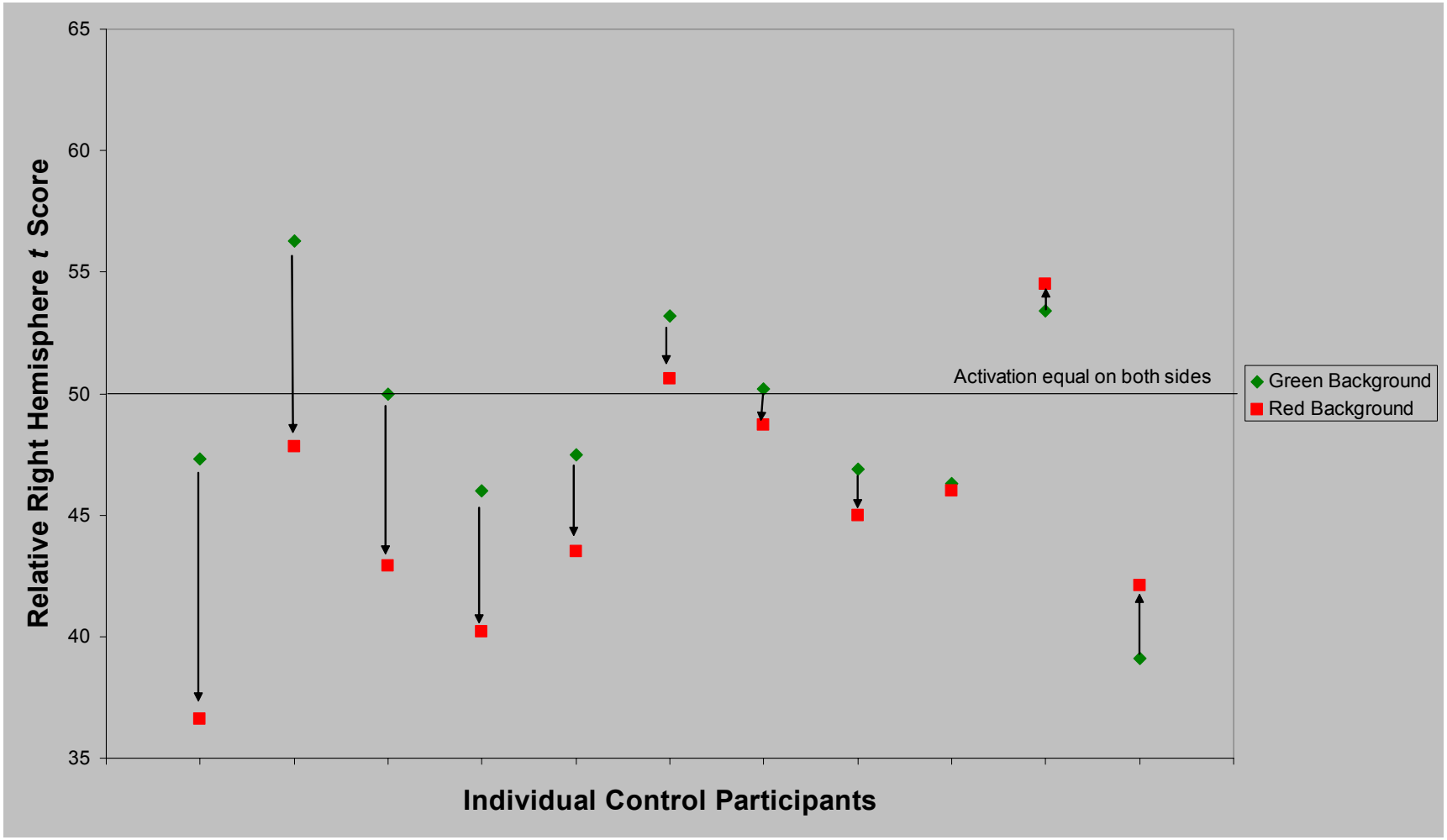

Figure 3.2. Change in relative right hemisphere V5 fMRI *t* score in response to red light by participant.

Paired $t = 2.74$, $p = .02$.

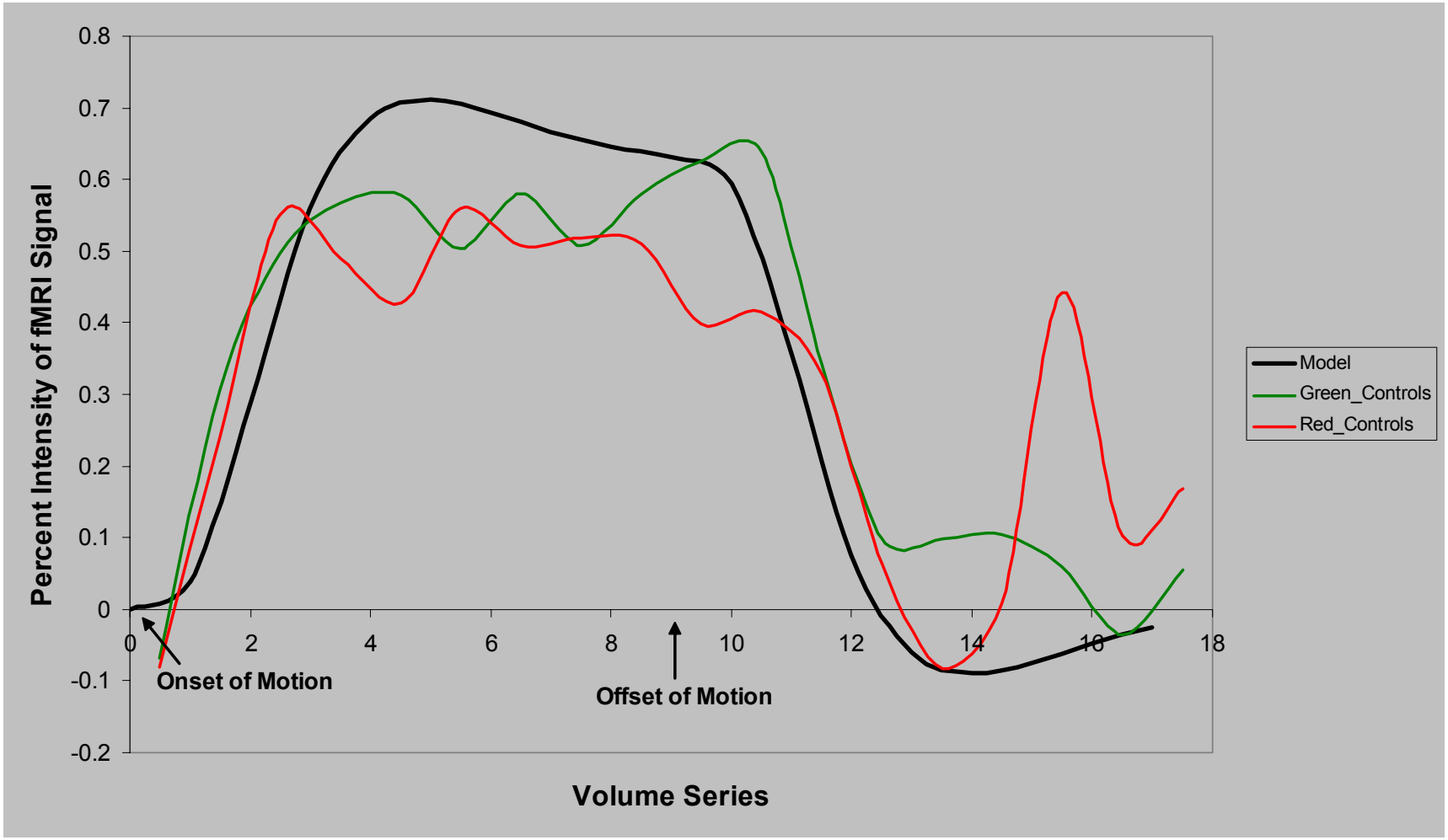

Figure 3.3. Averaged[1] volume series of fMRI signal in right hemisphere V5 in response to motion and color of background.

[1] Volume series represents average over all epochs (each time moving and stationary stimuli occurred) across all participants. Each volume represents 2.4 sec. of scanning time. Epochs 4 and 5, which occurred at the end of the first fMRI run and the beginning of the second run, were not included in this average. The concatenation of the two fMRI scanning runs into one analysis creates a small, artificial distortion in this figure of the first and last few points of the time course.

CHAPTER 4

FUNCTIONAL MAGNETIC RESONANCE IMAGING EXAMINATION OF THE MAGNOCELLULAR VISUAL PATHWAY IN NONPSYCHOTIC RELATIVES OF PERSONS WITH SCHIZOPHRENIA [1]

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[1] Bedwell, J.S., Miller, L.S., Brown, J.M., McDowell, J.E., and Yanasak, N.E. Submitted to *Schizophrenia Research*.

Abstract

Previous psychophysical research has suggested impaired visual processing related to genetic risk for schizophrenia that appears specific to the magnocellular (M) visual pathway. A few studies using physiological methods have examined persons with schizophrenia and reported evidence for a hypoactive M pathway. However, it does not appear that any published study has used physiological methods to examine the M pathway in relatives of persons with schizophrenia to help determine if this dysfunction is related to genetic risk for the disorder. Functional magnetic resonance imaging (fMRI) was used to examine 13 nonpsychotic first-degree relatives of persons with schizophrenia and 11 controls. Moving and stationary concentric rings were presented in a blocked format to stimulate the M pathway. The fMRI signal strength in bilateral cortical region V5 (MT) was measured as a marker of M pathway functioning. The relatives did not differ from controls in fMRI measures of V5 signal strength when this signal was averaged from the two hemispheres. However, when lateralized effects were examined, the relatives showed weaker fMRI signal strength in only the right hemisphere V5 (Mann-Whitney $U = 38.0$, $p = .05$). Results are consistent with previous physiological reports of a hypoactive M pathway in schizophrenia, but extend findings to provide physiological evidence of a similar deficit in first-degree relatives. The present study found that V5 was hypoactive only in the right hemisphere in this group of relatives.

Introduction

Research on visual processing in humans and primates has identified two unique but interactive physiological subsystems in the visual system (Breitmeyer and Ganz, 1976; Livingstone and Hubel, 1987). The magnocellular (M) visual pathway is primarily responsible

for processing location information and motion, while the parvocellular (P) visual pathway is primarily responsible for processing detail and color.

Psychophysical investigations of these pathways in persons with schizophrenia have revealed that the M pathway appears dysfunctional, as these individuals show impaired performance on tasks of motion perception (Brenner et al., 2003; Chen et al., 1999a; Chen et al., 1999b; Stuve et al., 1997), visual backward masking (Butler et al., 1996, 2003; Cadenhead et al., 1998; Green et al., 1994a, 1994b, 1999, 2003; Rund, 1993; Saccuzzo et al., 1996; Schechter et al., 2003), and spatial localization (Cadenhead et al., 1998; O'Donnell et al., 1996). Persons with schizophrenia have also shown deficits on smooth-pursuit eye tracking tasks (for review, see Holzman, 2000). As the M pathway is required for proper control of eye movements (Page et al., 1994; Schiller and Lee, 1994), deficits on eye movement tasks may be secondary to a primary deficit specific to the M pathway. In contrast to the M pathway, the P pathway appears relatively intact in persons with schizophrenia, as research has found no evidence of impairment in discrimination of stationary high spatial frequencies and patterns (O'Donnell et al., 1996; Schwartz et al., 1987).

Examining nonpsychotic first-degree relatives of persons with schizophrenia is advantageous because unique characteristics found in these individuals may offer insight into genetic expression of schizophrenia without confounds such as neuroleptic exposure, chronic hospitalization, or active symptom effects (Adler et al., 1999; Weinberger, 1999). Several markers of M pathway dysfunction in first-degree relatives have been reported, which include irregularities in motion sensitivity (Chen et al., 1999a), visual backward masking (Green et al., 1997; Keri et al., 2001), smooth-pursuit eye tracking (Holzman, 2000), and change in backward

masking accuracy in response to diffuse red light (Bedwell et al., 2003), supporting M pathway dysfunction as a potential genetic marker for schizophrenia.

Only a few studies have used physiological methods to specifically examine M pathway functioning in persons with schizophrenia. Three studies used electroencephalography (EEG) and reported reduced amplitude of signal in posterior cortical regions along the M pathway in persons with schizophrenia, with relatively normal activation along brain regions in the P pathway (Butler et al., 2001; Doniger et al., 2002; Foxe et al., 2001). One study used functional magnetic resonance imaging (fMRI) and reported relative hypoactivation of the M pathway (particularly in the right hemisphere) in persons with schizophrenia, but found no evidence of abnormal functioning in the P pathway (Braus et al., 2002). Another study used fMRI to examine brain responses in response to smooth pursuit eye tracking in first-degree relatives of persons with schizophrenia, which included areas of the M pathway (O'Driscoll et al., 1999). However, this paper did not statistically examine differences in the strength of the M pathway response between the relatives and controls.

Thus, psychophysical and physiological studies provide converging evidence of M pathway dysfunction in persons with schizophrenia, with most evidence suggesting normal P pathway functioning. Psychophysical evidence has extended this M pathway dysfunction to first-degree relatives, but related physiological studies have not been adequately addressed in relatives. The current study uses fMRI to examine M pathway functioning in a group of first-degree relatives, as compared to healthy controls. Cortical localization of the M pathway was assessed by targeting a specific region of cortex (V5), which is well established as a primary center along the M pathway (Ahlfors et al., 1999; Hasnain et al., 1998; Tootell et al., 1995a; Watson et al., 1993). It was hypothesized that a subset of the relatives would show evidence of a

hypoactive M pathway, as evidenced by a reduced fMRI signal in cortical region V5 compared to controls, with a possible exaggeration of this deficit in the right hemisphere (as suggested by previous research).

Methods and Materials

Participants

Thirteen nonpsychotic first-degree relatives of persons with schizophrenia and 11 controls were recruited from a larger sample previously reported in an earlier study (Bedwell et al., 2003). Participants in the relatives group included: 9 full-siblings, 2 biological parents, and 2 biological children. Five of the siblings were related to the same proband, while the remaining relatives were each related to unique probands. Participant demographics are listed in Table 4.1. While the groups were well-matched on age, visual acuity, and gender; the relatives had significantly lower socioeconomic status, more individuals from a racial minority group, and a statistical trend for a lower IQ. However, the average estimated Full Scale IQ for the relatives group was 96, within the average range of functioning.

First-degree relatives of persons with schizophrenia were recruited from a community mental health center through within-agency requests to patients. A clear diagnosis of DSM-IV (American Psychiatric Association, 1994) schizophrenia was confirmed in all probands by a staff psychiatrist after thorough chart review of existing schizophrenia patients in the clinic. Healthy controls were recruited from the local community using a cable television advertisement and printed advertisements placed throughout the community. All participants in the study were asked to read and sign a consent form after the procedures had been fully explained.

Exclusionary criteria for the control group included: 1) past or present DSM-IV Axis I psychiatric diagnosis as determined through a SCID-I diagnostic interview (First et al., 1998), with allowance for Specific Phobia; 2) current use of psychoactive medication; 3) corrected visual acuity less than 20/50; 4) past or present history of a neurological disorder or insult; 5) presence of schizotypal or paranoid personality disorder, as determined by SCID-II diagnostic interview (First et al., 1997); and 6) self-reported biological relation (however distant) to a person with probable psychosis. None of the controls met criteria for substance abuse within the past three months.

Exclusionary criteria for the relatives group included: 1) history of mania or psychotic disorder as determined through a SCID-I diagnostic interview; 2) corrected visual acuity less than 20/50; and 3) history of a neurological disorder or insult. The exclusionary criteria for the relative group were more liberal, as schizophrenia-related genes may increase the likelihood of other psychopathology (Johnstone et al., 2002), and the goal of this study was to examine persons with such genes in the absence of schizophrenia. The resulting group of relatives included one person with Major Depressive Disorder, Recurrent and one person with Dysthymic Disorder. Two of the relatives were taking antidepressants at the time of the study. None of the relatives met criteria for substance abuse within the past three months.

The full SCID-I diagnostic interview was completed in a previous study on the same participants, completed approximately one year prior to the current study (Bedwell et al, 2003). To assess possible changes in psychopathology over the past year, a diagnostic screen was created (see Appendix A), which was largely based on screening questions from the SCID-I. No significant change in psychopathology was noted for any participant.

Stimuli

A hardware and software package (Integrated Functional Imaging Systems, IFIS; Psychology Software Tools) was used to present the psychophysical task in the fMRI environment. This system included a monitor placed above the head within the bore of the fMRI device for viewing visual stimuli (subtending a visual angle of 14.69º (h) x 19.22º (v))**.**

Participants were asked to maintain fixation on a small cross located in the middle of the screen. Stimuli consisted of nine concentric black rings on a green background (see Figure 4.1). The largest ring subtended 13.09º of the visual angle, while the smallest ring subtended 1.86º. The rings were presented sequentially, creating the illusion of a single ring expanding or contracting. In this manner, the rings expanded for 3.6 sec at the rate of 5 Hz and then contracted for the same duration at the same rate. The expansion and contraction repeated three times for a total motion period of 21.6 sec. This was followed by all nine rings appearing simultaneously and remaining stationary (as in Figure 4.1) for 21.6 sec. The cycle of motion and stationary rings was repeated two times for a total block length of 86.4 sec. This block was presented eight times over two separate fMRI scanning runs, with different color backgrounds, in the order – Sequence #1: red, green, red, green; Sequence #2: green, red, green, red (order counterbalanced between participants). Thus, the 86.4 second block was repeated a total of four times with the green background. Scans from the red background were not included in the present study.

Magnetic Resonance Imaging Parameters

MRI scans were acquired on a 1.5 Tesla Signa LX Horizon (General Electric, Milwaukee, WI) whole body magnetic resonance scanner configured with a GE head coil. For

fMRI imaging, a T_2-sensitive gradient recalled echo pulse sequence with spiral readout was used with the following parameters: TR = 1200 ms, TE = 40 ms, two interleaves, 77º flip angle, reconstructed matrix = 64 x 64 mm, FOV = 240 mm, slice thickness = 5 mm, zero gap. This sequence collects one of two k-space readouts for each slice of the image volume every 1.2 seconds, reading out the second interleave for every slice in the next 1.2 seconds. In this manner, a full image volume is collected in 2.4 seconds, and the signal in each slice is partially-sampled twice over this interval. Fifteen adjacent, non-oblique, axial planes of fMRI data were acquired in each image volume, broadly covering bilateral V5 regions. In each scanning run, 144 image volumes were collected at the rate of 2.4 seconds per volume. A T_1-sensitive series of 120 axial anatomical slices, covering the entire brain, were collected for subsequent spatial normalization of the fMRI images, which used the following parameters: TR = 10.8 ms, TE = 2.8 ms, one interleave, 20º flip angle, FOV = 240 mm, slice thickness = 1.3 mm, zero gap.

fMRI Data Analysis

The fMRI data were processed and analyzed using Statistical Parametric Mapping software (SPM2, Wellcome Department of Cognitive Neurology, London, UK). The SPM2 software used in this study contained in-house modifications (by N.Y.) for extracting parameters not available in the standard package (e.g, percent intensity change measure and measures averaged over a region of interest). Imaging data was pre-processed in the following manner for each participant: 1) images from the two runs acquired during the green background condition were collapsed temporally into a single analysis; 2) images were realigned to adjust for participant movement; 3) the anatomical image was spatially normalized to a T_1 template (from the Montreal Neurological Institute; Evans et al, 1993) and resulting normalization parameters

were used to transform fMRI images (resulting in 2 mm isotropic voxel size); 4) normalized fMRI images were spatially smoothed using an isotropic Gaussian kernel having a 15 mm full width at half maximum (based on the average anatomical size of V5 - (Tootell and Taylor, 1995b); and 5) a model that defined temporal periods of moving and stationary stimuli was constructed.

Within this model, fMRI signal during moving stimuli was specified as an explicit variable, and signal during the stationary period was considered to be the baseline. A model contrast of moving vs. stationary was applied for all results in this study in order to determine brain regions more active during the period of moving stimuli than during stationary stimuli (e.g., V5). Temporal variation of the signal intensity was compared to the expected hemodynamic response functional time dependence and saved as a statistical map for each individual.

Area V5 was determined bilaterally on resulting statistical maps using the following two-step procedure: 1) statistically-significant voxels ($p < .05$, uncorrected for multiple comparisons) were identified within a sphere, with a radius of 18 mm, defined by a center with Talairach coordinates (Talairach and Tournoux, 1988) of x = ±40 (bilateral), y = -70, and z = 3 (average reported location of V5 from previous neuroimaging studies – (Barton et al., 1996; O'Driscoll et al., 1999; Orban et al., 1998; Tootell et al., 1995a; Watson et al., 1993); and 2) the voxel of highest statistical significance was chosen and a new subset of statistically-significant ($p < .01$ [$t = 2.50$]; uncorrected) voxels within a sphere, with a radius of 10 mm, from this center was identified. These final two clusters of voxels (one for each side of the brain) were then considered "V5." If a particular sphere contained no voxels that met the initial statistical threshold, the threshold was lowered to $p < .05$. This progressive thresholding method was

modeled after the method used in a V5 neuroimaging study by Watson and colleagues (1993), which allowed for detection of low levels of V5 activity in particular participants. This method resulted in a decrease in threshold (from $p < .01$) to $p < .05$ in one control and three relatives (in each case - for only one of the bilateral V5 locations).

For each defined V5 cluster, the cluster-averaged *t* score, cluster-averaged percent intensity change (PIC), and cluster volume (number of voxels meeting threshold of $p < .01$) were recorded. In this study, PIC is defined as the average fit signal magnitude within a cluster of voxels during the motion condition as compared to the magnitude during the stationary condition, normalized by the overall intensity of the brain volume scanned for expression in units of percent. These quantities were averaged across V5 bilaterally and also examined independently to assess proportional laterality effects. Proportional laterality for each measure was assessed by dividing the score from the right hemisphere by the sum of that measure from both hemispheres. This laterality parameter indicates what proportion of the bilaterally-summed signal resides in the right hemisphere, and hereafter this proportional laterality for a measure is referred to as the 'right hemispheric proportion' for that measure. Scores from the bilateral PIC score measure and right hemispheric proportion for the *t* score measure followed a normal distribution within each group, so a *t* test was used to compare the two groups on these measures. The remaining scores did not follow a normal distribution, so a Mann-Whitney *U* test was used to compare the groups on these measures.

Results

All participants in both groups showed activation in bilateral V5 (a primary center along M pathway) in response to the moving concentric rings. The mean Talairach coordinates for the

location of the most statistically significant voxel in the V5 cortical region in both the control (-37, -75, 5 [left] and 53, -72, 6 [right]) and relatives group (-39, -73, -1 [left] and 47, -72, 6 [right]) were within the range reported by others (Hasnain et al., 1998; O'Driscoll et al., 1999; Watson et al., 1993). However, the groups showed a statistically significant difference in the right *x*-coordinate (with relatives showing a more medial location; $t(22) = 2.44$, $p = .02$) and in the left *z*-coordinate (with relatives showing a more inferior location; $t(22) = 2.05$, $p = .05$).

Relatives did not differ from controls on any fMRI measure of inferred M pathway activation in cortical region V5 when activation from the two hemispheres was averaged together (see Table 4.2). However, when the right hemispheric proportion for the PIC in V5 was examined, the relatives showed reduced activation (45.8 ± 8.81%), compared to controls (50.0 ± 6.72%), Mann-Whitney $U(22) = 38.0$, $p = .05$ (see Table 4.2 and Figure 4.2). This proportional lateralized effect appears to be driven by a statistical trend toward reduction in PIC in right hemisphere (non-proportional) V5 in the relatives, $t(22) = 1.71$, $p = .10$, as the PIC measure from left hemisphere (non-proportional) V5 showed no suggestion of difference between the groups, $t(22) = 0.49$, $p = .63$. The groups did not differ significantly on the remaining right hemispheric proportion measures (see Table 4.2).

Discussion

Results from the present study are consistent with reports by others of physiological evidence for a hypoactive M pathway in persons with schizophrenia (Braus et al., 2002; Butler et al., 2001; Doniger et al., 2002; Foxe et al., 2001), although the current findings are specific to a group of first-degree relatives. The appearance of this feature in first-degree relatives suggests that a hypoactive M pathway is related to genetic risk for schizophrenia rather than secondary to

confounds such as neuroleptic exposure or active symptom effects. The current study focuses on a specific cortical region (V5) that is well-defined in basic vision research to be a primary center of the M pathway. The Talairach coordinates of V5 found in the present study for both groups were within the range reported by previous neuroimaging studies (which demonstrate that this region can vary in location by as much as 27 mm in healthy adults – e.g., Watson et al., 1993). However, the relatives showed specific differences in the location of the most statistically significant voxel in the V5 region, as compared to controls. The reason for this difference is unclear and needs further replication.

The present study found that the hypoactivity in the M pathway (V5) appears to be specific to the right hemisphere. This is consistent with a previous neuroimaging study, which reported that hypoactivity related to M pathway stimulation was more apparent in the right hemisphere in persons with schizophrenia (Braus et al., 2002). However, this previous report needs to be interpreted with caution, as both auditory and visual stimuli were presented simultaneously in this study – limiting interpretation of brain activity specific to M pathway (visual) stimulation. Another previous fMRI study reported V5 activity in a group of first-degree relatives compared to controls during a smooth-pursuit eye tracking task (O'Driscoll et al., 1999). While this paper did not statistically compare the groups on the strength of activation in V5, examination of z-scores in the tables indicates possible V5 (M pathway) hypoactivity in the relatives, specifically in the right hemisphere. Previous EEG studies reporting reduced signal amplitude in the M pathway in persons with schizophrenia did not appear to examine potential laterality effects (Butler et al., 2001; Doniger et al., 2002; Foxe et al., 2001).

The groups did not differ in gross visual acuity (see Table 4.1), making it unlikely that reduced visual acuity in the relatives could account for reduced right hemispheric proportion of

V5 activation in the relatives. Similarly, as both groups showed robust left hemisphere V5 activation, it is unlikely that the reduced right hemispheric proportion of V5 activation in the relatives is secondary to gross inattention to the visual stimuli. Therefore, the reduced right hemispheric proportion of activation in cortical region V5 likely represents altered magnocellular visual pathway functioning related to genetic risk for schizophrenia – consistent with previous psychophysical and physiological studies.

In the present study, the five relatives with the lowest PIC from right hemisphere V5 were siblings related to the same proband. When the average of this measure from these five siblings was used in place of the individual values in the group analysis, there was no longer a statistically significant difference between the groups on this measure ($U = 35.0$, $p = .27$). This loss of statistical significance may in part be a consequence of loss of statistical power, as the relatives group was reduced from an already small sample size (N = 13), to a sample size of 9, when these five siblings were collapsed into a single average. However, this may also reflect a differential impact of genes present in this particular family that may or may not be related to schizophrenia. Therefore, it will be important to replicate the primary findings of this report in a new sample of relatives for validation.

Of the three fMRI measures examined, only percent intensity change (PIC) showed a significant group difference. This measure primarily reflects the magnitude of the neural response and is relatively insensitive to error from temporal fit to the predefined model, compared to the *t* score measure. Thus, as only the PIC measure showed a statistically significant group difference, it is possible that groups differed in both magnitude of neural response (source of signal in *t* score) and speed of onset and offset of this response (source of error in *t* score). Visual inspection of the right hemisphere V5 response in Figure 4.3 reveals that

the magnitude of the signal appeared to be suppressed in the relatives group. However, the question of a differential group time course is difficult to address. Because our MRI protocol used the in-slice interleaving scheme as discussed in the methodology section above, each data point in the response curve is sampled twice over a 2.4 second interval. The resulting effect of this protocol is a slight decrease of the apparent response time and a slight smoothing of the sharpness of the leading and trailing edges of the block response. Thus, a detailed comparison in the temporal course of fMRI signal between groups in this study is not straightforward.

Despite its limitations, the current study supports the hypothesis that a hypoactive M visual pathway, particularly in right hemisphere V5, is related to genetic risk for schizophrenia by providing evidence of this effect in nonpsychotic first-degree relatives. Future studies are needed to replicate this finding in larger samples of first-degree relatives and in persons with schizophrenia prior to neuroleptic exposure. In addition, future studies are needed to further examine potential laterality effects, relation of neural abnormality to behavioral performance, and possible abnormalities in the speed of the M pathway response, as related to genetic risk for schizophrenia.

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References

Adler, L.E., Freedman, R., Ross, R.G., Olincy, A.,Waldo, M.C., 1999. Elementary phenotypes in the neurobiological and genetic study of schizophrenia. Biol. Psychiatry 46**,** 8-18.

Ahlfors, S.P., Simpson, G.V., Dale, A.M., Belliveau, J.W., Liu, A.K., Korvenoja, A., Virtanen, J., Huotilainen, M., Tootell, R.B., Aronen, H.J.,Ilmoniemi, R.J., 1999. Spatiotemporal activity of a cortical network for processing visual motion revealed by MEG and fMRI. J. Neurophysiol. 82**,** 2545-2555.

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders, 4th Edition. American Psychiatric Association, Washington, DC.

Barton, J.J., Simpson, T., Kiriakopoulos, E., Stewart, C., Crawley, A., Guthrie, B., Wood, M.,Mikulis, D., 1996. Functional MRI of lateral occipitotemporal cortex during pursuit and motion perception. Ann. Neurol. 40**,** 387-398.

Bedwell, J.S., Brown, J.M.,Miller, L.S., 2003. The magnocellular visual system and schizophrenia: what can the color red tell us? Schizophr. Res. 63**,** 273-284.

Braus, D.F., Weber-Fahr, W., Tost, H., Ruf, M.,Henn, F.A., 2002. Sensory information processing in neuroleptic-naive first-episode schizophrenic patients: a functional magnetic resonance imaging study. Arch. Gen. Psychiatry 59**,** 696-701.

Breitmeyer, B.G.,Ganz, L., 1976. Implications of sustained and transient channels for theories of visual pattern masking, saccadic suppression, and information processing. Psychol. Rev. 83**,** 1-36.

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

Butler, P.D., DeSanti, L.A., Maddox, J., Harkavy-Friedman, J.M., Amador, X.F., Goetz, R.R., Javitt, D.C.,Gorman, J.M., 2003. Visual backward-masking deficits in schizophrenia: relationship to visual pathway function and symptomatology. Schizophr. Res. 59**,** 199-209.

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

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

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

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

Chen, Y., Palafox, G.P., Nakayama, K., Levy, D.L., Matthysse, S.,Holzman, P.S., 1999b. Motion perception in schizophrenia. Arch. Gen. Psychiatry 56**,** 149-154.

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

First, M.B., Gibbon, M., Spitzer, R.L., Williams, J.B.W.,Benjamin, L.S., 1997. Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II). American Psychiatric Press, Washington, DC.

First, M.B., Spitzer, R.L., Gibbon, M.,Williams, J.B.W., 1998. Structured Clinical Interview for DSM-IV Axis I Disorders - Non-patient Edition (SCID-I/NP Version 2.0). Biometrics Research Department, New York.

Foxe, J.J., Doniger, G.M.,Javitt, D.C., 2001. Early visual processing deficits in schizophrenia: impaired P1 generation revealed by high-density electrical mapping. Neuroreport 12**,** 3815-3820.

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

Green, M.F., Nuechterlein, K.H., Breitmeyer, B.,Mintz, J., 1999. Backward masking in unmedicated schizophrenic patients in psychotic remission: possible reflection of aberrant cortical oscillation. Am. J. Psychiatry 156**,** 1367-1373.

Green, M.F., Nuechterlein, K.H., Breitmeyer, B., Tsuang, J.,Mintz, J., 2003. Forward and backward visual masking in schizophrenia: influence of age. Psychol. Med. 33**,** 887-895.

Green, M.F., Nuechterlein, K.H.,Mintz, J., 1994a. Backward masking in schizophrenia and mania. I. Specifying a mechanism. Arch. Gen. Psychiatry 51**,** 939-944.

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

Hasnain, M.K., Fox, P.T.,Woldorff, M.G., 1998. Intersubject variability of functional areas in the human visual cortex. Hum. Brain Mapp. 6**,** 301-315.

Hollingshead, A.B., 1965. Two Factor Index of Social Position. Yale Station, New Haven.

Holzman, P.S., 2000. Eye movements and the search for the essence of schizophrenia [In Process Citation]. Brain Res. Brain Res. Rev. 31**,** 350-356.

Johnstone, E.C., Lawrie, S.M.,Cosway, R., 2002. What does the Edinburgh high-risk study tell us about schizophrenia? Am. J. Med. Genet. 114**,** 906-912.

Keri, S., Kelemen, O., Benedek, G.,Janka, Z., 2001. Different trait markers for schizophrenia and bipolar disorder: a neurocognitive approach. Psychol. Med. 31**,** 915-922.

Livingstone, M.S.,Hubel, D.H., 1987. Psychophysical evidence for separate channels for the perception of form, color, movement, and depth. J. Neurosci. 7**,** 3416-3468.

O'Donnell, B.F., Swearer, J.M., Smith, L.T., Nestor, P.G., Shenton, M.E.,McCarley, R.W., 1996. Selective deficits in visual perception and recognition in schizophrenia [see comments]. Am. J. Psychiatry 153**,** 687-692.

O'Driscoll, G.A., Benkelfat, C., Florencio, P.S., Wolff, A.L., Joober, R., Lal, S.,Evans, A.C., 1999. Neural correlates of eye tracking deficits in first-degree relatives of schizophrenic patients: a positron emission tomography study. Arch. Gen. Psychiatry 56**,** 1127-1134.

Orban, G.A., Dupont, P., De Bruyn, B., Vandenberghe, R., Rosier, A.,Mortelmans, L., 1998. Human brain activity related to speed discrimination tasks. Exp. Brain Res. 122**,** 9-22.

Page, W.K., King, W.M., Merigan, W.,Maunsell, J., 1994. Magnocellular or parvocellular lesions in the lateral geniculate nucleus of monkeys cause minor deficits of smooth pursuit eye movements. Vision Res. 34**,** 223-239.

Rund, B.R., 1993. Backward-masking performance in chronic and nonchronic schizophrenics, affectively disturbed patients, and normal control subjects. J. Abnorm. Psychol. 102**,** 74-81.

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

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

Schiller, P.H.,Lee, K., 1994. The effects of lateral geniculate nucleus, area V4, and middle temporal (MT) lesions on visually guided eye movements. Vis. Neurosci. 11**,** 229-241.

Schwartz, B.D., McGinn, T.,Winstead, D.K., 1987. Disordered spatiotemporal processing in schizophrenics. Biol. Psychiatry 22**,** 688-698.

Stuve, T.A., Friedman, L., Jesberger, J.A., Gilmore, G.C., Strauss, M.E.,Meltzer, H.Y., 1997. The relationship between smooth pursuit performance, motion perception and sustained visual attention in patients with schizophrenia and normal controls. Psychol. Med. 27**,** 143-152.

Talairach, J.,Tournoux, P., 1988. Co-planar stereotaxic atlas of the human brain. Georg Thieme Verlag, Stuttgart.

Tootell, R.B., Reppas, J.B., Kwong, K.K., Malach, R., Born, R.T., Brady, T.J., Rosen, B.R.,Belliveau, J.W., 1995a. Functional analysis of human MT and related visual cortical areas using magnetic resonance imaging. J. Neurosci. 15**,** 3215-3230.

Tootell, R.B.,Taylor, J.B., 1995b. Anatomical evidence for MT and additional cortical visual areas in humans. Cereb. Cortex 5**,** 39-55.

Watson, J.D., Myers, R., Frackowiak, R.S., Hajnal, J.V., Woods, R.P., Mazziotta, J.C., Shipp, S.,Zeki, S., 1993. Area V5 of the human brain: evidence from a combined study using positron emission tomography and magnetic resonance imaging. Cereb. Cortex 3**,** 79-94.

Wechsler, D., 1999. Wechsler Abbreviated Scale of Intelligence. The Psychological Corporation, San Antonio.

Weinberger, D.R., 1999. Schizophrenia: new phenes and new genes [editorial]. Biol. Psychiatry 46**,** 3-7.

Table 4.1. Participant Demographics.

	Controls (N=11)	Relatives (N=13)	Test Statistic	*p*
Age	47.3 ± 12.3 (range: 29 - 66)	50.5 ± 10.1 (range: 31 - 65)	$t = 0.70$	0.49
Gender	64% Female	69% Female	$X^2 = .08$	0.77
Race	18% Minorities	69% Minorities	$X^2 = 6.25$	**0.01**
Visual Acuity [a]	0.87 ± 0.31	0.90 ± 0.31	$U = 63.0$	0.90
IQ Estimate [b]	110.1 ± 19.3	95.8 ± 16.2	$U = 37.5$	0.09
Socioeconomic Status [c]	2.90 ± 1.10	4.08 ± 0.76	$U = 26.0$	**0.01**

[a] Based on the Snellen Visual Acuity Chart. Each ratio was changed into a number by dividing the top number by the bottom (e.g,. 20/40 was converted to 0.50). The higher the resulting number, the better the visual acuity.

[b] Based on the 2-subtest version of the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). This measure was not available on one control.

[c] Hollingshead Social Class based on education and occupation (Hollingshead, 1965). Lower numbers represent a higher social class.

Table 4.2. Group Comparisons on fMRI Measures of V5 Activation.

fMRI Measure	Controls	Relatives	Statistic	*p*
Bilateral *t* score	4.45 ± 1.45	3.89 ± 1.09	*U* = 51.0	0.24
Bilateral PIC [a] score	0.62 ± 0.18	0.54 ± 0.13	*t* = 1.26	0.22
Bilateral Volume [b]	720 ± 234	596 ± 297	*U*= 60.0	0.51
Right hemispheric proportion [c] for *t* score	48.7% ± 4.65	48.4% ± 10.5	*t* = 0.12	0.91
Right hemispheric proportion [c] for PIC	50.0% ± 6.72	45.8% ± 8.81	*U* = 38.0	**0.05**
Right hemispheric proportion [c] for volume	45.2% ± 18.7	47.5% ± 28.1	*U* = 69.5	0.91

[a] PIC = Percent intensity change in fMRI signal

[b] Volume = Number of contiguous activated 2 x 2 x 2 mm voxels (size of voxels after normalization procedure)

[c] Right hemispheric proportion = value in right hemisphere divided by sum of values from both hemispheres

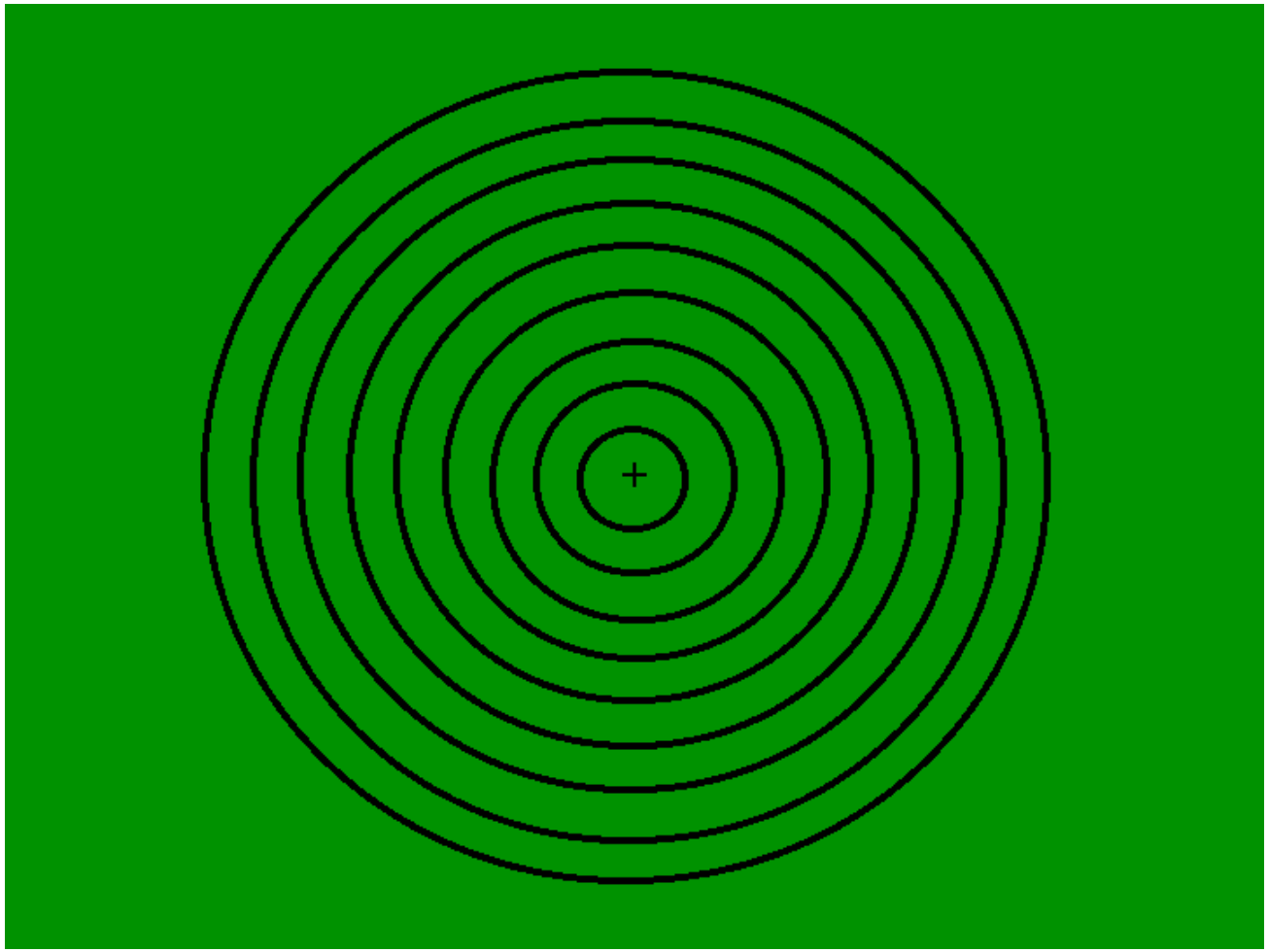


Figure 4.1. Example stationary stimulus.

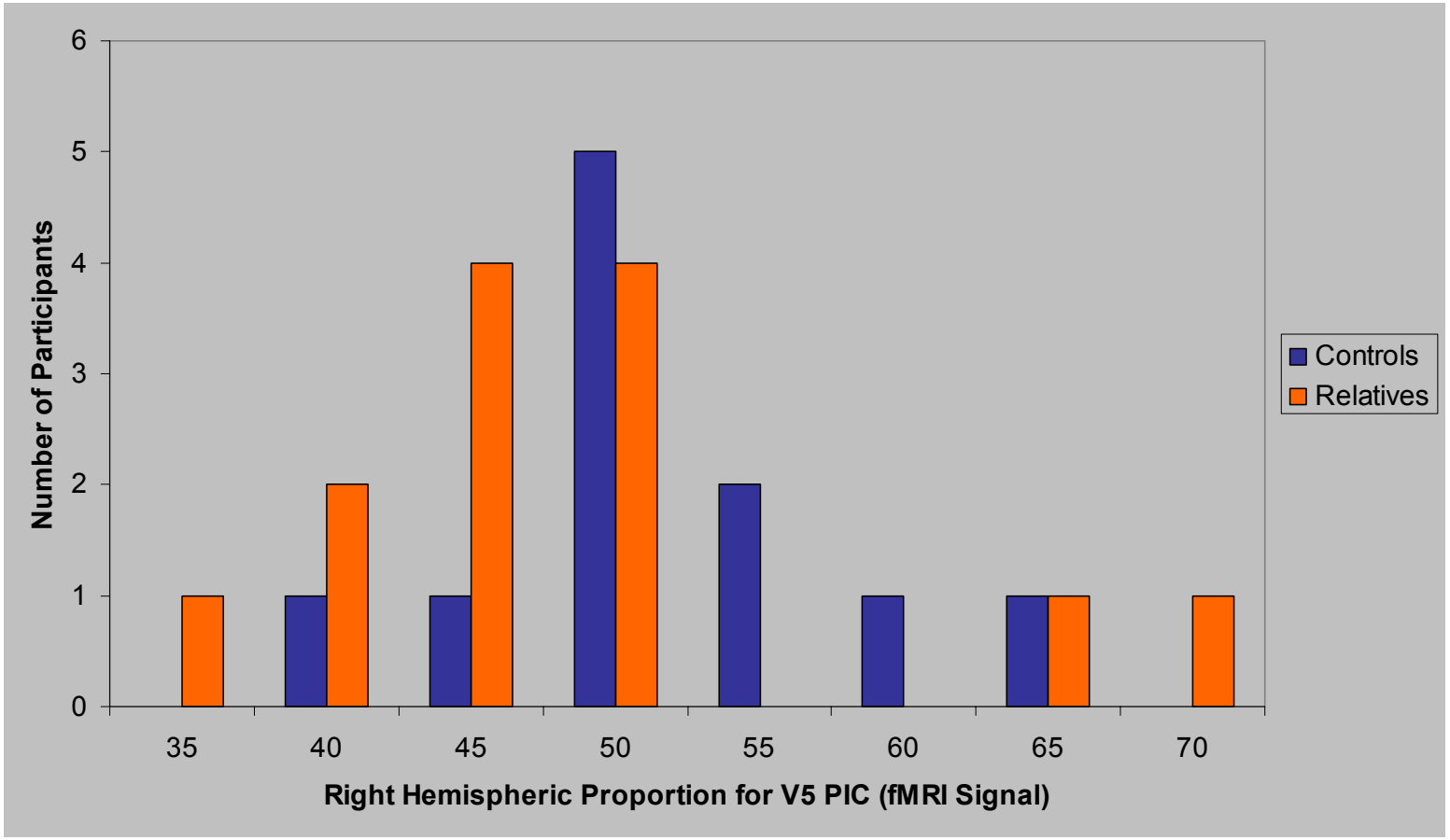
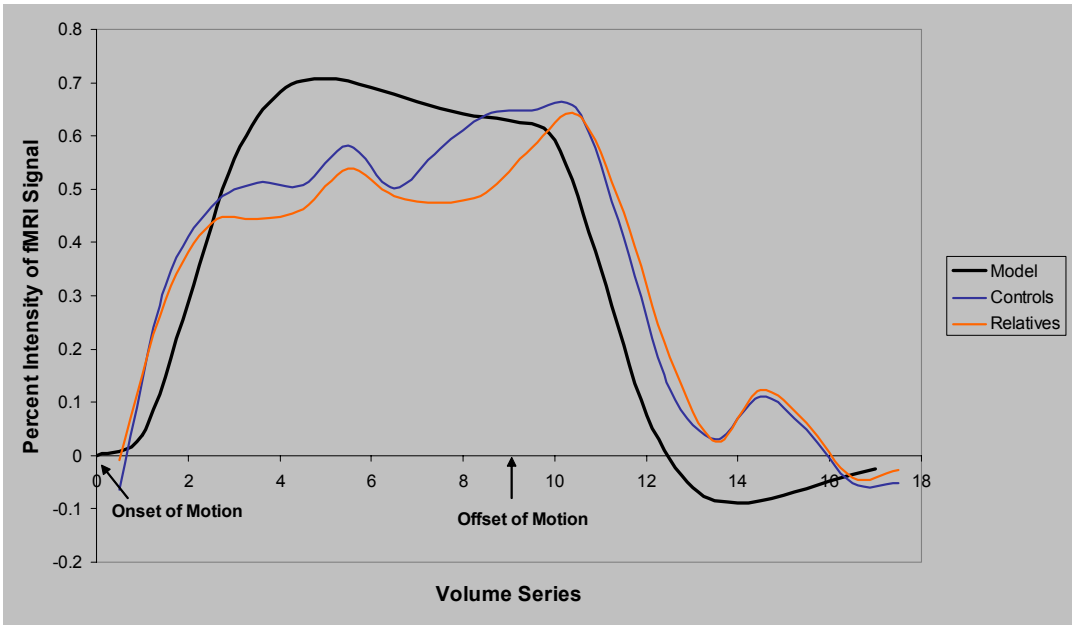


Figure 4.2. Histogram of right hemispheric proportion of V5 percent intensity change response to movement by group.

Left V5



Right V5

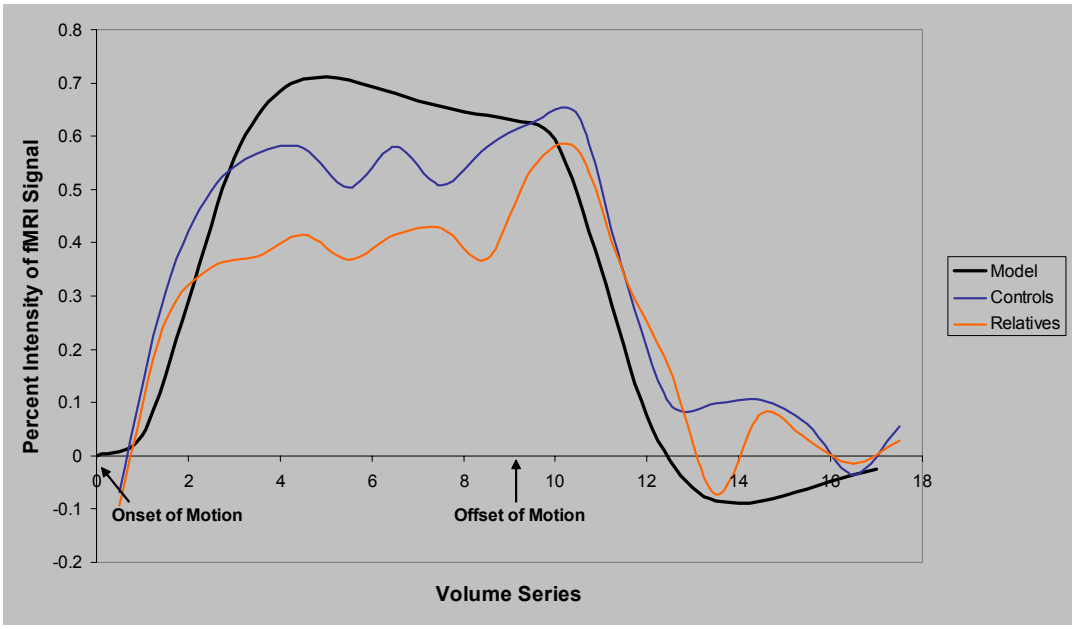


Figure 4.3. Group difference in averaged [a] time series of percent intensity of fMRI signal in response to motion.

[a] Time series represents average over all epochs (each time moving and stationary stimuli occurred). Epochs 4 and 5, which occurred at the end of the first fMRI run and the beginning of the second run, were not included in this average. The concatenation of the two fMRI scanning runs into one analysis creates a small, artificial distortion in this figure of the first and last few points of the time course.

CHAPTER 5

SCHIZOPHRENIA AND RED LIGHT: FUNCTIONAL MAGENETIC RESONANCE IMAGING EVIDENCE FOR A NOVEL BIOBEHAVIORAL MARKER [1]

[1] Bedwell, J.S., Miller, L.S., Brown, J.M., and Yanasak, N.E. To be submitted to Biological Psychiatry.

Abstract

Background: Physiological studies with non-human primates and psychophysical studies with humans have demonstrated the ability of diffuse red light (in particular) to suppress activity in the magnocellular (M) visual pathway. A previous psychophysical study found that a subset of nonpsychotic relatives of persons with schizophrenia showed the opposite effect when compared to healthy adults (Bedwell et al, 2003), suggesting a novel biobehavioral marker for the disorder. The present study attempts to replicate and explore the mechanism for this effect using fMRI. **Methods:** Functional MRI was used to examine 13 nonpsychotic first-degree relatives of persons with schizophrenia and 11 controls. Moving and stationary concentric rings were presented on both red and green backgrounds in a counterbalanced format to stimulate the M pathway. The fMRI signal strength in bilateral cortical region V5 (MT) was measured as a marker of M pathway functioning. **Results:** The control group showed evidence for the suppression of right hemisphere V5 activity to red light, while a subset of relatives showed the opposite response. The group difference in change of right hemisphere V5 activity to red light was statistically significant ($t = 2.43$, $p = .02$). This effect was not seen in left V5 within controls or between groups. **Discussion:** Results provide physiological confirmation that the M pathway response to red light is in the opposite direction than expected in a subset of nonpsychotic relatives of persons with schizophrenia. This effect may represent a novel biobehavioral marker for schizophrenia, but requires further replication and refinement of psychophysical methods.

Introduction

Research on visual processing in humans and primates has identified two unique but interactive physiological subsystems in the visual system (Breitmeyer and Ganz 1976;

Livingstone and Hubel 1987). The magnocellular (M) visual pathway is primarily responsible for processing location information and motion, while the parvocellular (P) visual pathway is primarily responsible for processing detail and color.

Early single-cell recording research with non-human primates reported that a small portion of M pathway neurons showed tonic suppression of on-center responses when the monkey was exposed to diffuse red light. These neurons were labeled as "Type-IV" (Wiesel and Hubel 1966) and have been reported in several locations along the M pathway, including the retinal ganglia (de Monasterio 1978), lateral geniculate nucleus (Dreher et al 1976; Kruger 1977; Wiesel and Hubel 1966), and striate cortex (Livingstone and Hubel 1984). Research using psychophysical tasks has inferred a similar effect in humans based on behavioral performance change in response to red light (e.g., Breitmeyer and Breier 1994; Breitmeyer and Williams 1990; Brown and Koch 2000).

A recent psychophysical study found evidence of reduced accuracy on a particular condition of a visual backward masking task (which required identification of the location of the initial target) with a red, compared to grey, background in healthy adults (Bedwell et al 2003). This study reported that, in contrast to the control group, a subset of nonpsychotic first-degree relatives of persons with schizophrenia showed the opposite behavioral response to red light (increase in accuracy), while performance on the neutral (grey) background condition did not differ from controls. Examining nonpsychotic first-degree relatives of persons with schizophrenia is advantageous because unique characteristics found in these individuals may offer insight into genetic expression of schizophrenia without confounds such as neuroleptic exposure, chronic hospitalization, or active symptom effects (Adler et al 1999; Weinberger 1999).

Recent research examining persons with schizophrenia have reported evidence of a hypoactive M pathway. Three studies used electroencephalography (EEG) and reported reduced amplitude of signal in posterior cortical regions along the M pathway in persons with schizophrenia, with relatively normal activation along brain regions in the P pathway (Butler et al 2001; Doniger et al 2002; Foxe et al 2001). One study used functional magnetic resonance imaging (fMRI) and reported relative hypoactivation of the M pathway (particularly in the right hemisphere) in persons with schizophrenia, but found no evidence of abnormal functioning in the P pathway (Braus et al 2002). Evidence of a hypoactive M pathway, restricted to the right hemisphere, was also found in a small group of nonpsychotic first-degree relatives (N=13) under neutral (non-red) light conditions (Bedwell et al, 2004).

There is some psychophysical evidence that the right hemisphere is more involved with processing M pathway information, such as spatial relationships (Hellige 1996; Kosslyn et al 1995; Roth and Hellige 1998). Thus, any suppressive effect of red light may be more evident in the right hemisphere. However, recent visual half-field experiments have tested this hypothesis using psychophysical methods and concluded that red light suppressed the M pathway equally in both hemispheres (Hellige and Cumberland 2001; Roth and Hellige 1998). As it does not appear that any physiological research has been published examining the red light effect in humans, the question of hemispheric lateralization remains unclear.

The current study used fMRI to examine the M pathway response to diffuse red light in a group of nonpsychotic first-degree relatives of persons with schizophrenia, compared to a group of controls. Cortical localization of the M pathway was assessed by targeting a specific region of cortex (V5), which is well established as a primary center along the M pathway (Ahlfors et al 1999; Hasnain et al 1998; Tootell et al 1995; Watson et al 1993). It was hypothesized that,

compared to the control group, a proportion of the relatives would show evidence of a differential V5 fMRI signal response to red light.

Methods

Participants

Thirteen nonpsychotic first-degree relatives of persons with schizophrenia and 11 controls were recruited from a larger sample previously reported in an earlier study (Bedwell et al 2003). Participants in the relatives group included: 9 full-siblings, 2 biological parents, and 2 biological children. Five of the siblings were related to the same proband, while the remaining relatives were each related to unique probands. Participant demographics are listed in Table 5.1. While the groups were well-matched on age, visual acuity, and gender; the relatives had significantly lower socioeconomic status, more individuals from a racial minority group, and a statistical trend for a lower IQ. However, the average estimated Full Scale IQ for the relatives group was 96, within the average range of functioning.

First-degree relatives of persons with schizophrenia were recruited from a community mental health center through within-agency requests to patients. A clear diagnosis of DSM-IV (American Psychiatric Association 1994) schizophrenia was confirmed in all probands by a staff psychiatrist after thorough chart review of existing schizophrenia patients in the clinic. Healthy controls were recruited from the local community using a cable television advertisement and printed advertisements placed throughout the community. All participants in the study were asked to read and sign a consent form after the procedures had been fully explained.

Exclusionary criteria for the control group included: 1) past or present DSM-IV Axis I psychiatric diagnosis as determined through a SCID-I diagnostic interview (First et al 1998),

with allowance for Specific Phobia; 2) current use of psychoactive medication; 3) corrected visual acuity less than 20/50; 4) past or present history of a neurological disorder or insult; 5) presence of schizotypal or paranoid personality disorder, as determined by SCID-II diagnostic interview (First et al 1997); and 6) self-reported biological relation (however distant) to a person with probable psychosis. None of the controls met criteria for substance abuse within the past three months.

Exclusionary criteria for the relatives group included: 1) history of mania or psychotic disorder as determined through a SCID-I diagnostic interview; 2) corrected visual acuity less than 20/50; and 3) history of a neurological disorder or insult. The exclusionary criteria for the relative group were more liberal, as schizophrenia-related genes may increase the likelihood of other psychopathology (Johnstone et al 2002), and the goal of this study was to examine persons with such genes in the absence of schizophrenia. The resulting group of relatives included one person with Major Depressive Disorder, Recurrent and one person with Dysthymic Disorder. Two of the relatives were taking antidepressants at the time of the study. None of the relatives met criteria for substance abuse within the past three months.

The full SCID-I diagnostic interview was completed in a previous study on the same participants, completed approximately one year prior to the current study (Bedwell et al, 2003). To assess possible changes in psychopathology over the past year, a diagnostic screen was created (see Appendix A), which was largely based on screening questions from the SCID-I. No significant change in psychopathology was noted for any participant.

Stimuli

A hardware and software package (Integrated Functional Imaging Systems, IFIS; Psychology Software Tools) was used to present the psychophysical task in the fMRI

environment. This system included a monitor placed above the head within the bore of the fMRI device for viewing visual stimuli (subtending a visual angle of 14.69º (h) x 19.22º (v))**.**

Participants were asked to maintain fixation on a small black cross located in the middle of the screen. Stimuli consisted of nine concentric black rings on either a red or green background (see Figure 5.1), with green serving as the neutral background color. The red and green backgrounds were matched for luminance (0.9 cd/m^2) using a Tektronix J17 digital photometer on the fMRI monitor. The largest ring subtended 13.09º of the visual angle, while the smallest ring subtended 1.86º. The rings were presented sequentially, creating the illusion of a single ring expanding or contracting. In this manner, the rings expanded for 3.6 sec at the rate of 5 Hz and then contracted for the same duration at the same rate. The expansion and contraction repeated three times for a total motion period of 21.6 sec. This was followed by all nine rings appearing simultaneously and remaining stationary (as in Figure 5.1) for 21.6 sec. The cycle of motion and stationary rings was repeated two times for a total block length of 86.4 sec. This block was presented multiple times over two separate fMRI scanning runs, with different color backgrounds, with each run following one of two color-ordering schemes – Sequence #1: red, green, red, green; Sequence #2: green, red, green, red. The usage of a particular sequence for the first run and the remaining sequence for the subsequent run was counterbalanced between participants. Thus, the 86.4 sec. block was repeated a total of eight times, four times with each background.

Magnetic Resonance Imaging Parameters

MRI scans were acquired on a 1.5 Tesla Signa LX Horizon (General Electric, Milwaukee, WI) whole body magnetic resonance scanner configured with a GE head coil. For

fMRI imaging, a T_2-sensitive gradient recalled echo pulse sequence with spiral readout was used with the following parameters: TR = 1200 ms, TE = 40 ms, two interleaves, 77º flip angle, reconstructed matrix = 64 x 64 mm, FOV = 240 mm, slice thickness = 5 mm, zero gap. This sequence collects one of two k-space readouts for each slice of the image volume every 1.2 seconds, reading out the second interleave for every slice in the next 1.2 seconds. In this manner, a full image volume is collected in 2.4 seconds, and the signal in each slice is partially-sampled twice over this interval. Fifteen adjacent, non-oblique, axial planes of fMRI data were acquired in each image volume, broadly covering bilateral V5 regions. In each scanning run, 144 image volumes were collected at the rate of 2.4 seconds per volume. A T_1-sensitive series of 120 axial anatomical slices, covering the entire brain, were collected for subsequent spatial normalization of the fMRI images, which used the following parameters: TR = 10.8 ms, TE = 2.8 ms, one interleave, 20º flip angle, FOV = 240 mm, slice thickness = 1.3 mm, zero gap.

fMRI Data Analysis

The fMRI data were processed and analyzed using Statistical Parametric Mapping software (SPM2, Wellcome Department of Cognitive Neurology, London, UK). The SPM2 software used in this study contained in-house modifications (by N.Y.) for extracting parameters not available in the standard package (e.g, percent intensity change measure and measures averaged over a region of interest). Imaging data was pre-processed in the following manner for each participant: 1) images from the two runs, within each background color, were collapsed temporally into a single analysis (forming a continuous series of red background scans and a separate series of green background scans); 2) images were realigned to adjust for participant movement; 3) the anatomical image was spatially normalized to a T_1 template (from the

Montreal Neurological Institute; Evans et al, 1993) and resulting normalization parameters were used to transform fMRI images; 4) normalized fMRI images were spatially smoothed using an isotropic Gaussian kernel having a 15 mm full width at half maximum (based on the average anatomical size of V5 - (Tootell and Taylor 1995); and 5) a model that defined temporal periods of moving and stationary stimuli within each color background was constructed.

Within this model, fMRI signal during moving stimuli was specified as an explicit variable, and signal during the stationary period was considered to be the baseline. A model contrast of moving vs. stationary was applied for all results in this study in order to determine brain areas more active during the period of moving stimuli than during stationary stimuli (e.g., V5). Temporal variation of the signal intensity was compared to the expected hemodynamic response functional time dependence and saved as a statistical map for each individual (within each color condition).

Area V5 was determined bilaterally on resulting statistical maps using the following two-step procedure: 1) statistically-significant voxels ($p < .05$, uncorrected for multiple comparisons) were identified within a sphere, with a radius of 18 mm, defined by a center with Talairach coordinates (Talairach and Tournoux 1988) of x = ±40 (bilateral), y = -70, and z = 3 (average reported location of V5 from previous neuroimaging studies – Barton et al 1996; O'Driscoll et al 1999; Orban et al 1998; Tootell et al 1995; Watson et al 1993); and 2) the voxel of highest statistical significance was chosen and a new subset of statistically-significant ($p < .01$ [$t = 2.50$]; uncorrected) voxels within a sphere, with a radius of 10 mm, from this center was identified. These final two clusters of voxels (one for each side of the brain) were then considered "V5." The coordinates used to determine each 10 mm sphere from the green background condition were used to determine the 10 mm spheres from the red background condition. Within each

color condition, if a particular sphere contained no voxels that met the initial statistical threshold, the threshold was progressively lowered to $p < .05$ and, when necessary, $p < .20$. This progressive thresholding method was modeled after the method used in a V5 neuroimaging study by Watson and colleagues (1993), which allowed for detection of low levels of V5 activity in particular participants. This method resulted in a decrease in threshold (from $p < .01$) to $p < .05$ in one control and three relatives with the green background and in two controls and two relatives with the red background (in each case - for only one of the bilateral V5 locations). The decrease in threshold to $p < .20$ was not necessary for any participant with the green background, but was used with one control and one relative with the red background (for only one of the bilateral V5 locations).

For each defined V5 cluster, the cluster-averaged *t* score, cluster-averaged percent intensity change (PIC), and cluster volume (number of voxels meeting threshold of $p < .01$) were recorded. In this study, PIC is defined as the average fit signal magnitude within a cluster of voxels during the motion condition as compared to the magnitude during the stationary condition, normalized by the overall intensity of the brain volume scanned for expression in units of percent. These quantities were averaged across V5 bilaterally and also examined independently to assess proportional laterality effects. Proportional laterality for each measure was assessed by dividing the score from the right hemisphere by the sum of that measure from both hemispheres. This laterality parameter indicates what proportion of the bilaterally-summed signal resides in the right hemisphere, and hereafter this proportional laterality for a measure is referred to as the 'right hemispheric proportion' for that measure. Change scores for volume of activation in response to a red background did not have a normal distribution, so a Mann-

Whitney *U* test was used to examine group differences. The remaining fMRI activation change scores followed a normal distribution, so *t*-tests were used to examine group differences.

Results

All participants in both groups showed bilateral V5 activation with the green background. With the green background, the mean Talairach coordinates for the location of the most statistically significant voxel in the V5 cortical region in both the control (-37, -75, 5 [left] and 53, -72, 6 [right]) and relatives group (-39, -73, -1 [left] and 47, -72, 6 [right]) were within the range reported by others (Hasnain et al 1998; O'Driscoll et al 1999; Watson et al 1993). A previous study found that, during the green background condition, the relatives showed reduced activation only on the right hemispheric proportion for PIC measure, Mann-Whitney $U(22) = 38.0$, $p = .05$ (Bedwell et al, 2004).

Results revealed that the relatives differed in V5 activation change to the red (compared to green) background, only on the right hemispheric proportion for PIC measure ($t = 2.43$, $p = .02$; see Table 5.2 and Figure 5.2). On this measure, controls showed a statistically significant decrease in activation from the green to red background (paired $t = 2.41$, $p = .04$; see Figure 5.3), while the relatives showed no consistent group change in activation from the green to red background (paired $t = 1.09$, $p = .30$; see Figures 5.4 and 5.5). Examination of Figure 5.4 reveals that a subset of relatives <u>increased</u> activation from the green to red background – the opposite direction expected based on the controls. Right hemispheric proportion for PIC with the green background did not appear to adequately explain this group difference, as the group difference in change to red light still approached statistical significance after controlling for this measure from the green background condition, $F(1,21) = 4.12$, $p = .06$.

Discussion

Consistent with the hypothesis, the relatives demonstrated evidence of a differential neural response in response to red light compared to controls. While controls showed a statistically significant reduction in the right hemispheric proportion of fMRI signal in V5 in response to red light, relatives showed no suggestion of change and a subset showed a proportional increase (instead of decrease) of fMRI signal in right hemisphere V5 (see Figure 5.2). This group difference may reflect an underlying M pathway deficit that may be more evident in the right hemisphere, as suggested in studies examining persons with schizophrenia (Braus et al 2002) and in a group of first-degree relatives (Bedwell et al, 2004).

It appears that the differential change in M pathway functioning in response to diffuse red light found in a subset of the relatives, both in the current study and in an earlier visual backward masking study (Bedwell et al 2003), is a biobehavioral genetic marker for schizophrenia that is independent of baseline differences in M pathway functioning. The current study found that group difference in fMRI signal change to red light remained (although was somewhat less robust) after controlling for group differences in fMRI signal under neutral light conditions. Similarly, a previous visual backward masking study (Bedwell et al 2003) found a group difference in change in accuracy to red light, even though the groups did not differ in accurac from the neutral light condition.

Thus, converging evidence suggests that a differential response in the M pathway to diffuse red light may represent a novel and potentially useful biobehavioral marker for schizophrenia. The current study is limited by a small sample size. However, this effect was statistically significant with a sample of 13 relatives, suggesting that it may be a particularly sensitive marker. Further replication of this effect using a variety of psychophysical and

physiological techniques in persons with schizophrenia and other psychiatric disorders will be needed to establish the sensitivity and specificity of this marker to genetic loading for schizophrenia.

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References

Adler LE, Freedman R, Ross RG, Olincy A, Waldo MC (1999): Elementary phenotypes in the neurobiological and genetic study of schizophrenia. *Biol Psychiatry* 46:8-18.

Ahlfors SP, Simpson GV, Dale AM, et al (1999): Spatiotemporal activity of a cortical network for processing visual motion revealed by MEG and fMRI. *J Neurophysiol* 82:2545-55.

American Psychiatric Association (1994): *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition*. Washington, DC: American Psychiatric Association.

Barton JJ, Simpson T, Kiriakopoulos E, et al (1996): Functional MRI of lateral occipitotemporal cortex during pursuit and motion perception. *Ann Neurol* 40:387-98.

Bedwell JS, Miller LS, Brown JM, McDowell JE, and Yanasak NE (2004): *Functional magnetic resonance imaging examination of the magnocellular visual pathway in nonpsychotic relatives of persons with schizophrenia.* Manuscript submitted for publication.

Bedwell JS, Brown JM, Miller LS (2003): The magnocellular visual system and schizophrenia: what can the color red tell us? *Schizophrenia Research* 63:273-284.

Braus DF, Weber-Fahr W, Tost H, Ruf M, Henn FA (2002): Sensory information processing in neuroleptic-naive first-episode schizophrenic patients: a functional magnetic resonance imaging study. *Arch Gen Psychiatry* 59:696-701.

Breitmeyer BG, Breier JI (1994): Effects of background color on reaction time to stimuli varying in size and contrast: inferences about human M channels. *Vision Res* 34:1039-45.

Breitmeyer BG, Ganz L (1976): Implications of sustained and transient channels for theories of visual pattern masking, saccadic suppression, and information processing. *Psychol Rev* 83:1-36.

Breitmeyer BG, Williams MC (1990): Effects of isoluminant-background color on metacontrast and stroboscopic motion: interactions between sustained (P) and transient (M) channels. *Vision Res* 30:1069-75.

Brown JM, Koch C (2000): Influences of occlusion, color, and luminance on the perception of fragmented pictures. *Percept Mot Skills* 90:1033-44.

Butler PD, Schechter I, Zemon V, et al (2001): Dysfunction of early-stage visual processing in schizophrenia. *Am J Psychiatry* 158:1126-33.

de Monasterio FM (1978): Properties of concentrically organized X and Y ganglion cells of macaque retina. *J Neurophysiol* 41:1394-1417.

Doniger GM, Foxe JJ, Murray MM, Higgins BA, Javitt DC (2002): Impaired visual object recognition and dorsal/ventral stream interaction in schizophrenia. *Arch Gen Psychiatry* 59:1011-20.

Dreher B, Fukada Y, Rodieck RW (1976): Identification, classification and anatomical segregation of cells with X-like and Y-like properties in the lateral geniculate nucleus of old-world primates. *J Physiol* 258:433-52.

First MB, Gibbon M, Spitzer RL, Williams JBW, Benjamin LS (1997): *Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II)*. Washington, DC: American Psychiatric Press.

First MB, Spitzer RL, Gibbon M, Williams JBW (1998): *Structured Clinical Interview for DSM-IV Axis I Disorders - Non-patient Edition (SCID-I/NP Version 2.0)*. New York: Biometrics Research Department.

Foxe JJ, Doniger GM, Javitt DC (2001): Early visual processing deficits in schizophrenia: impaired P1 generation revealed by high-density electrical mapping. *Neuroreport* 12:3815-20.

Hasnain MK, Fox PT, Woldorff MG (1998): Intersubject variability of functional areas in the human visual cortex. *Hum Brain Mapp* 6:301-15.

Hellige JB (1996): Hemispheric asymmetry for visual information processing. *Acta Neurobiol Exp (Wars)* 56:485-97.

Hellige JB, Cumberland N (2001): Categorical and coordinate spatial processing: more on contributions of the transient/magnocellular visual system. *Brain Cogn* 45:155-63.

Hollingshead AB (1965): *Two Factor Index of Social Position*. New Haven: Yale Station.

Johnstone EC, Lawrie SM, Cosway R (2002): What does the Edinburgh high-risk study tell us about schizophrenia? *American Journal of Medical Genetics* 114:906-912.

Kosslyn SM, Maljkovic V, Hamilton SE, Horwitz G, Thompson WL (1995): Two types of image generation: evidence for left and right hemisphere processes. *Neuropsychologia* 33:1485-510.

Kruger J (1977): Stimulus dependent colour specificity of monkey lateral geniculate neurones. *Exp Brain Res* 30:297-311.

Livingstone MS, Hubel DH (1984): Anatomy and physiology of a color system in the primate visual cortex. *J Neurosci* 4:309-56.

Livingstone MS, Hubel DH (1987): Psychophysical evidence for separate channels for the perception of form, color, movement, and depth. *J Neurosci* 7:3416-68.

O'Driscoll GA, Benkelfat C, Florencio PS, et al (1999): Neural correlates of eye tracking deficits in first-degree relatives of schizophrenic patients: a positron emission tomography study. *Arch Gen Psychiatry* 56:1127-34.

Orban GA, Dupont P, De Bruyn B, Vandenberghe R, Rosier A, Mortelmans L (1998): Human brain activity related to speed discrimination tasks. *Exp Brain Res* 122:9-22.

Roth EC, Hellige JB (1998): Spatial processing and hemispheric asymmetry. Contributions of the transient/magnocellular visual system. *J Cogn Neurosci* 10:472-84.

Talairach J, Tournoux P (1988): *Co-planar stereotaxic atlas of the human brain.* Stuttgart: Georg Thieme Verlag.

Tootell RB, Reppas JB, Kwong KK, et al (1995): Functional analysis of human MT and related visual cortical areas using magnetic resonance imaging. *J Neurosci* 15:3215-30.

Tootell RB, Taylor JB (1995): Anatomical evidence for MT and additional cortical visual areas in humans. *Cereb Cortex* 5:39-55.

Watson JD, Myers R, Frackowiak RS, et al (1993): Area V5 of the human brain: evidence from a combined study using positron emission tomography and magnetic resonance imaging. *Cereb Cortex* 3:79-94.

Wechsler D (1999): *Wechsler Abbreviated Scale of Intelligence*. San Antonio: The Psychological Corporation.

Weinberger DR (1999): Schizophrenia: new phenes and new genes [editorial]. *Biol Psychiatry* 46:3-7.

Wiesel TN, Hubel DH (1966): Spatial and chromatic interactions in the lateral geniculate nucleus body of the rhesus monkey. *Journal of Neurophysiology* 29:1115-1156.

Table 5.1. Participant demographics.

	Controls (N=11)	Relatives (N=13)	Test Statistic	*p*
Age	47.3 ± 12.3 (range: 29 - 66)	50.5 ± 10.1 (range: 31 - 65)	$t = 0.70$	0.49
Gender	64% Female	69% Female	$X^2 = .08$	0.77
Race	18% Minorities	69% Minorities	$X^2 = 6.25$	**0.01**
Visual Acuity [1]	0.87 ± 0.31	0.90 ± 0.31	$U = 63.0$	0.90
IQ Estimate [2]	110.1 ± 19.3	95.8 ± 16.2	$U = 37.5$	0.09
Socioeconomic Status [3]	2.90 ± 1.10	4.08 ± 0.76	$U = 26.0$	**0.01**

[1] Based on the Snellen Visual Acuity Chart. Each ratio was changed into a number by dividing the top number by the bottom (e.g,. 20/40 was converted to 0.50). The higher the resulting number, the better the visual acuity.

[2] Based on the 2-subtest version of the Wechsler Abbreviated Scale of Intelligence (Wechsler 1999). This measure was not available on one control.

[3] Hollingshead Social Class based on education and occupation (Hollingshead 1965). Lower numbers represent a higher social class.

Table 5.2. Group comparisons on change[1] in fMRI measures in response to red light.'

fMRI Measure	Controls	Relatives	Statistic	*p*
Bilateral *t* score	-0.46 ± 1.13	-0.13 ± 0.72	*t* = 0.85	.41
Bilateral PIC[2] score	-0.01 ± 0.13	0.01 ± 0.15	*t* = 0.28	.79
Bilateral Volume[3]	-91 ± 320	-88 ± 269	*U* = 63.0	.62
Right hemispheric proportion[4] for *t* score	-3.48 ± 4.22%	-2.18 ± 6.87%	*t* = 0.54	.59
Right hemispheric proportion[4] for PIC	-3.69 ± 5.09%	1.71 ± 5.68%	*t* = 2.43	**.02**
Right hemispheric proportion[4] for volume	-2.70 ± 9.65%	-4.68 ± 23.0%	*U* = 61.0	.54

[1] All means listed represent change scores, which represent the value from the green background condition subtracted from the value from the red background condition. Therefore, a negative value represents a decrease in signal in response to the red background.

[2] PIC = Percent intensity change in fMRI signal

[3] Volume = Number of contiguous activated 2 x 2 x 2 mm voxels (size of voxels after normalization procedure)

[4] Right hemispheric proportion = value in right hemisphere divided by sum of values from both hemispheres

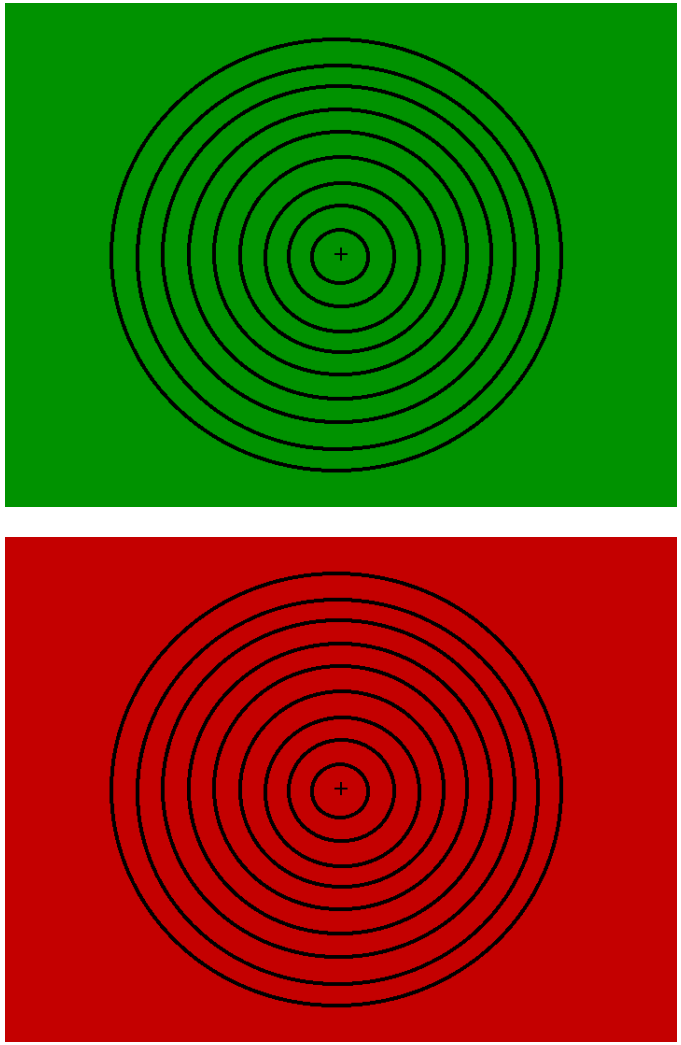

Figure 5.1. Example stationary stimulus on the green and red backgrounds.

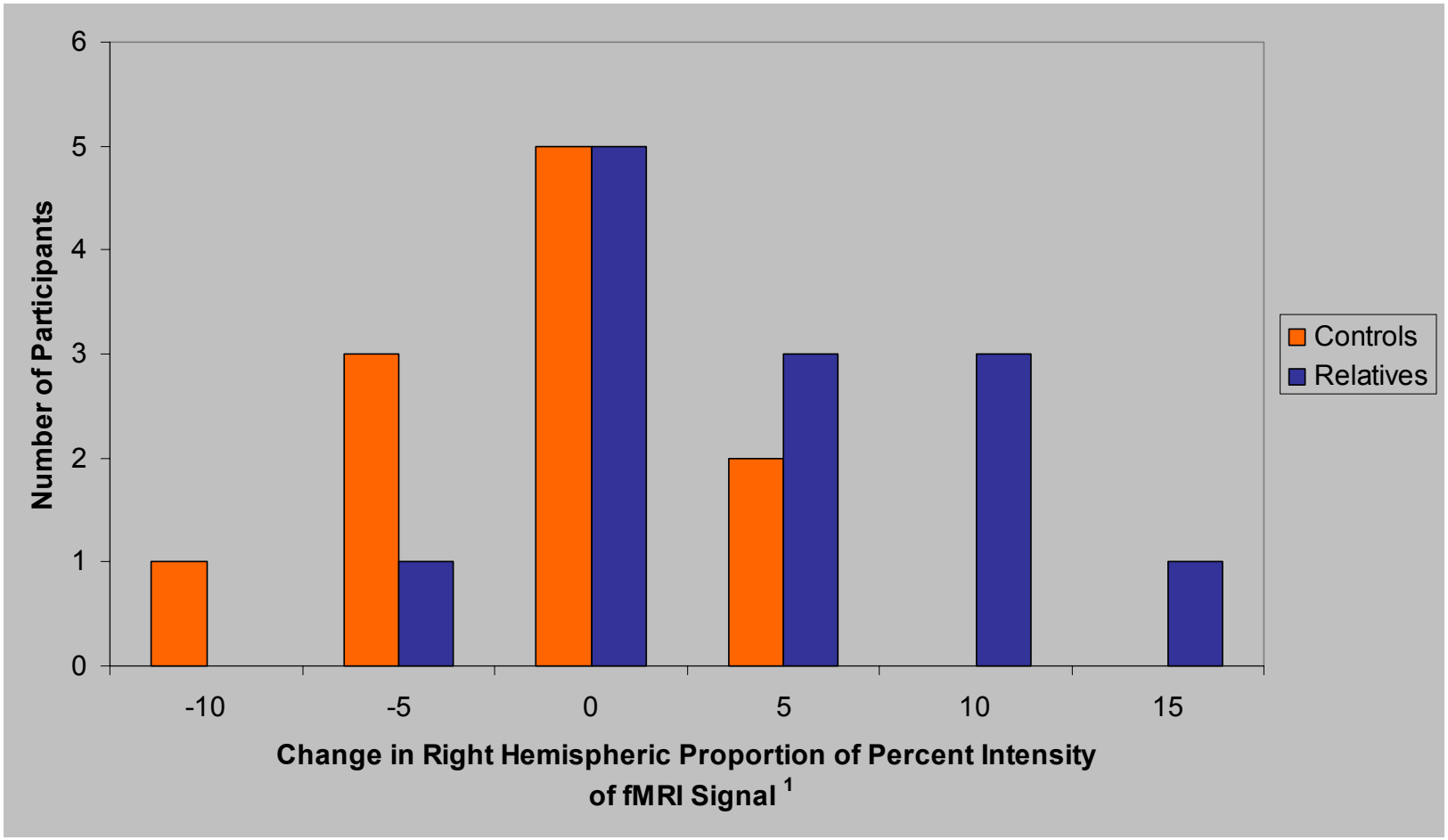

Figure 5.2. Histogram of group difference in proportional right hemisphere percent intensity of fMRI signal in response to red light.

Paired $t = 2.43$, $p = .02$.

[1] Change represents value with green background subtracted from value with red background

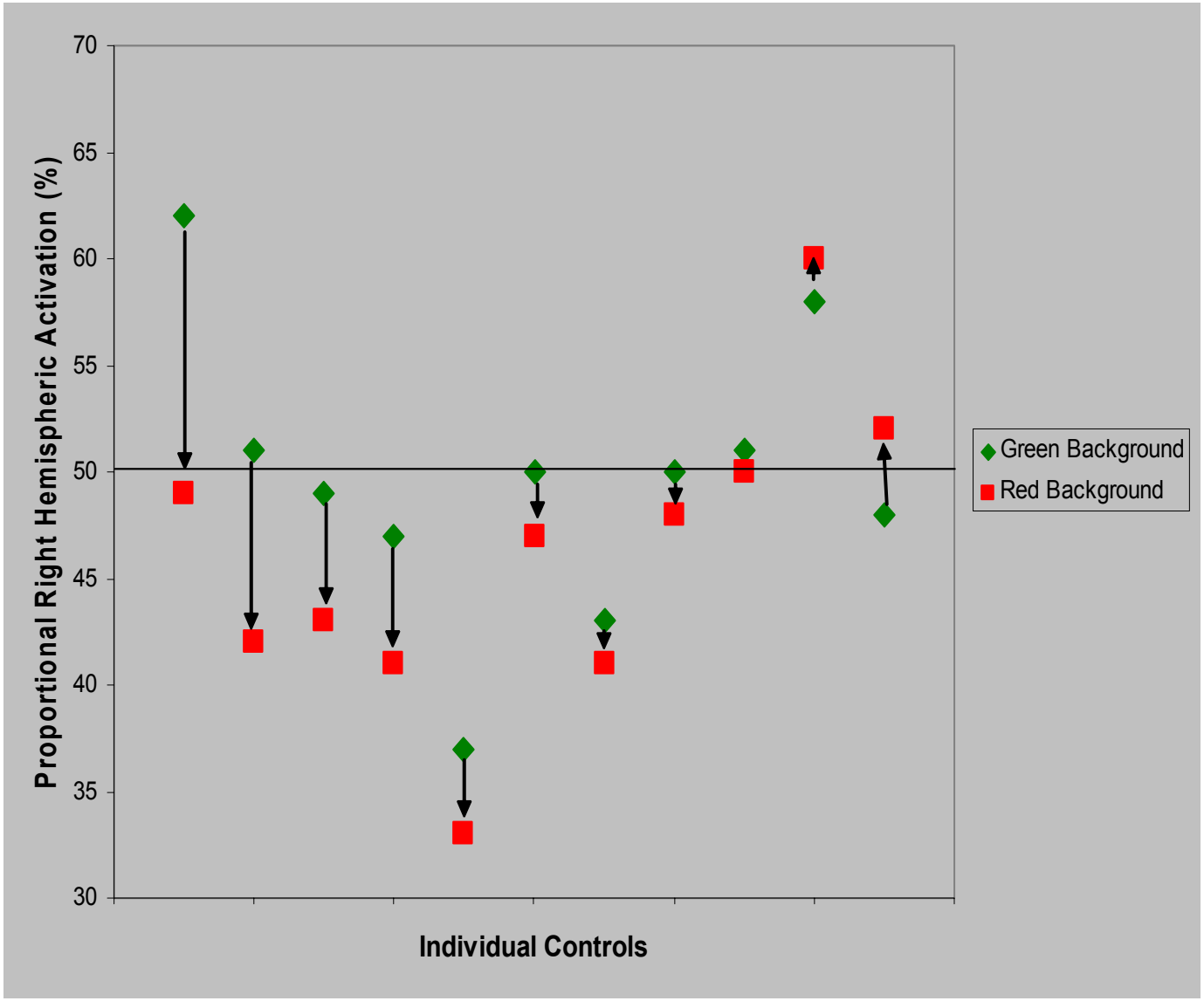

Figure 5.3. Controls: Change in proportional right hemisphere percent intensity of fMRI signal in response to red light.

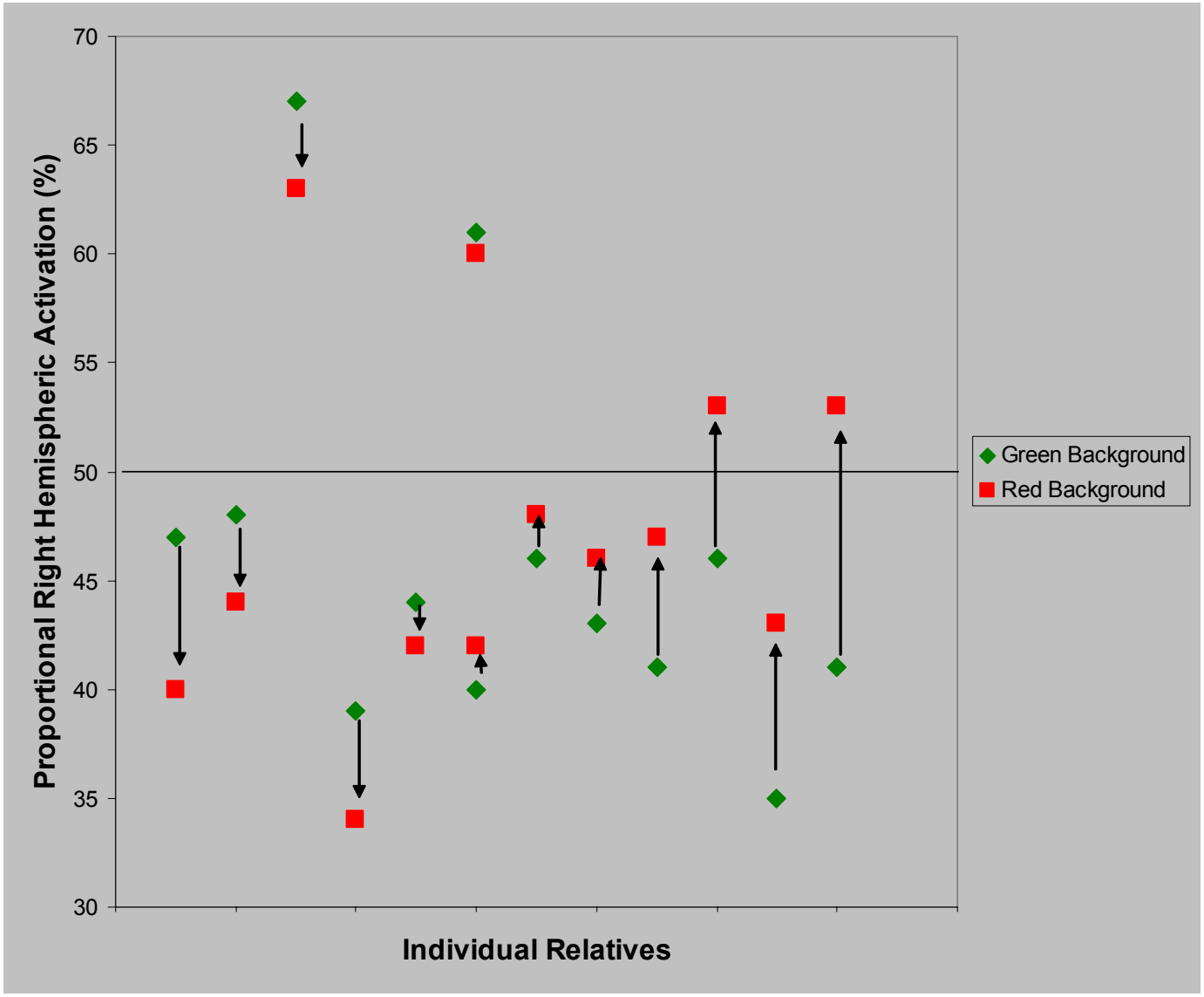

Figure 5.4. Relatives: Change in proportional right hemisphere percent intensity of fMRI signal in response to red light.

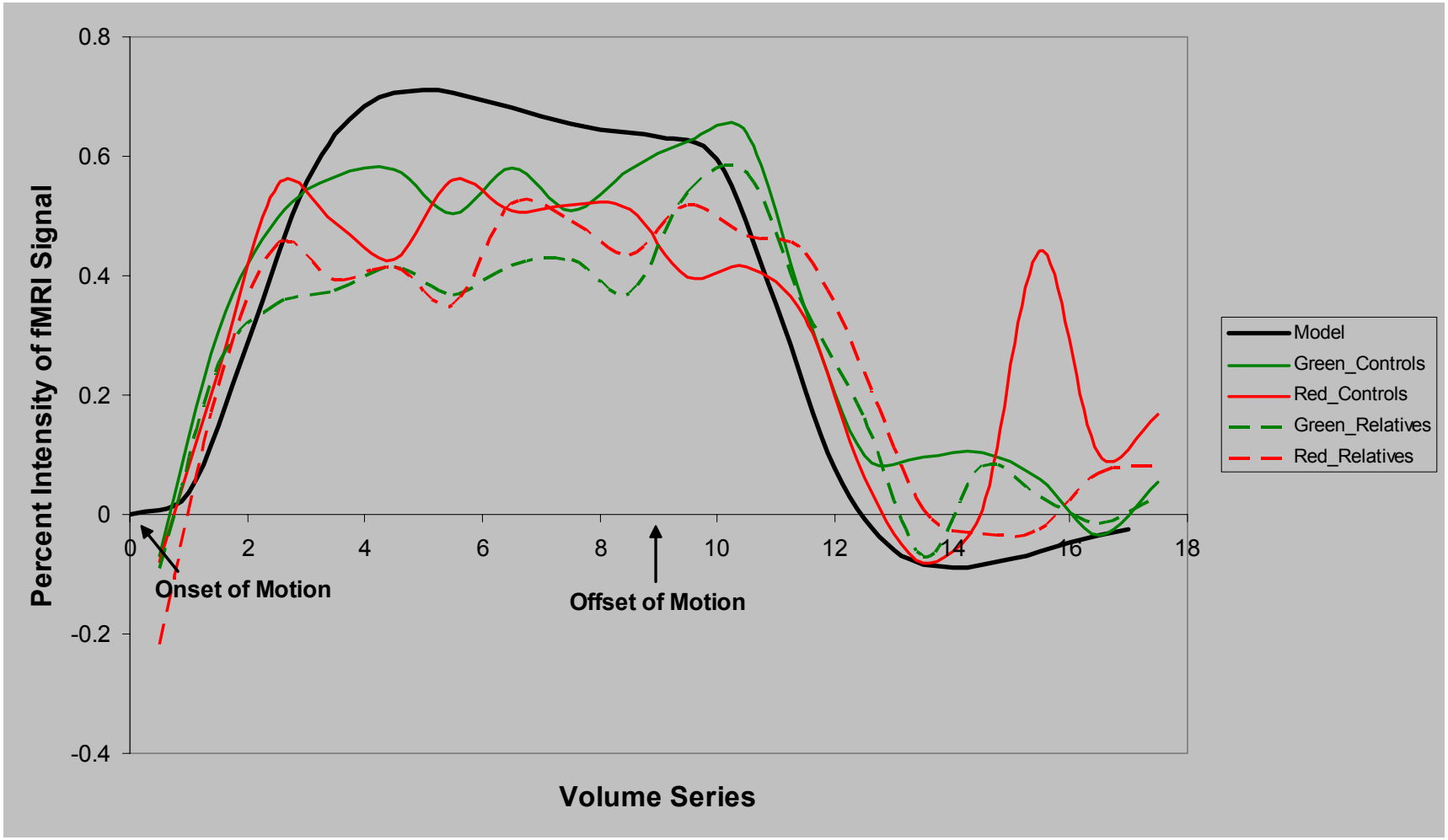

Figure 5.5. Group difference in averaged[1] volume series of percent intensity of fMRI signal in response to motion and red light.

[1] Volume series represents average over all epochs (each time moving and stationary stimuli occurred). Each volume represents 2.4 sec. of scanning. Epochs 4 and 5 were not included in figure, as these epochs contained artificial distortion secondary to concatenation of the two fMRI scanning sessions.

CHAPTER 6

DISCUSSION

Results are generally consistent with the three hypotheses, as data indicated that, as a group, controls showed reduced fMRI signal in V5 in response to red light, relatives showed reduced fMRI signal in V5, and relatives did not show evidence of a reduction in fMRI signal in V5 in response to red light. The hypotheses predicted that these differences would be present bilaterally in both the fMRI signal strength measures and the volume of significantly activated voxels. However, in contrast to the hypotheses, all of the above findings were restricted to the t-test and PIC measures (e.g., not present with volume measures) that examined the proportion of fMRI signal present in right hemisphere V5 compared to that present in bilateral V5. This proportional right hemisphere measure was not a planned comparison and was conducted *ad hoc*. The dependence on this measure is therefore a weakness of the study, as there were no *a priori* reasons to believe that a proportional hemisphere measure would prove to be most sensitive to the hypothesized effects.

While there were no specific reasons to believe that the findings of this study would be limited to a proportional right hemisphere measure, there were some indications that the effects would be more robust in the right hemisphere. There is psychophysical evidence that the right hemisphere is more involved with processing M pathway information, such as spatial relationships (Hellige, 1996; Kosslyn, Maljkovic, Hamilton, Horwitz, & Thompson, 1995; Roth & Hellige, 1998). Thus, subtle differences between the groups in M pathway activity may be

more apparent in the right hemisphere. In addition, the effect of red light on suppressing the M pathway may be more apparent in this hemisphere. However, recent visual half-field experiments have tested this latter hypothesis using psychophysical methods and concluded that red light appeared to suppress the M pathway equally in both hemispheres (Hellige & Cumberland, 2001; Roth & Hellige, 1998). As it does not appear that any physiological research has been published examining the red light effect in humans (or in V5 in monkeys), the question of hemispheric lateralization remains unclear. The finding that the hypothesized effects were not present when looking at differences in the volume of activation may reflect less sensitivity in this particular measure to subtle within- and between-group differences, when compared to the t-test and PIC measures. However, this needs to be further investigated.

Additional weaknesses of this study include a relatively small sample size and a low luminance level of the projected red light. As first-degree relatives share approximately 50% of their genes with the proband, only a proportion of any randomly selected group of first-degree relatives of persons with schizophrenia would be expected to have one or more schizophrenia-related genes. A larger sample size would increase the proportion of relatives that have genetic loading for schizophrenia and would thereby increase the effect sizes of between-group findings. The luminance of the background colors was in the mesopic range at 0.9 cd/m^2, which was partially a result of hardware limitations from the monitor used in the scanner. It is possible that stronger luminance levels of red light would produce a stronger and more consistent suppressive effect on the M pathway across participants.

Despite these limitations, results demonstrate that, at least in the right hemisphere, diffuse red light appears to suppress neural activity of the M pathway in most healthy adults, similar to the effect found in non-human primates. It also appears that a subset of persons at genetic risk

for schizophrenia do not show this effect. Closer inspection of the results indicates that a subset of the relatives appeared to show the opposite effect to red light (increase in right hemisphere proportion of fMRI signal). This pattern of a subset of relatives showing evidence for the opposite M pathway response to red light is similar to that seen in an earlier behavioral study with a larger sample of relatives (Bedwell, Brown, & Miller, 2003).

It appears that the differential change in M pathway functioning in response to diffuse red light found in a subset of the relatives, both in the current study and in the earlier visual backward masking study (Bedwell et al., 2003), is a biobehavioral genetic marker for schizophrenia that is independent of baseline differences in M pathway functioning. The current study found that the group difference in fMRI signal change to red light remained (although was somewhat less robust) after controlling for group differences in fMRI signal under neutral light conditions. Similarly, the previous visual backward masking study (Bedwell et al., 2003) found a group difference in change in accuracy to red light, even though the groups did not differ in accuracy from the neutral light condition. Thus, converging evidence suggests that a differential response in the M pathway to diffuse red light may represent a novel and potentially useful biobehavioral marker for schizophrenia.

Future studies will attempt to replicate these findings in an independent group of relatives and in persons with schizophrenia. The proportional right hemisphere measures will be predicted *a priori* to investigate whether findings remain specific to these measures. New psychophysical techniques will be established in an attempt to produce a more consistent change in M pathway activity in healthy controls. If this can be accomplished, subtle group differences may become more robust. Future studies will also investigate the specificity and sensitivity of these methods toward genetic loading for schizophrenia. If this technique can be adequately

refined to be highly sensitive and selective for schizophrenia-related genes, it may prove useful as a biobehavioral marker in genetic linkage studies that attempt to identify which genes transfer risk for the disorder.

References

Bedwell, J. S., Brown, J. M., & Miller, L. S. (2003). The magnocellular visual system and schizophrenia: what can the color red tell us? Schizophrenia Research, 63(3), 273-284.

Hellige, J. B. (1996). Hemispheric asymmetry for visual information processing. Acta Neurobiol Exp (Wars), 56(1), 485-497.

Hellige, J. B., & Cumberland, N. (2001). Categorical and coordinate spatial processing: more on contributions of the transient/magnocellular visual system. Brain Cogn, 45(2), 155-163.

Kosslyn, S. M., Maljkovic, V., Hamilton, S. E., Horwitz, G., & Thompson, W. L. (1995). Two types of image generation: evidence for left and right hemisphere processes. Neuropsychologia, 33(11), 1485-1510.

Roth, E. C., & Hellige, J. B. (1998). Spatial processing and hemispheric asymmetry. Contributions of the transient/magnocellular visual system. J Cogn Neurosci, 10(4), 472-484.

APPENDIX A

DIAGNOSTIC SCREEN

EXTENTION OF DIAGNOSTIC INTERVIEW TO COVER LAST YEAR:
Schizophrenia fMRI Study – Bedwell and Miller

Participant #: _____

Date: _____

Has you use of alcohol increased notably in amount and frequency in the past year?
YES / NO

Have you taken street drugs in the past year or become "hooked" on a prescription medicine?
YES / NO

Are you currently taking any prescriptions? YES / NO

_____ _____ _____

_____ _____ _____

Have you had a head injury or seizure in the past year? YES / NO

Have you been diagnosed with any neurological or psychiatric condition in the past year?
YES / NO

In the past year, have you become notably more anxious or nervous? YES / NO

In the past year, have you had a period that lasted at least two weeks where you felt depressed or down most of the day nearly every day? YES / NO

In the past year, have you had a period that lasted at least three days when you were feeling so good, "high", excited, or hyper that other people thought you were not your normal self or you were so hyper that it got you into trouble? YES / NO

In the past year, have you started to become bothered by thoughts that didn't make any sense and kept coming back to you even when you tried not to have them? YES / NO

In the past year, have you noticed that you have to do a certain behavior over and over again and couldn't resist doing it, like washing your hands again and again, counting up to a certain number, or checking something several times to make sure you've done it right? YES / NO

In the past year, has your eating become out of control or have you begun to weigh much less than others think you ought to weigh? YES / NO

In the past year, have you been assaulted or experienced an event where you felt your life was in danger? YES / NO

In the past year, have you often worried that other people are talking bad about you or are plotting to hurt you? YES / NO

In the past year, have you started to feel that you have special magical powers to do things that other people can't seem to do? YES / NO

In the past year, have you heard noises or voices of people whispering or talking and could not figure out where it was coming from? YES / NO

In the past year, have you had visions or seen things that other people couldn't see?
YES / NO

In the past year, have you noticed the onset of any other significant psychological problems that I have not asked about? YES / NO

Describe: