THE NOISY INPUT HYPOTHESIS OF SCHIZOPHRENIA

by

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ABSTRACT

Introduction: Differences in the level of scotopic intrinsic noise were examined in a group of 15 schizophrenia participants and 15 matched controls in order to test the *Noisy Input Hypothesis of Schizophrenia*, which states that many of the higher-order disturbances that characterize the disorder may be partly due to increased intrinsic noise at the level of sensory input. In addition to intrinsic noise, a number of other variables were measured including scotopic sensitivity (SS), macular pigment optical density (MPOD), critical flicker fusion frequency (CFF), and lens optical density (OD). With the exception of CFF, none of these variables have been assessed in schizophrenia but, based on past evidence, might be expected to differ for this group. Method: Intrinsic noise was assessed by measuring variability in scotopic thresholds. Thresholds were measured using the method of constant stimuli and a two-alternative forced choice procedure. The stimuli consisted of three 1.85-degree diameter test stimuli (at 410, 510, and 565 nm) presented at 10-degrees in the periphery. Lens OD was derived by subtracting the 410 nm log relative scotopic sensitivity (LRSS) values from the 565 nm values. MPOD was measured with a 1-deg test stimulus using heterochromatic flicker photometry. CFF values were obtained with a 1-deg, 570 nm stimulus using the method of limits. Results: The schizophrenia participants did not differ from the control participants with respect to intrinsic noise, LRSS, or

lens OD. In contrast, average CFF thresholds ($p < 0.004$) were significantly lower in the schizophrenia group. The MP density of the schizophrenia participants was 24% lower than the controls and marginally significant ($p < 0.08$). There were no significant associations between the dependent variables except for MPOD and LRSS. Discussion: The main result of this study, similar intrinsic noise levels in schizophrenia and control participants, does not support the *Noisy Input Hypothesis.* In fact, the schizophrenia participants were most similar on those items which might be expected to be most linked to the hypothesis (lens OD, LRSS, and intrinsic noise). The largest difference between the groups was in CFF, which is widely considered to be determined by processing at the level of the visual cortex. One interpretation of these results is that many of the visual disturbances reported in schizophrenia are mediated by post-receptoral mechanisms. More data (e.g., larger samples using non-medicated schizophrenia participants), particularly photopic, however, are needed to confirm this interpretation.

INDEX WORDS: Schizophrenia, Intrinsic noise, Scotopic sensitivity, Macular pigment, Critical flicker fusion frequency, Lens optical density

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DEDICATION

I dedicate this dissertation to my wonderful husband, Corey, and my family. Without their love and support I could not have accomplished so many of my life goals.

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CHAPTER 1

INTRODUCTION

Specific Aims.

1.) The main objective of the present study was to test the *Noisy Input Hypothesis of Schizophrenia*. Specifically, whether schizophrenia participants have greater intrinsic noise in their sensory systems than matched controls was investigated by measuring the variability in scotopic visual thresholds. Thus, the current study assessed scotopic intrinsic noise, which is hereafter referred to as *scotopic intrinsic noise* or simply *intrinsic noise*.

2.) Another goal of this project was to provide baseline data on the scotopic vision of schizophrenia patients, a group particularly prone to lower-level visual problems. Although many studies have evaluated the photopic vision of schizophrenia participants, there are no published data regarding the scotopic vision of schizophrenia participants. Thus, whether or not the scotopic sensitivity (SS) of schizophrenia patients significantly differed from controls was assessed. Critical flicker fusion frequency (CFF) values were also measured in these two groups. Unlike scotopic thresholds (sensitivity = 1/threshold), CFF is probably determined post-receptorally and is often not considered as part of the input stage in visual processing. Some limited data has suggested that CFF is decreased in schizophrenia.

3.) Another goal of the present study was to test some additional factors that may influence intrinsic noise. For example, increased lens optical density (OD) could influence intrinsic noise based on gain related to compensation effects necessary due to increased optical filtering. Retinal macular pigment could influence intrinsic noise based on both filtering and

biological effects. If these variables influence intrinsic noise and differed according to schizophrenia status, they may partially explain any intrinsic noise differences found between schizophrenia and normal control participants.

Overview and Rationale.

Past studies have found that schizophrenia patients exhibit specific deficits in lower-level visual functioning. For example, schizophrenia patients have impairments in contrast sensitivity (Kéri, Antal, Szekeres et al., 2002), temporal vision (Slaghuis & Bishop, 2001), spatio-temporal vision (Kéri et al., 2002; Schwartz, McGinn, & Winstead, 1987), and backward masking (Butler, Harkavy-Friedman, Amador et al., 1996; Cadenhead, Serper, & Braff, 1998; Slaghuis & Bakker, 1995) when compared to control participants. The findings of many of these studies suggest a magnocellular (M) pathway deficit in schizophrenia (e.g., Slaghuis & Bishop, 2001; Cadenhead et al., 1998). The M pathway extends from the retina to higher cortical areas, and whether the origin of the deficit is sensory or cortical is unknown.

Since the primary symptoms of schizophrenia are higher-order cognitive deficits (e.g. hallucinations, delusions, impoverished speech, etc.), the majority of the research on the etiology and treatment of the disorder has focused on higher-order processing and has adopted a top-down view of the origin of the symptoms. From a top-down view-point, sensory dysfunction would result from cortical dysfunction. However, a recent study on the steady state visual evoked potentials (ssVEPs) of schizophrenia participants indicated that visual deficits could originate earlier, e.g. pre-cortical (Kim, Zemon, Saperstein et al., 2005). The authors also suggested that lower-level processing deficits likely contribute to the higher-level cognitive and perceptual disturbances that are the hallmark symptoms of the disorder.

Therefore, the present study proposes a new bottom-up theory of schizophrenia: the *Noisy Input Hypothesis of Schizophrenia*. According to this hypothesis, the higher-order disturbances found in schizophrenia (e.g. visual or auditory hallucinations, etc.) may be largely due to increased intrinsic noise at the level of sensory input (e.g. retina, cochlea, etc.), which the brain would interpret as actual sensory signals (i.e., impaired input results in impaired output). The present study focuses on how this hypothesis applies to the visual system; it could, however, be applied to other sensory systems. A certain level of intrinsic noise is inherent in all visual thresholds; therefore, performance at threshold is heavily limited by intrinsic noise (Donner, 1992). Although it can arise at numerous levels of the visual system, intrinsic noise associated with scotopic thresholds is thought to originate at the input stage, i.e., at the level of the retina (van Rossum & Smith, 1998). When in a fully dark-adapted state, the visual system is maximally sensitive, and the effects of intrinsic noise should be most evident. Thus, as a first test of the *Noisy Input Hypothesis of Schizophrenia*, the present study investigated the scotopic or dark-adapted thresholds of schizophrenia participants compared to controls. A further rationale for selecting scotopic measures as opposed to photopic thresholds is that no published data exists regarding the scotopic thresholds of schizophrenia patients. This information would be particularly informative in the literature on M pathway deficits in schizophrenia, since both the M pathway and scotopic thresholds are mediated by the rod photoreceptors.

If schizophrenia participants have increased intrinsic noise at the retinal stage of visual processing, one could question what factors might promote such increases. One possibility is increased absorbance of light by dense ocular media. A denser lens could decrease the amount of light incident on the retina. In order to deal with an overall decrease in input, the visual system may increase gain to offset such loss (Werner, 1996). Such increases in gain might be

accompanied by increases in intrinsic noise. Another possibility is that a more opaque lens would cause increased light scattering. Although some of this scattered light would still strike the photoreceptors in the direct light beam path, most of it would likely strike other photoreceptors. Thus, increased intrinsic noise could be due to the decreased light in the beam path and/or scattered light striking other photoreceptors. In any event, increased lens OD could influence intrinsic noise.

Schizophrenia participants are often required to take antipsychotic medications for extended periods of time, and studies have indicated that common antipsychotic drugs such as chlorpromazine and several other phenothiazines are associated with increased lens OD (see Shahzad, Suleman, Shahab et al., 2002 for review). In order to control for the possibility that schizophrenia participants have denser lenses compared to control participants, lens OD was assessed. Moreover, whether or not changes in lens OD are related to changes in intrinsic noise was evaluated.

Another factor that may influence scotopic intrinsic noise is retinal concentrations of macular pigment (MP). Past studies have found that macular pigment optical density (MPOD) and LRSS (Hammond, Wooten, & Snodderly, 1998) are positively related. MP is primarily composed of the dietary carotenoids lutein (L) and zeaxanthin (Z) (Bone, Landrum, & Tarsis, 1985), which are highly concentrated in rod outer-segments (Rapp, Maple, & Choi, 2000). Moreover, Hammond and Wooten (2005) have suggested that MP might be related to intrinsic noise based on numerous biological effects throughout the visual system. Thus, MP was measured as another possible factor that could help explain any differences found between the schizophrenia and normal control participants.

Finally, CFF values were obtained. One past study has indicated that CFF values are reduced in schizophrenia participants compared to controls (Black, Franklin, de Silva et al., 1975). Therefore, CFF was measured with two goals in mind. The first was simply to measure at least one variable that had been shown to differ in schizophrenia to assure that the current sample was characteristic of other schizophrenia samples. The second goal was to measure a variable that would not reflect the subtle alterations in input that were addressed with the other variables (such as intrinsic noise and SS). Obviously, CFF can be altered by gross alterations in input. For example, disease changes in the retina such as age-related macular degeneration have been shown to cause flicker abnormalities (Phipps, Dang, Vingrys et al., 2004). In most cases, however, CFF thresholds are determined by the central nervous system (CNS) (for review see Simonson & Brožek, 1952). In fact, CFF thresholds are often used as an overall indicator of CNS functioning (e.g., Curran & Wattis, 2000; Curran, Wilson, Musa et al., 2004). Moreover, animal studies have indicated that CFF is determined by the cells of the primary visual cortex (e.g., Wells, Bernstein, Scott et al., 2001). Therefore, if differences in CFF are found in the absence of alterations in input (e.g. SS) for the patient population, this would argue against a retinal origin for visual disturbances in schizophrenia.

Lower-Level Visual Deficits Found in Schizophrenia.

Contrast Sensitivity.

Past studies have indicated that schizophrenia participants have significantly altered contrast sensitivity (CS) compared to control participants. The normal contrast sensitivity function (CSF) of humans is an inverted U-shaped curve with peak sensitivity to spatial frequencies around 4-6 cycles per degree of visual angle (c/deg). Kéri, Antal, Szekeres et al. (2002) found that medicated schizophrenia patients exhibit CS deficits for medium and high

spatial frequencies (2.9-14.4 c/deg) and that the differences were more marked in the patients receiving higher doses of conventional antipsychotics (e.g., haloperidol). Studies have also indicated that there is a difference between the CS of Type I (schizophrenia patients with mostly positive symptoms such as visual and auditory hallucinations and delusions) and Type II schizophrenia patients (patients with mostly negative symptoms such as anhedonia or impoverished speech). For instance, Slaghuis (1998) found that Type I schizophrenia participants only showed deficits in CS at the higher spatial frequencies (i.e., 4, 8, & 12 c/deg) and that Type II schizophrenia participants had attenuated CS at all spatial frequencies tested (i.e., 0.5, 1, 2, 4, 8, & 12 c/deg). Although the effects of medication cannot be completely ruled out, the results of Slaghuis (1998) cannot be explained by medication-use alone. Slaghuis found that there were no significant differences in medication-use between the Type I and Type II schizophrenia patients; thus, if medication was the sole cause of changes in the CS deficits then there should have been a global and uniform decline in visual performance in the patients compared to the controls. However, as mentioned, there were differential impairments in the two groups of patients with Type I schizophrenia patients only exhibiting deficits at certain frequencies. Therefore, it is evident from the literature that individuals with schizophrenia have significantly impaired CS, but the exact nature of their deficit depends on whether they present more negative or positive symptoms of the disorder and the role of medication is not completely understood.

Temporal Vision.

In addition to deficits in CS, schizophrenia patients also exhibit temporal vision deficits compared to normal controls (e.g., Slaghuis & Bishop, 2001; Black et al., 1975). Temporal vision is characterized by the temporal modulation transfer function (TMTF) (sensitivity vs. temporal frequency). Like spatial vision, human sensitivity for temporal frequencies drops off at

lower and higher presentation rates. A common visual measure of human temporal vision is the high frequency cut-off value of the TMTF, critical flicker fusion frequency (CFF). CFF is the average rate that a given stimulus (usually presented as a square wave) begins flickering (as the rate is slowed) and fuses (as the rate is increased). Since CFF is linearly related to luminance (the Ferry-Porter law), it is also possible to keep presentation rate constant, and measure thresholds by varying luminance (in this case, the value is called flicker sensitivity, FS).

Studies have found impairments in both FS and CFF in schizophrenia. For example, Slaghuis and Bishop (2001) found that Type II schizophrenia patients have reductions in luminance FS at medium (8-10 Hertz, Hz) and high temporal frequencies (>16 Hz); Type I schizophrenia patients did not show a deficit in FS. Thus, consistent with Slaghuis (1998), the results of Slaghuis and Bishop (2001) cannot be explained by medication-use alone. Again, all their patients were on a stable regime of antipsychotic medication; however, they did not find a global reduction in FS in schizophrenia. In addition, one past study found that medicated schizophrenia patients have reduced CFF values (mean CFF = 37 Hz) compared to controls (mean CFF = 40 Hz; Black et al., 1975). However, since many of the participants were on antipsychotic medication, the effects of medication could not be ruled out. In general, it appears that schizophrenia patients have significant FS and CFF deficits. The influence of medication, however, is not completely understood.

Spatio-temporal Vision.

Schizophrenia participants also exhibit dysfunctions in spatio-temporal (S-T) processing. The normal visual system tends to have a single peak that drops off at low and high frequencies for both spatial and temporal domains. Sensitivity to high spatial frequencies decreases slightly at high temporal frequencies, and sensitivity to low spatial frequencies is increased substantially.

At very low temporal frequencies, sensitivity to low spatial frequencies is decreased (Kelly, 1983, 1984). Kéri et al. (2002) found that medicated schizophrenia patients have impaired performance compared to normal controls over a large range of spatial frequencies (i.e., 0.5-14.4 c/deg) at a temporal frequency of 8 Hz and that the differences were more marked in the patients receiving higher doses of conventional antipsychotics (e.g., haloperidol). Consistent with Kéri et al. (2002), Schwartz et al. (1987) found that medicated schizophrenia patients have S-T deficits; however, unlike the former authors, they did not find an effect of medication. Their results indicate that schizophrenia patients tend to be poorer at detecting temporal changes at medium to high spatial frequencies (i.e., 3.25 & 6.5 Hz), independent of medication dosage, compared to controls (Schwartz et al., 1987). Therefore, past studies reveal that schizophrenia participants have significant S-T CS deficits; however, again the influence of medication is not entirely understood.

Backward Masking.

Perhaps the most well-researched lower-level visual parameter in the schizophrenia literature is backward masking (BM). Masking paradigms can provide information on both spatial and temporal vision. They involve using one stimulus, the mask, to reduce the visibility of another stimulus, the target (usually a spatial frequency grating). BM involves presenting the mask after the target stimulus. By presenting the mask quickly after the target, the processing of the target is disrupted. Schizophrenia patients show marked deficits in BM tasks (Butler et al., 1996; Cadenhead et al., 1998; Slaghuis & Bakker, 1995). For example, they require longer interstimulus intervals between the target stimulus and mask in order to correctly identify the target compared to controls (Braff, Saccuzzo, & Geyer, 1991). Moreover, past studies have indicated that these BM deficits are not due to antipsychotic medication (e.g., Butler et al.,

1996). In addition, remitted schizophrenia patients (Green, Nuechlerlein, Breitmeyer et al., 1999) and unaffected siblings of schizophrenia patients (Green, Nuechterlein, & Breitmeyer, 1997) also show significant deficits in BM, which lends support to the idea that the impairments are independent of medication-use. Therefore, BM impairments appear to be one of the stronger visual indicators of susceptibility to schizophrenia; poor performance on BM tasks is often considered a vulnerability factor for developing the disorder.

Some studies have found that the negative symptoms of schizophrenia are more strongly correlated with BM disparities (e.g., Voruganti, Heslegrave, & Awad, 1997) and that Type II schizophrenia patients are more affected by BM than controls and Type I schizophrenia patients (e.g., Slaghuis & Curran, 1999; Slaghuis & Bakker, 1995). Thus, although past studies have consistently found BM impairments in schizophrenia (independent of medication-use), there seems to be a differential effect in Type I and Type II schizophrenia.

Taken together, it is clear that schizophrenia can be characterized as a condition associated with a high degree of visual co-morbidity. Although many visual parameters have been measured (particularly photopic, temporal, and spatially-defined stimuli), many visual parameters have not been evaluated. Evaluating the relation between schizophrenia and visual performance using different types of stimuli (e.g. scotopic measures of visual sensitivity) is important since differences on these measures (or similarities) may reveal fundamental aspects of the condition.

Possible Scotopic Sensitivity Deficits in Schizophrenia.

An extensive literature search revealed only one article that mentioned psychiatric disorders and scotopic thresholds (i.e., Granger, 1957). Granger reported that participants with psychiatric disorders (neuroses and psychoses) have significantly higher scotopic thresholds than

controls. Although it is likely that some of Granger's participants had schizophrenia, the author did not report the exact nature of the psychiatric disorders. Therefore, given the information available, it was concluded that no published data exists specifically regarding the scotopic sensitivity (SS) of schizophrenia patients.

There are at least three lines of evidence consistent with the possibility that schizophrenia patients have SS deficits. (1.) A number of past studies have indicated that the visual deficits found in schizophrenia are due to a dysfunction in the transient or M pathway (e.g., Butler, Schechter, Zemon et al., 2001; Cadenhead et al., 1998). Moreover, psychophysical and electrophysical evidence has indicated that the M pathway plays a dominant role in scotopic vision (Benedek, Benedek, Kéri et al., 2003). Benedek et al. (2003) measured static and dynamic CS and ssVEPs (in non-diseased individuals) under photopic and scotopic conditions, and their results indicated that the M pathway most likely mediates scotopic visual activity. Therefore, if schizophrenia patients have imparied M pathways and M pathways mediate scotopic vision, then it follows that schizophrenia participants should also have impaired SS.

(2.) Medicated and drug-naïve schizophrenia patients have reduced docosahexaenoic acid (DHA) (Khan, Evans, Gunna et al., 2002), which is the most abundant essential polyunsaturated fatty acid in the phospholipids of the rod outer segment membranes. Since human SS is mediated by the rod photoreceptors, it is possible that reduced DHA affects rod function and in turn SS. Consistent with this idea, reduced retinal DHA content by dietary means alters rod photopigment content and function *in vivo* in rats (Bush, Malnoë, Remé et al., 1994). Therefore, if schizophrenia patients have reduced DHA and DHA alters rod-mediated functions such as SS, it is possible that schizophrenia participants may also have SS deficits.

(3.) Schizophrenia patients have altered electroretinogram (ERG) waveforms compared to normal controls. Specifically, they have reduced a-wave amplitudes, which originate from rod and cone photoreceptor function (Warner, Laugharne, Peet et al., 1999). Thus, if schizophrenia patients have altered rod function compared to controls, as suggested by ERG studies, it is probable that this difference would be reflected in psychophysical studies comparing the SS of schizophrenia patients versus controls.

Taken together, these three lines of evidence form a strong argument for the possibility of a SS deficit in schizophrenia. Thus, one objective of the present study was to provide baseline data on this visual parameter in schizophrenia. If such an impairment exists in the disorder, it would provide further support for the idea of a M pathway deficit in schizophrenia. Furthermore, information on the scotopic vision of schizophrenia participants would aid in a better understanding of the underlying pathology in the disorder.

Intrinsic Noise in the Visual System

The main objective of the present study was to investigate whether schizophrenia patients have greater intrinsic noise in their visual systems than controls by measuring the intrinsic noise inherent in scotopic visual thresholds. Noise, in general, can be defined as "a stochastic disturbance that obscures information of interest" (Cohn & Lasley, 1986, p. 501). Consistent with this definition, the present study defined intrinsic noise as stochastic disturbances that occur within a system (i.e., the visual system) that obscures the information of interest (i.e., the stimuli used in the study). Intrinsic noise is a fundamental part of every neurological system, including the visual system, and all visual thresholds are affected by intrinsic noise (for a review see Cohn & Lasley, 1986 or Cohn, 2004). For instance, studies have consistently found that scotopic or rod-mediated thresholds are significantly limited by intrinsic noise (Donner, 1992; Copenhagen,

Donner, & Reuter, 1987). Results of single-cell recordings of membrane currents from rod outer-segments of healthy monkeys show continuous random fluctuations in activity in the absence of any stimulation (in the dark) (Baylor, Nunn, & Schnapf, 1984); thus, there is a significant level of ongoing intrinsic noise generated in the rod outer-segments of primates. Furthermore, as mentioned in the overview, intrinsic noise associated with scotopic thresholds is thought to originate at the level of the retina (van Rossum & Smith, 1998).

Also as mentioned in the overview, biological changes in the density of the crystalline lens could influence intrinsic noise. Studies have indicated that common antipsychotic drugs, which schizophrenia participants are often required to take for extended periods of time, have been strongly associated with increased lens OD (see Shahzad et al., 2002 for review). Increased lens OD could significantly reduce the amount of light incident upon the photoreceptors and/or affect the amount of light scattering within the eye. These changes would undoubtedly effect the functioning of the photoreceptors and influence the level of intrinsic noise within the visual system. In order to assess the possibilities that schizophrenia participants have denser lenses compared to controls and that increased lens OD is related to elevated intrinsic noise, lens OD was measured and a correlational analysis was conducted on lens OD and intrinsic noise.

Possible Influence of MP & DHA on Intrinsic Noise & Their Relations to Schizophrenia.

In addition to the biological changes, another factor that may contribute to scotopic intrinsic noise is retinal concentrations of dietary-derived substances such as carotenoids and fatty acids. As mentioned, the carotenoids L and Z, which when located in the retina are referred to as MP, are heavily concentrated in the rod outer segments (Rapp et al., 2000). Moreover, past studies have indicated there is a significant positive relation between MPOD and SS (e.g., Hammond et al., 1998). Similarly, (as also mentioned) DHA is the most abundant essential

polyunsaturated fatty acid (EPUFA) in the rod outer segments and may influence rhodopsin activation. Therefore, it is probable that reductions in either MPOD or DHA could influence rod photoreceptor functioning and thereby influence scotopic intrinsic noise in the schizophrenia and control participants of the current study.

In addition, recent monkey and human studies have indicated that there is a significant interaction between MP and omega-3 fatty acids, such as DHA, in the eye (Leung, Sandstrom, Zucker et al., 2004; Snodderly, Chung, Caldarella et al., 2005). Snodderly et al. (2005) supplemented 50 healthy women (ages 60-80 years) with either a placebo, L, DHA, or a combination of L and DHA and measured the effects of the supplementation on MPOD. They found that L alone increased MPOD eccentrically (i.e., 3-deg and 5-deg eccentricity) in the retina, and DHA alone increased MPOD in the most central portion of the retina where MP is generally the highest in concentration. The most interesting finding was the changes that occurred in the combination group; there were increases in both central and peripheral MPOD. This result indicated that DHA facilitated the accumulation of L in the blood.

Although it would be optimal to directly measure both MPOD and DHA in the retinas of the schizophrenia and control participants, there is not a direct method available to assess retinal concentrations of DHA *in vivo*. There is, however, an *in vivo* method for measureing retinal concentrations of MP, which recent studies have now shown may be a marker for DHA (Leung et al, 2004; Snodderly et al., 2005). MPOD values were obtained for the present study using a standard psychophysical procedure called heterochromatic flicker photometry. A difference between the mean MPOD of the schizophrenia participants and the controls was expected for the following reason: Past studies have indicated that schizophrenia patients have significant differences in DHA concentrations compared to controls. For example, schizophrenia

participants (medicated and drug naïve) have overall reduced cortical levels of the DHA compared to normal controls (Arvindakshan, Ghate, Ranjekar et al., 2003a; Khan et al., 2002; Assies, Lieverse, Vreken et al., 2001). Additionally, studies have found that schizophrenia patients have an increased rate of loss of DHA from the Sn2[1] position of the phospholipids (PLs) of their cell membranes. This loss leads to changes in the functioning of the membrane-associated proteins and cell signaling and a reduced rate of incorporation of the fatty acids into membrane PLs (for review see Horrobin, 1998). Thus, if DHA is significantly reduced in schizophrenia and DHA significantly influences MPOD, it is likely that schizophrenia participants also have reduced MPOD. Furthermore, it is possible these reductions could be related to increased scotopic intrinsic noise.

Hypotheses of the Present Study.

Hypotheses 1& 2: Schizophrenia participants have higher levels of scotopic intrinsic noise and elevated scotopic thresholds compared to matched controls.

Hypothesis 3: Intrinsic noise is positively related to SS.

Hypotheses 4 & 5: Schizophrenia participants have significantly increased lens OD compared to controls, and lens OD is positively correlated with intrinsic noise.

Hypotheses 6 & 7: Schizophrenia participants have reduced MPOD compared to matched controls, and MPOD is negatively correlated with intrinsic noise.

Hypothesis 8: Schizophrenia patients have decreased CFF values compared to normal, healthy participants.

Hypotheses 9 & 10: MPOD is positively related to CFF and SS.

[1] The three carbon atoms of the glycerol backbone of the general structure of a phospholipid are designated Sn1, Sn2, & Sn3.

Past studies have indicated that there is a significant positive relation between MPOD and CFF (Hammond & Wooten, 2005). This relation was seen for both younger and older participants. In contrast, Hammond et al. (1998) found a relation between MPOD and SS that was age-dependent; it was not present in the younger participants tested (i.e., ages 24-36 years). It was predicted that the results of the present study would be consistent with these past results.

CHAPTER 2

RESEARCH DESIGN AND METHODS

Participants.

Fifteen individuals diagnosed with schizophrenia (8 men and 7 women, mean age = 41.5, range = 26-55 yrs.) and fifteen matched control participants (8 men and 7 women, mean age = 41.13, range = 23-57 yrs.) were recruited for this study from various Georgia communities (e.g. Athens, Atlanta, etc.). In addition to age and sex, participants were matched on ethnicity and smoking history (see Table 1), and participants were excluded if they reported any ocular or systemic diseases that would be expected to influence the outcome of this study (e.g. macular degeneration). Furthermore, participants were matched to some extent on diet. Specifically, self-report information on the participants' average number of servings of fruits and vegetables per week was obtained on all but one participant (who did not provide this information) via a personal data questionnaire. Again, see Table 1 for a summary of that data.

All schizophrenia patients were on atypical antipsychotic medication, (e.g., olanzapine and risperidone), except for two patients who were reportedly unmedicated at the time of the study. Moreover, patients were psychologically assessed by two clinical psychologists on the Structured Clinical Interview for the DSM-IV (SCID-IV) in order to confirm their diagnosis of schizophrenia. Participants in the control group reported no personal or family history of schizophrenia or any other mental disorder.

Methodology for CFF Measures.

Apparatus.

A Newtonian-view optical device was used (for schematics see Wooten, Hammond, Land et al., 1999). The stimulus was a 1-deg, 570 nm circular test field with a luminance of 5.62 cd/m^2. A 2 mm artificial pupil was utilized to control for the effects of pupil size.

Table 1.

Demographic characteristics of Participants: Schizophrenia vs. Control Participants

	Schizophrenia Group	Control Group
Age	*M* = 41.47 years, *SD* = 8.2, Range = 26-55 years	*M* = 41.13 years, *SD* = 10.38, Range = 23-57 years
Sex	8 men 7 women	8 men 7 women
Ethnicity	10 Caucasians 4 African-Americans	10 Caucasians 4 African-Americans
Smoking History	7 current smokers 3 past smokers 5 non-smokers	10 current smokers 1 past smoker 4 non-smokers
Diet (mean number of servings of fruits & vegetables per week)	*M* = 8.25 (*SD* = 3.92)	*M* = 12.23 (*SD* = 8.52)

Method and Procedures.

CFF was measured psychophysically using the ascending and descending method of limits. The experimenter adjusted the flickering rate of the stimulus (1-50 Hz range) until a threshold was obtained. Only the left eye was assessed. In order to expedite the progress of the experiment, dark adaptation for the SS portion of the study began during the CFF measurements.

This was done by tightly patching the right eye of each participant at the beginning of the experiment. SS was only assessed in the participants' right eyes.

Methodology for MPOD Measures.

Apparatus.

The same Newtonian-view optical device used for CFF was employed for MPOD. A foveal test stimulus and a parafoveal reference stimulus were employed. The test stimulus was a 1-deg circular light, and the reference stimulus was a 2-deg circular light that fell approximately 7-deg out in the periphery. Both stimuli alternated between a 460 nm (8.6 cd/m^2) measuring field (peak MP absorbance) and a 550 nm (3.0 cd/m^2) reference field (minimal MP absorbance). A 10-deg, 2.75 cd/m^2, 470 nm circular background was also utilized for both stimuli. For parafoveal measurements, a 5-minute red fixation point was located in the left nasal hemi-retina on which participants were instructed to focus.

Method and Procedures.

MPOD was assessed using heterochromatic flicker photometry in accordance with the CAREDS protocol (Snodderly, Mares, Wooten et al., 2004), a standard protocol for measuring MPOD. The protocol included having the participants watch a short training film, which familiarized them with the stimuli and helped them understand exactly what they would be expected to do during the experiment. Measurements were acquired in the fovea (where MP is greatest) and in the parafovea (where light absorption by MP is negligible). The measuring and reference fields were superimposed and presented out of phase at an alternation rate of 11 to 12 Hz in the fovea condition and 6 to 7 Hz in the parafovea condition. These flicker rates were optimized for each participant using an algorithm based on flicker sensitivity thresholds (Snodderly et al., 2004). The participants adjusted the radiance of the 460 nm measuring field to

achieve minimal flicker with the 550 nm reference. Each experimental session consisted of multiple trials in order to obtain an average value.

Only the left eye of each participant was assessed. The MPOD of the left and right eyes of younger participants are usually well matched (Hammond & Fuld, 1992); however, studies have found small inter-ocular differences in older participants (i.e., participants over 50 years of age). For example, Snodderly et al. (2004) measured MPOD in the left and right eyes in participants between the ages of 50 and 79 years on two separate occasions and found a high correlation between the two eyes both times ($r = 0.79$ and $r = 0.8$, respectively). Although they did find some asymmetries in their data (i.e., measurements in the left eye were consistently lower), the differences were small (i.e., 0.05 OD), and the authors state that they were likely due to sampling bias.

Calculation of MPOD Values.

MPOD values were calculated by subtracting the log of measurements taken in the fovea (where MP is most densely concentrated) from the log of the measurements taken in the parafovea (where there is no MP). For a more complete discussion of the rationale behind this method of obtaining MPOD values see Snodderly and Hammond (1999).

Methodology for SS Measures.

Apparatus.

A Maxwellian-view optical system (see *Figure 1* for schematics) with a Fiber-Lite PL-900 DC Regulated Illuminator light source (Dolan-Jenner Industries: Lawrence, MA.) was constructed for the purposes of this project. Maxwellian-view allows the stimuli to be directly projected onto the retina and controls for any variations in pupil size. Two infrared cameras allowed constant viewing of the participant's iris and pupil and were used to constantly assure

that the stimuli were precisely aligned. Precise alignment was facilitated by a chin- and forehead-rest assembly that controlled for head movements.

Three different wavelengths were employed for the SS measures. All three stimuli were 1.85-degrees in diameter and located at 10-deg eccentricity. The main wavelength measured was 510 nm, which falls near the peak of the human SS curve (i.e., approximately 507 nm) and rod spectral sensitivity curve (see *Figure 2*). A 410 nm stimulus and a 565 nm stimulus were also tested. The purpose of assessing these particular wavelengths was to acquire lens density values. Since the lens absorbs a small amount of light at 510 nm (Wyszecki & Stiles, 1982), measurements of lens density allowed an analysis of the effect of lens absorption on the thresholds obtained for each participant. Light at 565 nm is not absorbed by the lens, but light at 410 nm is heavily absorbed. Consequently, these two wavelengths were used to obtain lens density values based on the classic scotopic threshold method (for a review see Snodderly and Hammond, 1999).

Method and Procedures.

The present study did not obtain absolute SS measures. The SS measures obtained for this study were relative to the actual stimulus and experimental parameters employed in the study; thus, our SS measures will be hereafter referred to as log relative scotopic sensitivity (LRSS) values. Participants were dark adapted for a total of 40 minutes prior to testing. They were instructed to fixate on a red dot that was located in their right visual field throughout the entire experiment. The time of stimulus exposure was 1000 msec with a short interval before the next set of tones were presented. LRSS for the 410 nm and 565 nm stimuli was assessed using the method of limits to obtain an approximate threshold and the method of constant stimuli to obtain more precise thresholds.

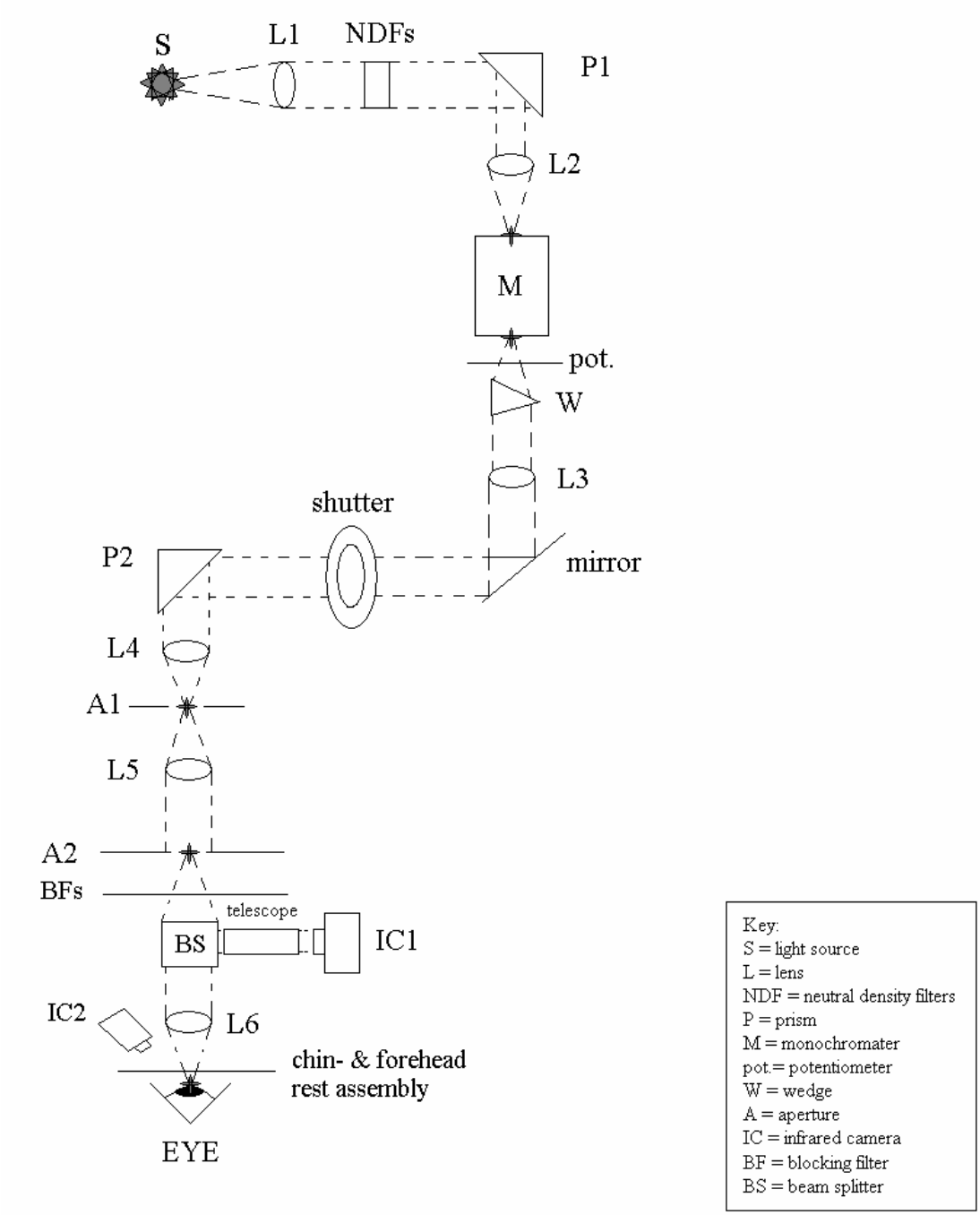

Figure 1. Schematics of the Maxwellian-view optical system.

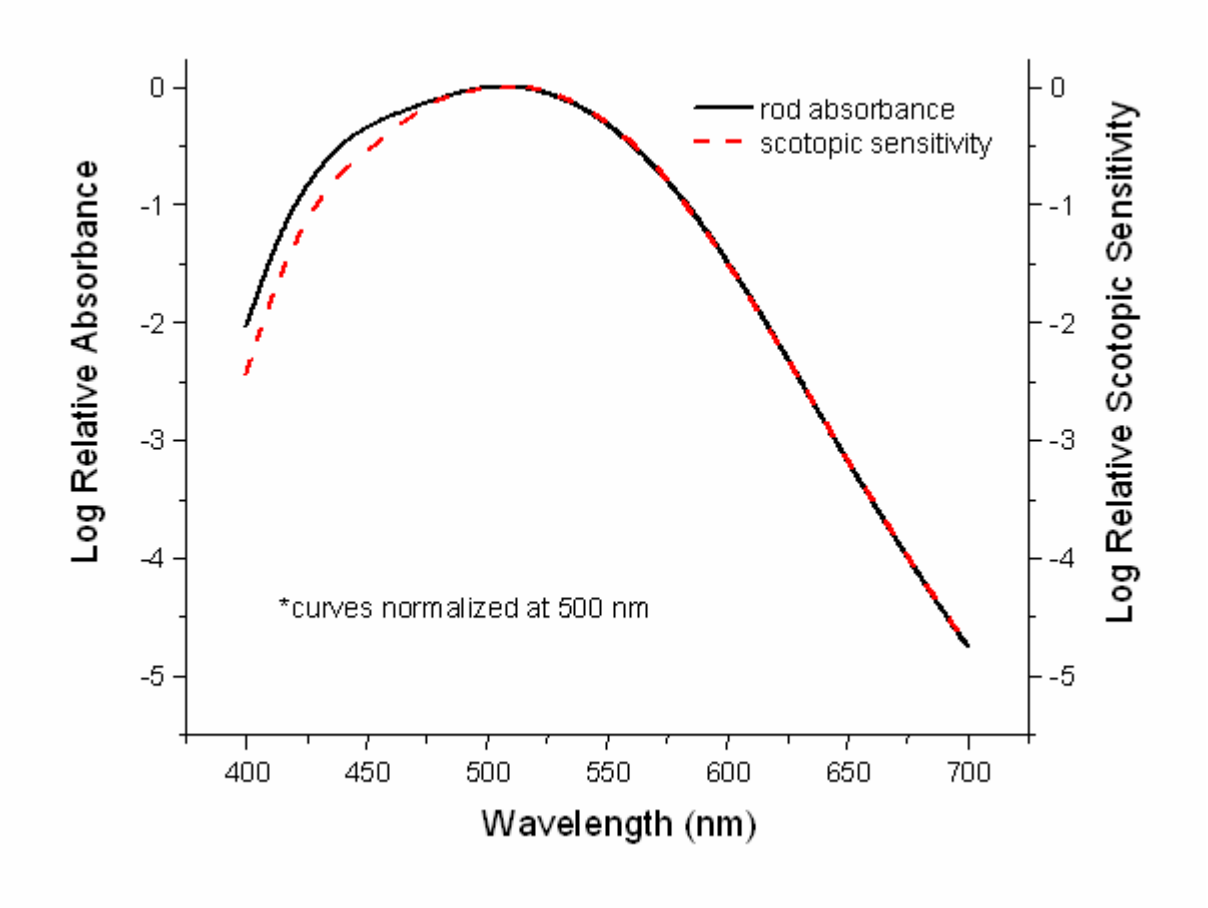

Figure 2. Rod extinction curve (solid line) with human scotopic sensitivity curve superimposed (dotted) (from Dartnall, 1953; CIE, 1951). Deviation at the shortwave end is due to the pre-retinal optical media (i.e., crystalline lens).

Much more extensive testing was done at 510 nm (compared to the 410 and 565 nm thresholds used for calculating lens OD). This testing was needed in order to generate the variability values that were used to derive the estimate of intrinsic noise. LRSS for the 510 nm stimulus was measured using a temporal two-alternative forced choice (2-AFC) paradigm. The

2-AFC paradigm developed for this project was similar to the one employed by Sturr, Zhang, Taub et al. (1997), and consisted of alternating trials when the stimulus was present and absent. The trials were presented by the experimenter and separated by two different auditory tones. Approximate thresholds were first assessed using the ascending and descending method of limits (the intensity of the test stimulus was varied progressively by approximately 0.05-log increments over a range of about 1 log unit) and the method of constant stimuli. The precise scotopic threshold was determined by utilizing the 2-AFC paradigm. The 510 nm stimulus was presented randomly after one of the two auditory tones. The participant's task was to indicate if the light appeared after the first or second tone. All correct and incorrect responses were recorded. Approximately 12 evenly spaced intensities (all intervals consisted of about 0.05 log units) below or above the previously estimated threshold was used. Each of these stimuli was presented a total of 8 times. Random performance (i.e., about 50% correct) was interpreted as the stimulus being below threshold. For the 2-AFC procedure, threshold was defined as the intensity that produced 75% correct responses. A similar cutoff was used for the 410 nm and 565 nm stimuli.

Calculation of Scotopic Thresholds.

In order to obtain scotopic thresholds, a probit regression analysis was conducted on the data from the 510 nm test stimulus. This analysis allows the derivation of a frequency-of-seeing curve (or psychometric function) from which threshold estimates were mathematically derived (for an example see *Figure 3*). These thresholds were corrected for lens absorbance at 510 nm for each individual participant. Although studies have indicated that the absolute thresholds for healthy participants vary, the overall shape of the psychometric function remains relatively constant (e.g. Hallett, 1969). Thus, differences in the shape of the psychometric functions of the two populations tested were not expected.

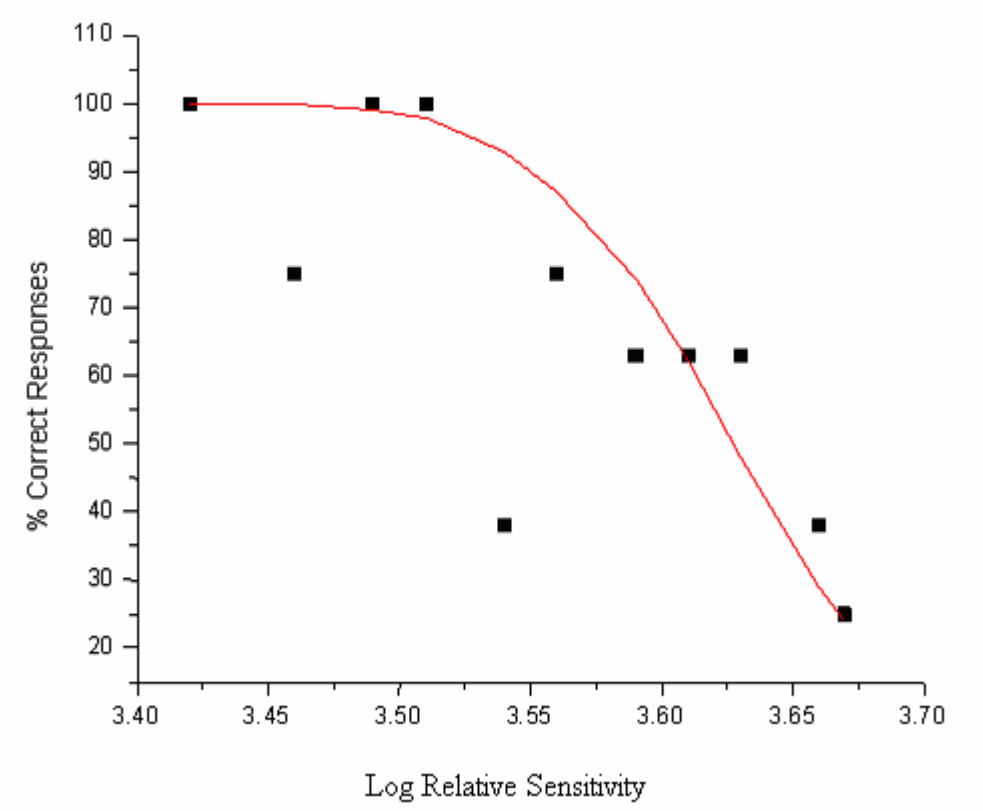

Figure 3. Sample psychometric function from control participant #9 (LRSS = 3.59).

Derivation of Intrinsic Noise from Scotopic Thresholds.

The present study used a traditional way of measuring intrinsic noise within visual thresholds. Specifically, the amount of variability in the value of the scotopic threshold at 510 nm was measured. In order to assess variability, the average deviation of the individual data points from the probit regression line (best fit line through a scatterplot of log relative sensitivity vs. probit values) was calculated. These average deviation values served as the measure of

intrinsic noise. Based on this procedure, individuals with larger deviation values would be interpreted as having higher amounts of intrinsic noise, and individuals with smaller deviation values would be interpreted as having smaller amounts of intrinsic noise (see *Figure 4* for examples). In order to assess the replicability of this procedure for deriving intrinsic noise values, two participants (1 woman and 1 man, ages 20 and 27) were asssesed on two separate occassions. Both participants had good ocular and systemic health and no history of mental disease. The average deviation values of the two participants from time one were 0.49 and 0.83, and the average deviation values of the participants from time two were 0.47 and 0.85, respectively. Although this comparison was only done on two participants, the fact that the values differed by only 0.02 suggests that the intrinsic noise estimates were reliable.

Derivation of Lens Optical Density.

Lens OD was calculated by subtracting the LRSS value at 410 nm (where there is high lens absorbance) from the LRSS value at 565 nm (where there is minimal lens absorbance) (Wyszecki & Stiles, 1982). This method is referred to as the balanced-rhodopisn method; see Snodderly and Hammond (1999) or van Norren and Vos (1974) for a discussion of the rationale behind using this technique for obtaining lens OD.

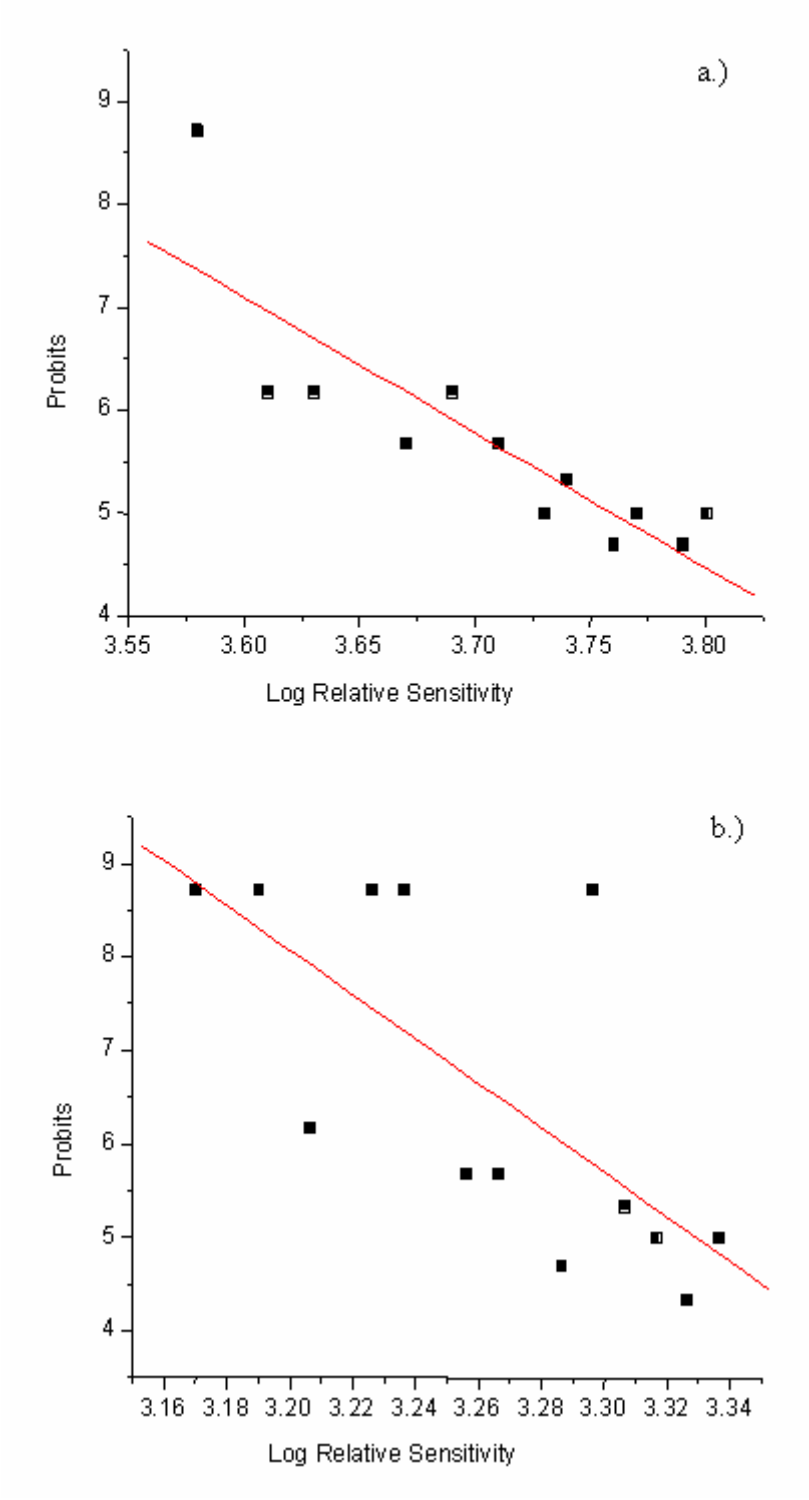

Figure 4. Scatterplots of LRSS vs. Probits: a.) Example of participant with low levels of intrinsic noise. b.) Example of participant with high levels of intrinsic noise.

CHAPTER 3

RESULTS

Statistical Analyses on Demographics.

Non-directional independent samples t-tests were conducted on the age and diet data. The significance level for both of these analyses was 0.05. The results of the analysis on age indicated that the mean age of the schizophrenia group (M = 41.47 years, SD = 8.2) was not significantly different from the mean age of the control group (M = 41.13 years, SD = 10.38) ($t(28) = -0.10$, $p < 0.92$). The results of the analysis on diet indicated that the average number of servings of fruits and vegetables reported by the schizophrenia group (M = 8.25, SD = 3.92) did not significantly differ from the average reported by the control group (M = 12.23, SD = 8.52) ($t(27) = 1.60$, $p < 0.12$). Thus, the results revealed that in addition to being matched on ethnicity, smoking, and sex (as seen in Table 1), the two groups were sufficiently matched on age and possibly diet if it is assumed that the self-report information on diet was valid.

Main Statistical Analyses.

The mean values of the schizophrenia and control participants on the five dependent variables (DVs), intrinsic noise, LRSS (at 510 nm), lens OD, MPOD, and CFF, were compared using one-tailed independent samples t-tests. The significance value was set at $p < 0.05$ for each of these tests. The total n of 30 was reduced to 29 on the tests of intrinsic noise, LRSS, and lens OD with the deletion of one case that was missing data on these variables. This participant was a schizophrenia patient whom could not be properly aligned with the Maxwellian-view system due to an extremely small pupil; even after 40 minutes of dark adaptation the participant's pupil was

still approximately 2-3 mm. In addition, one significant outlier was removed from the analyses involving LRSS. This participant was also a member of the schizophrenia group, and his LRSS value (i.e., 0.60) fell 4.63 standard deviation units away from the mean of the distribution of all of the LRSS scores (i.e., 3.01), which could have significantly skewed the results. This participant was not removed from the remaining analyses performed for this study because it was determined that his removal did not make any significant differences in the outcome of those analyses. Thus, for all analyses involving LRSS n = 28.

The results of the t-tests on intrinsic noise and LRSS were not significant, indicating that there were no mean differences in the levels of intrinsic noise ($t(27) = 0.10$, $p < 0.46$) or LRSS ($t(27) = 0.84$, $p < 0.21$) between the schizophrenia ($M = 0.76$, $SD = 0.14$; $M = 3.14$, $SD = 0.17$, respectively) and control participants ($M = 0.77$, $SD = 0.14$; $M = 3.07$, $SD = 0.26$, respectively). Similar to the intrinsic noise and LRSS findings, the results of the t-test on lens OD indicated that there were no significant differences between the two groups ($t(27) = 0.29$, $p < 0.39$, $n = 29$); the mean lens OD of the schizophrenia group was 0.96 ($SD = 0.24$), and the mean lens OD of the control group was 0.94 ($SD = 0.17$). However, the results revealed a marginally significant difference in MPOD ($t(28) = 1.45$, $p < 0.08$) and a strong statistical difference in CFF ($t(28) = 2.92$, $p < 0.004$) between the two groups, with the control group ($M = 0.29$, $SD = 0.14$; $M =$ 18.49 Hz, $SD = 2.41$, respectively) having slightly higher density values and much lower CFF values than the schizophrenia group ($M = 0.22$, $SD = 0.10$; $M = 16.13$ Hz, $SD = 2.00$, respectively). For a summary of the results see Table 2.1 and 2.2.

Table 2.1

Descriptive Statistics for the Schizophrenia and Control Participants on Intrinsic Noise, LRSS (at 510 nm), Lens OD, MPOD, and CFF.

	Schizophrenia Group	Control Group
Intrinsic Noise	$M = 0.76^{b}$ ($SD = 0.14$)	$M = 0.77^{a}$ ($SD = 0.14$)
LRSS (at 510 nm)	$M = 3.14^{c}$ ($SD = 0.17$)	$M = 3.07^{a}$ ($SD = 0.26$)
Lens OD	$M = 0.96^{b}$ ($SD = 0.24$)	$M = 0.94^{a}$ ($SD = 0.17$)
MPOD	$M = 0.22^{a}$ ($SD = 0.10$)	$M = 0.29^{a}$ ($SD = 0.14$)
CFF	$M = 16.13$ Hz^{a} ($SD = 2.00$)	$M = 18.49$ Hz^{a} ($SD = 2.41$)

a. $n = 15$
b. $n = 14$
c. $n = 13$

Table 2.2.

Results from the Directional Independent Samples T-tests Comparing Schizophrenia and Control Participants on Intrinsic Noise, LRSS (at 510 nm), Lens OD, MPOD, and CFF.

	t-value	df	p-value	n
Intrinsic Noise	0.10	27	0.46	29
LRSS (at 510 nm)	0.84	26	0.21	28
Lens OD	0.29	27	0.39	29
MPOD	1.45	28	0.08+	30
CFF	2.92	28	0.004*	30

* Statistically significant result.
+ Marginally significant result.

Correlational Analyses.

The possible relations between the five DVs (intrinsic noise, LRSS at 510 nm, lens OD, MPOD, and CFF) were investigated with a series of Pearson's r correlational analyses ($p < 0.05$). None of the correlational analyses were significant except for the analysis on MPOD and LRSS. There was a statistically significant positive association between MPOD and LRSS ($r = 0.54$, $p < 0.002$, $n = 28$). See Table 3 for a summary of the correlational analyses.

Table 3.

Pearson Correlation Matrix.

	Intrinsic Noise	LRSS (at 510 nm)	Lens OD	MPOD	CFF
Intrinsic Noise	1.0	0.07	-0.03	-0.18	0.05
LRSS (at 510 nm)	0.07	1.0	-0.24	0.54[a]	-0.08
Lens OD	-0.03	-0.24	1.0	0.09	0.24
MPOD	-0.18	0.54[a]	0.09	1.0	-0.009
CFF	0.05	-0.08	0.24	-0.009	1.0

a. Statistically significant at $p < 0.002$ level, one-tailed, n = 28

Note: For all correlations involving LRSS n = 28, and for all correlations involving intrinsic noise and/or lens OD (but not LRSS) n = 29. For all other correlations n = 30.

CHAPTER 4

DISCUSSION

Hypothesis 1.

The results failed to support the main hypothesis (i.e., the *Noisy Input Hypothesis of Schizophrenia*), which was based on the idea that schizophrenia participants would have increased levels of intrinsic noise compared to normal, matched controls. There were no differences in intrinsic noise between the schizophrenia participants and the controls. In fact, the mean intrinsic noise values of the two groups were almost identical and their standard deviation values were the same. The nearly identical results between the two groups argue strongly for both the precision of the measures and the strong similarity of the groups on these particular measures. Of course, schizophrenia participants could have other sources of visual input (e.g., photopic) that are noisier than controls, which future studies should explore.[2] One might assume, however, that high levels of intrinsic noise for one visual mechanism would predict high levels of intrinsic noise in another. If this assumption is true, it would suggest that schizophrenia participants do not have amplified intrinsic noise at the most initial stages of visual processing (i.e., retinal stage). The fact that schizophrenia participants are so similar to normal participants with respect to scotopic intrinsic noise at the retinal level implies that if they do have increased

[2] An initial attempt at addressing this question would be to simply evaluate the generalizability of intrinsic noise in the visual system. A literature search revealed, however, that this basic question has not been studied. This question would be easy to address in normal participants. If there is a significant correlation between intrinsic noise in scotopic and photopic thresholds, for example, there would be little reason to suspect that schizophrenia participants would have increased intrinsic noise in photopic thresholds given the results of the present study.

intrinsic noise compared to controls, the origin of that noise is post-receptoral. It is also important to note that, although schizophrenia participants may not have higher levels of noisy input compared to controls, they may actually suffer from such intrinsic noise more significantly. It is probably the case that intrinsic noise at all levels of the visual system interacts in complex ways. Thus, even normal amounts of scotopic intrinsic noise might be clinically meaningful if added to increased intrinsic noise at other levels (i.e., cortical-level) of the visual system.

The probability that schizophrenia participants have increased intrinsic noise at other levels of their visual system is high. For example, Winterer, Coppola, Goldberg et al. (2004) found that schizophrenia participants (and their clinically unaffected siblings) have significantly higher intrinsic noise in their frontal cortices than controls. They also determined that intrinsic noise was negatively correlated with the participants' performance on cognitive tasks, particularly those involving working memory and executive cognition. The authors postulate that increased prefrontal noise may be a genetic biomarker for suceptibility to schizophrenia. Although this finding has yet to be extended to the visual system, it provides rationale for studying cortical differences in sensory areas between patient and normal populations. Individuals with schizophrenia also have problems with cortical inhibition. Auditory event-related potential (ERP) studies have indicated that they exhibit significantly smaller P300 amplitudes to target attended stimuli than controls and reduced positive potentials in ERPs for unattended, non-target stimuli (Iwanami, Kanamori, Isono et al., 1996). Moreover, Clementz, Geyer, and Braff (1998) found that schizophrenia patients have decreased P50 supression compared to normal controls, which has been linked to impaired inhibition and a specific "vulnerability to sensory overload and cognitive fragmentation" (p. 1691). This phenomenon may exacerbate the influence of intrinsic noise on function and it more of a nuisance for

schizophrenia patients compared to controls. In particular, since schizophrenia patients have problems inhibiting irrelevant information (such as intrinsic noise), they may be more affected by scotopic intrinsic noise than controls.

Hypotheses 2 & 3.

The results of the present study also failed to support Hypotheses 2 and 3, which predicted the schizophrenia participants would have lower LRSS values than the controls and that LRSS would be negatively related to intrinsic noise. There were no significant group differences in LRSS and no association between LRSS and scotopic intrinsic noise. The lack of association between LRSS and scotopic intrinsic noise was not surprising, since there was very little variability in the LRSS measures (SD = 0.17, schizophrenia patients & SD = 0.26, controls) and even less variability in the intrinsic noise measures (SD = 0.14, schizophrenia patients & controls) compared to other variables measured (e.g., CFF: SD = 2.00, patients & SD = 2.40, controls). In contrast, the results of the test of Hypothesis 2 were surprising given the strong line of evidence (presented in the introduction) showing biological changes in schizophrenia participants that should result in LRSS deficits. For examples, past studies have found that participants with neuroses and psychoses have significantly lower SS (Granger, 1957), and schizophrenia participants have significantly impaired M pathways (Butler et al., 2001; Cadenhead et al., 1998), which plays a dominant role in scotopic vision (Benedek et al., 2003). One possible explanation as to why no differences in LRSS were found between the two groups was that the sample size was small. It is unlikely, however, that the sample was too small to obtain a reasonable estimate of the average LRSS of schizophrenia participants (e.g., the data were relatively normally distributed). If that is the case, a larger sample would only increase the

probability that the small difference found (2.3%) would be statistically significant. It is doubtful that such a small magnitude of difference is clinically meaningful.

Perhaps a more likely explanation is that the results were confounded by medication-use. The majority of the schizophrenia participants were on atypical antipsychotic medications (e.g. risperidone, olanzapine, etc.), which act on several neurotransmitter systems in the brain including the dopamine (DA) and serotonin (5-HT) systems. Past studies have found that DA and 5-HT affect the dark-adapted ERG response in the cat retina (Naarendorp, Hitchcock, & Sieving, 1993; Naarendorp & Sieving, 1991). However, Naarendorp et al. (1993) found that although DA (in particular) modulates signals in the rod pathway at higher stimulus intensities, it does not affect the absolute scotopic threshold. Thus, the effect of medication on the LRSS measures is unclear. In order to more closely examine this possibility, drug-naïve schizophrenia participants should be studied.

Hypotheses 4 & 5.

In addition to intrinsic noise and LRSS, lens OD was also tested in order to assess any group differences and investigate any relations between the density of the crystalline lens and intrinsic noise. Hypothesis 4 predicted that the schizophrenia participants would have significantly increased lens OD compared to the controls. Hypothesis 5 predicted that lens OD would be significantly related to intrinsic noise. The results did not support either hypothesis. The schizophrenia participants did not have significantly denser lenses, and lens OD and intrinsic noise were not significantly correlated. Similar to the LRSS measures, there was very little variation in the lens OD values of the two groups (SD = 0.24, schizophrenia patients & SD = 0.17, controls), which could account for the lack of association between lens OD and intrinsic noise. Two logical reasons for why there were no differences in lens OD between the two groups

are that the schizophrenia participants were taking atypical antipsychotic medications, which have not been linked to increased density of the crystalline lens, and two groups were matched on age. Age is strongly linked to increased lens OD (e.g. Pokorny, Smith, & Lutze 1987).

Hypothesis 6.

Hypothesis 6 stated that the schizophrenia participants would have significantly decreased MPOD compared to the controls. The results revealed that the schizophrenia patients had marginally decreased MPOD compared to matched controls. Although the results did not reach statistical significance, they were substantial. Given the high similarity between the schizophrenia participants and controls on most of the other variables, the differences in mean MPOD of the schizophrenia participants (M = 0.22, SD = 0.1) and the control participants (M = 0.29, SD = 0.14) were large (24%). The average value obtained for the control group is consistent with the mean density value (M = 0.28) reported in a recently published study, which assessed MPOD using the same stimulus parameters, apparatus, and procedures that were used in the present study and measured healthy individuals of approximately the same age range (Ciulla & Hammond, 2004). As evident from the standard deviation value reported in the Ciulla and Hammond article (i.e., SD = 0.21), MP tends to be more variable across participants, so the marginal statistical significance ($p < 0.08$), in this case, is probably due to an insufficient sample size. Furthermore, a power analysis revealed that there was insufficient statistical power ($1-\beta$ = 0.46) to detect a difference. In order to have sufficient power, 31 schizophrenia participants and 44 controls would need to be tested.

If schizophrenia participants have decreased MP, supplementing L and Z for these patients could produce clinically meaningful improvements. Studies have found that supplementation with omega fatty acids significantly reduced the symptoms of schizophrenia.

For example, supplementation with EPA (which is a precursor to DHA) was shown to reduce the positive and negative symptoms in a case study of a non-medicated schizophrenia patient over a sustained period of time (Puri, Steiner, & Richardson, 1998). In addition, Arvindakshan et al. (2003a) supplemented a group of schizophrenia participants with a combination of omega-3 fatty acids and antioxidants (in addition to their normal doctor-prescribed antipsychotic medication) and found a significant reduction in the negative and positive symptoms of the patients. DHA, in particular, seems to be related to a reduction in the negative symptoms of schizophrenia (Arvindakshan, Sitasawad, Debsikdar et al., 2003b). These results indicate that dietary modifications of omega fatty acids, DHA in particular, are an effective way of improving the symptoms of schizophrenia. As mentioned, past studies have found that DHA significantly influences retinal concentrations of MP (Leung et al., 2004; Snodderly et al., 2005). Therefore, it is possible that supplementation with DHA coupled with L and Z (the carotenoids that comprise MP) could provide additional benefits to schizophrenia participants in terms of their primary symptoms as well as other secondary symptoms. For example, based on the strong relation between MP and CFF (Hammond and Wooten, 2005), supplementation with DHA, L, and Z could improve the CFF deficits found in the disorder.

Hypothesis 7.

The results failed to support Hypothesis 7, which stated that intrinsic noise is positively correlated with MPOD. There was not a significant association between these two variables in the initial sample ($n = 29$). However, when 11 more control participants (5 men & 6 women; mean age = 31.36 years, age range = 19-59 years) were added, there was a significant, negative association ($r = -0.38$, $p < 0.01$, $n = 40$, see *Figure 5*) between MPOD ($M = 0.26$, $SD = 0.14$) and scotopic intrinsic noise ($M = 0.76$, $SD = 0.16$). Thus, the initial sample size was simply not large

enough to allow a sufficient evaluation of the relation between these two variables. A significant negative correlation between MPOD and intrinsic noise implies that increases in MPOD, which can be modified via dietary supplementation with the carotenoids L and Z (for review see Landrum & Bone, 2001), leads to decreases in intrinsic noise in the visual system and may improve visual functioning.

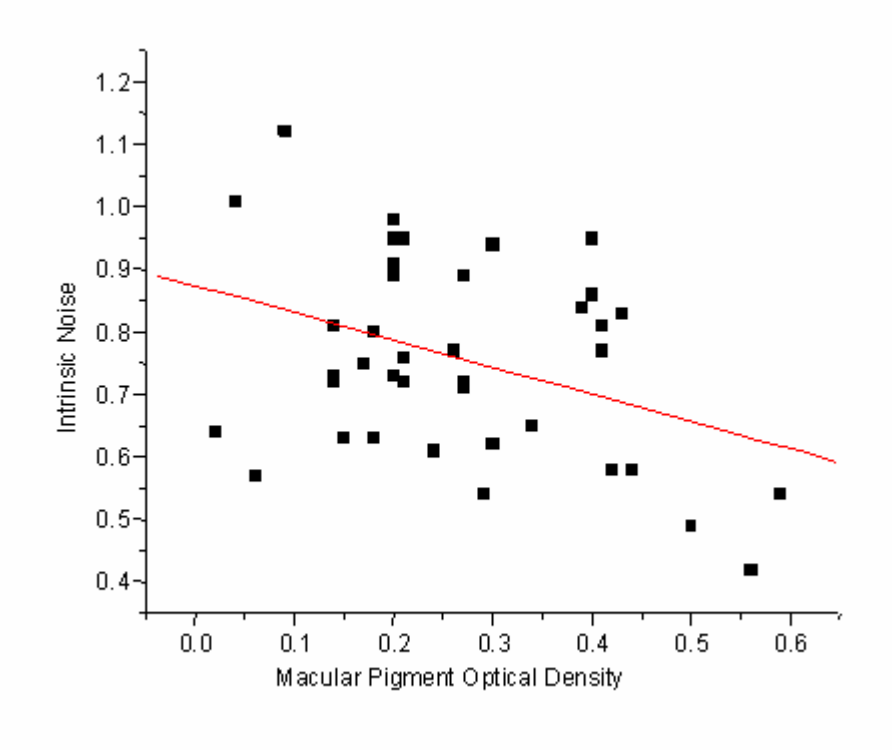

Figure 5. Scatterplot of MPOD vs. Intrinsic Noise with regression line [Y = 0.87 + (-0.43)x]. r = -0.38, $p < 0.01$, n = 40

Hypothesis 8.

Hypothesis 8 predicted that schizophrenia patients have decreased CFF values compared to normal, healthy participants. The results supported this hypothesis. The mean CFF value of the schizophrenia group was significantly lower than the mean CFF value of the control group, which was consistent with the findings of Black et al. (1975). However, future studies should test the entire TMTF on schizophrenia participants in order to see if they have any differences other than CFF (the high cut-off value of the TMTF).

Hypotheses 9 & 10.

Hypotheses 9 and 10 stated that MPOD is positively related to CFF and LRSS, respectively. Hypothesis 9 was not supported; the correlation between MPOD and CFF was not significant. This finding is inconsistent with that reported by Hammond and Wooten (2005) who found a significant positive correlation between these two variables. Since Hammond and Wooten also indicated that there is a significant relation between CFF and age, the data of the present study were reanalyzed after excluding the younger individuals (i.e., individuals under the age of 36). However, the test still did not reach statistical significance. One possible difference between the present study and Hammond and Wooten's study is that the average MP and CFF values of schizophrenia participants of the present study were low, and the strength of the correlation may have been reduced due to the restriction in range. In order to explore this possibility, an additional analysis excluding the patient population was conducted. The results of this analysis were also not significant. However, the exclusion criteria resulted in only 9 participants comprising the total sample; thus, it is unlikely that any correlational analysis would be significant with such a small sample of participants. The question of whether the present data adequately address hypothesis 9 is, therefore, open to question.

The results supported Hypothesis 10. Consistent with Hammond et al. (1998), there was a statistically significant positive relation between MPOD and LRSS. As noted, the macular carotenoids are found in rod outer-segments and could influence rod function. The overall strength of this relation, however, was not strong.

Concluding Remarks.

The fact that the schizophrenia and normal participants had such indistinguishable LRSS and scotopic intrinsic noise values has a number of implications. As noted by Cohn and Lasley (1986), noise can arise from many sources (e.g., externally, based on the quantum nature of light). External sources of noise would obviously not differ between the two groups; therefore, it was assumed that any differences in noise between these groups would arise from intrinsic sources. Intrinsic noise itself, however, could also originate from many sources ranging from fixation accuracy to changes in the membrane dynamics of photoreceptors. As such, the fact that the schizophrenia participants were so similar implies that, for the current experimental conditions, the schizophrenia participants did not differ. Furthermore, the finding that there was no relation between LRSS and scotopic intrinsic noise strongly supports Cohn's additional argument that scotopic thresholds are the least impacted by intrinsic noise.

In addition, the present results have important implications for past studies that have suggested that schizophrenia participants have an M pathway deficit (e.g., Kéri et al., 2002; Slaghius & Bishop, 2001; Cadenhead et al., 1998). For example, Slaghuis and Bishop (2001) found that schizophrenia participants displayed FS deficits only for stimuli thought to reflect M pathway function (i.e., stimuli modulated at medium and high temporal frequencies) versus stimuli thought to reflect parvocellular (P) pathway function (i.e., stimuli modulated at low temporal frequencies). Given that rod thresholds are thought to be mediated by the M pathway

and schizophrenia participants have an M pathway deficit, significant differences in rod thresholds (and accompanying intrinsic noise) were expected. The present study did not find such differences, which implies that if schizophrenia patients have impairments in the M pathway (a wide-held conclusion supported by a large amount of data), the loci of those deficits are most likely post-receptoral. This interpretation is consistent with the finding that schizophrenia participants have significantly reduced CFF thresholds compared to controls. As noted, CFF is considered to be determined by cortical processing at the level of the visual cortex but is also thought to be mediated by the M pathway. These results are similar to those reported for dyslexics.

Much like schizophrenia, it has been widely concluded through psychophysical, physiological, and anatomical data that there is an M pathway deficit in dyslexia (Demb, Boynton, Best et al., 1998; Livingstone, Rosen, Drislane et al., 1991; Stein, 2001; Stein & Walsh, 1997). For example, Livingstone et al. (1991) found that the cells of the magnocellular layers of the lateral geniculate nucleus (LGN) of 5 dyslexic brains were on average 27% smaller than those of control brains, and there were no differences in cell sizes in the parvocellular layers. Furthermore, it was widely assumed that dyslexics would also have scotopic impairments. For example, DHA supplementation for dyslexia has been suggested as a mean of addressing M pathway deficits based on the idea that altered rod function could be corrected by increased omega-fatty acids in the outer-segments of rods (Stordy, 1995; 2000). Careful testing, however, has shown that dyslexics do not actually have scotopic deficits (Greatrex, Drasdo, & Dresser, 2000). Moreover, the anatomical findings of the studies on dyslexia (i.e., smaller M cells in the LGN of dyslexics) lend further support to the implication that the M pathway deficit in schizophrenia is post-receptoral in origin. Specifically, it is possible that schizophrenia

participants also have anatomical changes in the M layers of the LGN. This possibility is consistent with the results of Kim et al. (2005), which suggested that the visual deficits found in schizophrenia may originate at the lower levels of processing (i.e., at the pre-cortical level or at the level of area V1). Future studies should explore this possibility.

One caveat to the firm conclusion that schizophrenia participants have similar LRSS to normal control participants is that the schizophrenia participants in the current study were not taking typical medications. The majority of the schizophrenia participants assessed in past studies, particularly the studies that indicated an M pathway deficit in the disorder (i.e., Kéri et al., 2002; Cadenhead et al., 1998; Slaghuis & Bishop, 2001), were taking typical antipsychotic medications. All antipsychotic drugs block DA receptors (specifically D2 receptors) in the brain. One main difference between typical and atypical antipsychotic drugs is that typical antipsychotics tend to be nonspecific and block DA receptors in many different pathways of the brain such as the the mesolimbic, mesocortical, tuberoinfundibular, and nigrostriatal pathways. In contrast, atypical antipsychotic drugs are more selective and target the intended pathway (i.e., mesolimbic pathway) to a much larger degree than the other pathways (for review see Serretti, De Ronchi, Lorenzi et al., 2004). In addition, most atypical antipsychotics also block or partially block 5-HT receptors. This combination of effects on the dopaminergic and serotinergic systems may explain why the newer, atypical antipsychotic medications tend to have fewer aversive side-effects. Therefore, it is possible that one reason past studies have found M pathway deficits in schizophrenia is that their schizophrenia patients were taking typical antipsychotic medications. It is unclear whether schizophrenia participants on atypical antipsychotic medications even have M pathway deficits, and they may not be representative of the other groups. This possibility is consistent with results from Antal, Kéri, Szekeres et al. (1999) who found that schizophrenia

patients taking the atypical antipsychotic, olanzapine, did not exhibit any CS deficits (as noted most studies using schizophrenia patients on typical medications do show CS deficits). Thus, future studies should assess the effects of typical and atypical antipsychotic medications on LRSS and magnocellular activity in the same participants, as well as the functioning of never-medicated schizophrenia participants, in order to further explore this implication.

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