
SCHIZOPHRENIA AND RED LIGHT: fMRI EVIDENCE FOR A NOVEL BIOBEHAVIORAL MARKER

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Previous research has demonstrated the ability of diffuse red light to suppress activity in the magnocellular (M) visual pathway. An earlier 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 attempted to replicate and explore the mechanism for this effect using fMRI. Results provide physiological evidence 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.

Keywords biobehavioral marker, endophenotype, first-degree relatives, functional magnetic resonance imaging, magnocellular visual pathway, red light

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.

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 & 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 & Hubel, 1966), and striate cortex (Livingstone & 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 & Breier, 1994; Breitmeyer & Williams, 1990; Brown & 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), whereas 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 in the region that the M pathway traverses (particularly in the right hemisphere) in persons with schizophrenia, but found no evidence of abnormal functioning in the area of the P pathway (Braus et al., 2002). Evidence of a hypoactive M pathway, restricted to the right hemisphere, was also reported in nonpsychotic first-degree relatives 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 & 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 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, and that this effect would be more evident in the right hemisphere.

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

Table 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

¹Based 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.

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

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

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, whereas the remaining relatives were each related to unique probands. Participant demographics are listed in Table 1. Although the groups were well-matched on age, visual acuity, and sex, 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.

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 14.69° (h) \times 19.22° (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, 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 13.09° of the visual angle, while the smallest ring subtended 1.86° . The rings were presented sequentially, creating the illusion of a single ring expanding or contracting. In this manner, the rings expanded for 3.6 s 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 s. This was followed by all nine rings appearing simultaneously and remaining stationary for 21.6 s. The cycle of motion and stationary rings was repeated two times for a total block length of 86.4 s. 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 use of a particular sequence for the first run and the remaining sequence for the subsequent run was counterbalanced between participants. Thus, the 86.4 s 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 T₂-sensitive gradient recalled echo pulse sequence with spiral readout was used with the following parameters: TR = 1200 ms, TE = 40 ms, two interleaves, 77° flip angle, reconstructed matrix = 64 × 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 s, reading out the second interleave for every slice in the next 1.2 s. In this manner, a full image volume is collected in 2.4 s, 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 s per volume. A T1-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, 20° 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., percentage intensity change measure and measures averaged over a region of interest). Imaging data were preprocessed 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 T₁ template (from the Montreal

Neurological Institute) 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 & 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 versus 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 $x = \pm 40$ (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 percentage 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, specific to the right hemispheric proportion for PIC measure (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 ($t = 2.43, p = .02$; Cohen's $d = 1.00$; see Table 2). On this measure, controls showed a statistically significant decrease in scores from the green to red background (paired $t = 2.41, p = .04$), whereas the relatives showed no consistent group change (paired $t = 1.09, p = .30$). Figure 1 depicts individual control participant proportional hemispheric fMRI signal change between the red and green color backgrounds (with the 50% line representing equal activation in both hemispheres). This figure shows that 9 of the controls showed a decreased right hemispheric proportion in activation with the red

Table 2. Group comparisons on change¹ in fMRI measures in response to red light

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

¹All 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.

²PIC = Percent intensity change in fMRI signal.

³Volume = Number of contiguous activated $2 \times 2 \times 2$ mm voxels (size of voxels after normalization procedure).

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

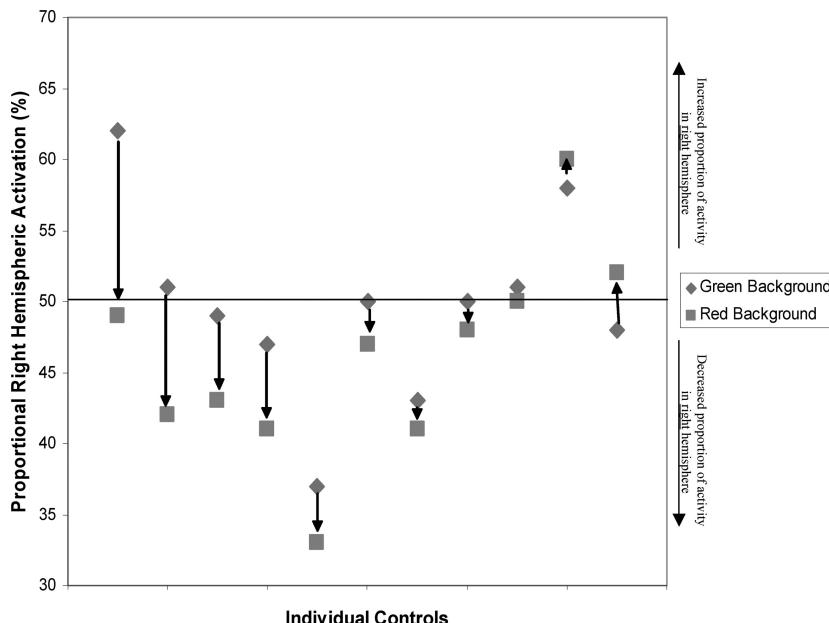
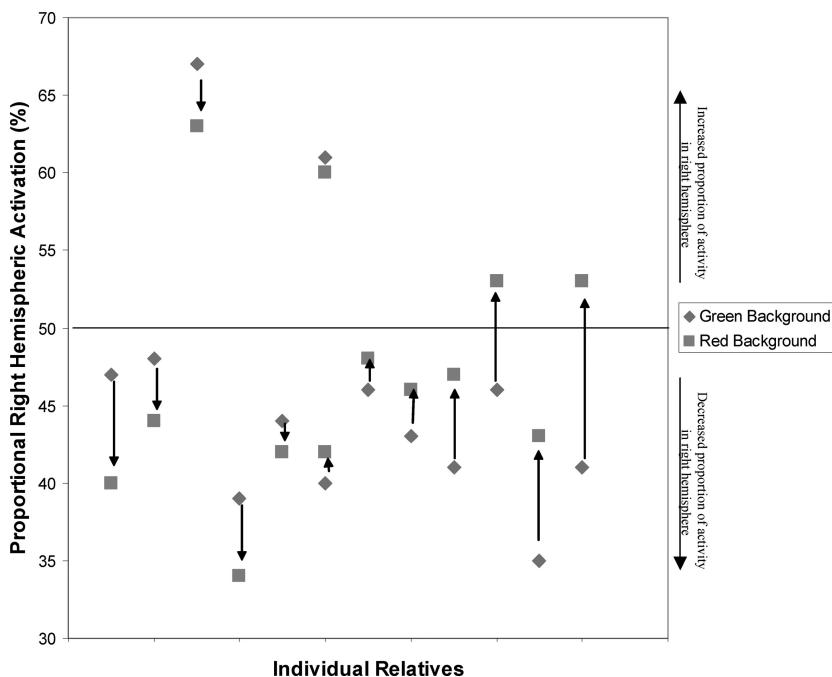


Figure 1. Controls: Change in proportional right hemisphere percent intensity of fMRI signal in response to red light. (See Color Plate I at the end of this issue.)



Although controls showed a statistically significant reduction in the right hemispheric proportion of fMRI signal in V5 in response to red light, the group of relatives showed no suggestion of consistent change. This effect appeared to be driven by a subset that showed a proportional increase (instead of decrease) of fMRI signal in right hemisphere V5. As first-degree relatives share 50% of their genes (on average) with the affected proband, this result is consistent with expectations that only a subset of the group will have genes related to schizophrenia and show related biobehavioral effects.

It is possible that the group difference found in this study may relate to an underlying M pathway deficit that may be more evident in the right hemisphere. However, it appears that the differential change in M pathway functioning in response to diffuse red light found in a subset of the relatives, found both in the current study and in an earlier visual backward masking study (Bedwell et al., 2003), represents a biobehavioral marker for schizophrenia that is largely 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 (in V5) 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 accuracy in 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, the results indicate a large effect size (Cohen's $d = 1.00$), suggesting that this effect may represent 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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