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Schizophrenia Research 63 (2003) 273–284
SCHIZOPHRENIA RESEARCH
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The magnocellular visual system and schizophrenia: what can the color red tell us?

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Received 9 April 2002; received in revised form 3 July 2002; accepted 8 July 2002

Abstract

Previous research has suggested that genetic loading for schizophrenia is related to a dysfunctional magnocellular (M) subcortical visual pathway—responsible for processing movement and location. However, data substantiating this mechanism remains inconclusive. The present study used a novel technique to selectively suppress the M system in order to investigate the impact of genetic loading for schizophrenia on its functioning. A visual backward masking task was administered to 28 healthy first-degree relatives of persons with schizophrenia and 31 healthy controls. The task was administered on both a red and neutral background, as diffuse red light has been shown to selectively suppress the M system in basic vision research. On a location condition of backward masking, controls demonstrated reduced accuracy on the red compared to the neutral background. In contrast, relatives did not display differential performance between the two backgrounds. The differential effect on the two groups appears to be attributable to a difference in activity of the M pathway. Performance in the relatives was consistent with the notion of a hyperactive M pathway.

Keywords: Backward masking; Schizophrenia; First-degree relatives; Magnocellular visual pathway; Endophenotype; Red light

1. Introduction

Research on visual processing in healthy humans and primates has identified two unique but interactive physiological subsystems in the visual system (Livingstone and Hubel, 1987). The ‘‘transient system’’ involves the magnocellular (M) subcortical visual pathway and is responsible for processing location information and movement. It is the relatively faster responding system with lower spatial resolution and greater contrast sensitivity (Breitmeyer and Ganz, 1976; Livingstone and Hubel, 1987). The ‘‘sustained system’’ involves the parvocellular (P) subcortical visual pathway and is responsible for processing detail and color. It is the relatively slower responding, higher spatial resolution system (Breitmeyer and Ganz, 1976; Livingstone and Hubel, 1987). The functional and anatomical divisions of these systems begin at the level of the retina and continue back to the lateral geniculate nucleus, the striate cortex, and the extra striate cortex; however, it has been noted that there is likely a great deal of communication between the M and P pathways throughout the pathways (Ferrera et

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doi:10.1016/S0920-9964(02)00356-0

al., 1992). Due to the relative location of these pathways, the M pathway is commonly referred to as the dorsal visual stream and the P pathway as the ventral visual stream.

Previous research in persons with schizophrenia and their healthy relatives has suggested that genetic loading for schizophrenia is related to a dysfunctional M pathway. This hypothesis is supported by Schwartz et al. (1990, 2001) who found that persons with schizophrenia had longer visual persistence linked to peripheral compared to foveal visual field stimulations, suggesting an M pathway deficit. Other researchers found that persons with schizophrenia had difficulty in a visual spatial location task, but were not impaired on a task that required discrimination of visual stimuli attributes (Cadenhead et al., 1998; O'Donnell et al., 1996), lending further support for a visual processing deficit specific to the M pathway. Similarly, several investigators have found that persons with schizophrenia (Chen et al., 1999b; Stuve et al., 1997) and their relatives (Chen et al., 1999a) display motion sensitivity impairment, a phenomenon also seen in primates (Newsome and Pare, 1988; Wurtz et al., 1990) and humans (Zihl et al., 1983) with damage to the M pathway. However, the notion of an early sensory processing deficit in schizophrenia may not be specific to the visual system, as investigators using mismatch negativity generation with auditory stimuli have noted an early auditory processing deficit occurring within several hundred milliseconds of stimulus presentation (Javitt et al., 2000a,b).

Another type of measurement used to support the notion of an M pathway deficit is performance on tests of visual backward masking. In visual backward masking, a brief visual stimulus (target) is followed very quickly by a second stimulus (mask). The interval between the offset of the target and the onset of the mask is the interstimulus interval (ISI). While participants can usually identify the target presented without a mask, the addition of a mask makes identification of the target more difficult. Both target and mask are thought to elicit a fast M system response and a slower P system response. Target visibility is worse when the P response to the target is disrupted by the M response to the mask. In addition, specific backward masking conditions have been developed to emphasize the M or P system. For example, a condition that requires location identification will rely more on the M system, while conditions that use a clearly focused target and require target identification rely more on the P system (Green et al., 1997).

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

Other investigators have produced evidence suggesting that schizophrenia is related to a hypoactive, rather than hyperactive, M pathway. One research team found significantly reduced signal-to-noise ratio for visual-evoked potentials in response to stimuli that biased processing towards the M pathway, suggesting that this pathway is hypoactive (Butler et al., 2001). This study additionally supported the notion that the dysfunction is specific to the M pathway, as visual-evoked potentials to stimuli that biased processing to the P pathway did not differ from controls. Similarly, other investigators found evidence of reduced activation in the inferior parietal lobe, where the M pathway transverses, in neuroleptic-naive persons with first-episode schizophrenia in response to a moving checkerboard visual stimulus—consistent with the notion of a hypoactive M pathway (Braus et al., 2002; Tost et al., 2001). Thus, while research consistently suggests that persons with schizophrenia have an M pathway deficit, it diverges in respect to whether such a deficit is marked by hyper- or hypo-activity.

In addition, several investigators have demonstrated reduced accuracy on backward masking tasks in healthy adult siblings of persons with schizophrenia (Green et al., 1997; Keri et al., 2001), supporting a genetic basis for the magnocellular deficit. In both of these studies, the authors found stronger effects in task conditions that emphasized the transient (magnocellular) channels. In contrast, Lieb et al. (1996) did not find a difference in backward masking accuracy at any

ISI examined for a sample of adolescents with one parent who had schizophrenia, which may be a result from the lack of a location condition in this study.

Researchers exploring the relative contributions of the M and P pathways to perception have capitalized on the M pathway's broad-band response to wavelength. In particular, a large proportion of M cells have inhibitory properties responsive to red light—the color with the longest perceptible wavelength—such that diffuse red light can create a tonic suppression of their response. The specific ability of red light to suppress firing from neurons associated with the M pathway has been noted throughout the dorsal visual stream in monkeys—including the retinal ganglion cells (de Monasterio, 1978), the lateral geniculate nucleus (Dreher et al., 1976; Kruger, 1977; Wiesel and Hubel, 1966), and the striate cortex (Livingstone and Hubel, 1984). While this phenomenon has not been reported on a physiological level in humans, many basic vision researchers have used isoluminant stimuli with red backgrounds during psychophysical tasks and reported behavioral results consistent with the suppression of the M pathway (e.g., see Breitmeyer and Breier, 1994; Brown and Koch, 2000; Cavanagh et al., 1984; Weisstein and Brannan, 1991).

Of particular interest are metacontrast masking studies that have used isolumnant stimuli with red backgrounds (Breitmeyer and Williams, 1990; Edwards et al., 1996). Metacontrast masking differs from the type of backward masking mentioned in the previous studies with schizophrenia, in that with metacontrast masking, the mask does not spatially overlap with the location of the target—while in the schizophrenia backward masking studies, the mask spatially overlapped the target. Thus, direct comparisons of the effect of a red background with metacontrast masking may not be directly comparable to studies using non-metacontrast backward masking. However, it is noteworthy that metacontrast masking studies have found a reduced effect of the mask (the M pathway process) with a red background as compared to white (Breitmeyer and Williams, 1990; Edwards et al., 1996) or green (Breitmeyer and Williams, 1990) backgrounds, resulting in improved accuracy in identifying the target. Similarly, masking is reduced for isoluminant red masks compared to isoluminant green, blue, or white masks (Williams et al., 1991). The authors were not aware of any published study that used a red background in non-metacontrast backward masking with any population or that used red light to manipulate M pathway functioning in any type of visual perception task with a schizophrenia population.

This study aimed to explore functioning of the magnocellular pathway as related to the genes for schizophrenia by utilizing a visual backward masking task in healthy first-degree relatives of persons with schizophrenia. In order to infer relative differences in the magnocellular visual pathway, a novel technique was used in which performance with diffuse red background (which is thought to suppress the magnocellular pathway) was compared to performance with a neutral background in task conditions that selectively emphasized the magnocellular (location) or parvocellular (identification) visual pathway.

We hypothesized that controls would display decreased accuracy on the location condition with a red compared to a neutral background, as the location condition is reliant on adequate magnocellular pathway functioning and the color red suppresses such functioning. However, it was thought that the relatives would be immune to the suppression effect of the red background, as there is some evidence to suggest they tend to have an overactive magnocellular pathway—which when "suppressed" may display a relatively normal level of activity. In addition, we expected that the relatives of persons with schizophrenia would display a difference in performance compared to controls on backward masking with the neutral background, particularly with the location condition.

2. Methods and materials

2.1. Participants

Data was collected from two participant populations: (1) 28 healthy first-degree biological relatives of persons with schizophrenia ($N=25$) or schizoaffective disorder ($N=3$); and (2) 31 healthy control participants recruited from the community. Participants in the relatives groups included: 15 full-siblings, five biological parents, and five biological children of a person with schizophrenia. Three of the relatives were full-siblings of a person with schizoaffective disorder, a disorder believed to be genetically related to schiz-

ophrenia (Kendler et al., 1995). Participant demographics are listed in Table 1.

First-degree relatives of persons with schizophrenia were recruited via the local community mental health center through within-agency requests to the probands (persons with schizophrenia). A clear diagnosis of DSM-IV (American Psychiatric Association, 1994) schizophrenia or schizoaffective disorder was confirmed in all probands by a staff psychiatrist. Probands agreeing to participate signed a consent form, on which they indicated particular first-degree relatives that could be contacted. Relatives of probands agreeing to participate were contacted (by telephone) by the primary investigator, requesting their participation. Healthy controls were recruited from the local community using a cable television advertisement and printed advertisements placed throughout the community.

Exclusionary criteria for the control group included: (1) any individual with a past or present Axis I psychiatric diagnosis (with the exception of a single past major depressive episode and substance abuse occurring more than three months prior) as determined through a SCID-I diagnostic interview (First et al., 1998); (2) current use of psychoactive medication; (3) corrected visual acuity less than 20/50 based on the Snellen Eye Chart (Carolina Biological Supply); (4) past or present history of a neurological disorder/insult (as determined by self-report); (5) the presence of a schizophrenia spectrum Axis II disorder (schizotypal or paranoid personality disorder) as determined by SCID-II diagnostic interview (First et al., 1997); and (6) biological relation (however distant) to a person with probable psychosis (by self-report).

Exclusionary criteria for the relatives group included: (1) any individual with a past or present history of mania or a psychotic disorder as determined through a SCID-IV diagnostic interview; (2) corrected visual acuity less than 20/50 based on the Snellen Eye Chart; and (3) past or present history of a neurological disorder/insult (as determined by self-report). The exclusionary criteria for the relative group was more liberal, as schizophrenia-related genes may cause other psychopathology and the goal of this study was to examine persons with such genes in the absence of schizophrenia.

The resulting group of relatives included three persons with Major Depressive Disorder, two persons with Paranoid Personality Disorder, and one person with Dysthymic Disorder. In addition, three persons were taking antidepressants and one was taking clonidine. Three relatives had a past history of Panic Disorder and one had a past history of Post-Traumatic Stress Disorder; however, these individuals did not report active symptoms of these disorders at the time of evaluation.

Participants from both groups were screened over the telephone for exclusionary criteria. Those passing this brief screen were scheduled for an appointment at the University of Georgia's Neuropsychology and Memory Assessment Laboratory to participate in the

Table 1
Descriptive factors for study participants

	Controls ($N=31$)	Relatives ($N=28$)	Test statistic	p
Age	50.1 ± 14.8 (range: 19–75)	49.1 ± 13.5 (range: 21–72)	$t=0.36$	ns
Visual Acuity[a]	0.94 ± 0.29	0.82 ± 0.28	$U=354.5$	ns
IQ Estimate[b]	114.4 ± 16.9	93.6 ± 16.2	$t=4.79$	<0.001
State Anxiety Estimate[c]	27.3 ± 5.47	27.5 ± 5.95	$t=0.11$	ns
Socioeconomic Status[d]	3.00 ± 1.10	4.04 ± 0.74	$U=207.5$	<0.001
Race	84% Caucasian	36% Caucasian	$X^2=14.34$	<0.001
Gender	61% female	79% female	$X^2=2.02$	ns

[a] Based on the Snellen Visual Acuity Chart. In order to make statistical comparisons with resulting scores, 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 is. A score of 1 represents average visual acuity (e.g., 20/20).

[b] Based on the two-subtest version of the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999).

[c] Based on the total from the State-Trait Anxiety Questionnaire (Form Y-1); two controls and one relative did not complete this measure.

[d] Hollingshead Social Class based on education and occupation (Hollingshead, 1965); 1 = highest socioeconomic status, 5 = lowest.

research. Further exclusionary screening was conducted during the research session. This project was approved by the institutional review boards of the University of Georgia, the local community mental health center, and the Human Resources Department of the State of Georgia. All participants in the study were asked to read and sign a consent form.

2.2. Stimuli and apparatus

The backward masking task was created using E-Prime software (Beta 5 version; Psychology Software Tools). A desktop PC (Dell Optiplex GX110) and monitor (Dell Trinitron UltraScan P991; 50–60 Hz) were used to present all stimuli. Stimuli were presented as white text (Arial font) on either a red or gray background (depending on task condition—see below), matched for luminance. The fixation stimuli consisted of a white cross-located in the center of the screen that subtended a visual angle of 0.60°. The target stimuli consisted of one of four possible white letters (S, C, O, or Q) that appeared in one of four locations (top, bottom, left, or right). Each target letter subtended a visual angle of 0.30° and appeared 2.10° from the center of the screen. This was followed by an interstimulus interval (ISI) during which no stimuli were present on the colored background. A patterned mask then appeared, consisting of overlapping white uppercase X's (each subtending a visual angle of 0.30°) that overlapped all possible areas that the target may have appeared. The viewing distance was held constant at 100 cm.

Ambient luminance (white light at 3.3 fL) was held constant across participants and was measured using a Tektronix J17 digital photometer. Luminance of the white fixation cross, targets, and mask stimuli was measured at 19.43 fL. The luminance of the red background was equivalent to that of the gray background (2.37 fL).

2.3. Procedure

2.3.1. Visual backward masking practice

Directions were presented on the screen and explained in detail by the principle investigator. For practice, the targets were presented for 13 ms with a mask of either 13 (for location condition) or 27 ms (for identification condition) at an ISI of 140 ms, an interval in which very little masking was expected based on previous studies (Green et al., 1997, 1999). Participants were required to correctly identify at least four out of five targets at this ISI with a neutral background (on both task conditions) before proceeding with the task. No participants were excluded based on this criterion.

2.3.2. Visual backward masking location task

Prior to each target presentation, the fixation cross was presented in the middle of the screen for 400 ms and ended 200 ms before target presentation. The target was presented for 13 ms, followed by a blank screen (ISI) and then the mask for 13 ms. The stimuli were presented in four blocks that included 16 trials (four at each location), with each block using a different ISI (13, 27, 40, and 80 ms). In addition, the entire sequence of four blocks was repeated on both a gray and isoluminant red background. The order of presentation for ISIs and background color was counterbalanced among participants.

After each trial, the participant was asked to state aloud the location (up, down, left, right) that the letter appeared before the mask. The participant was encouraged to point with their hands if they reported left/right confusion. Participants were encouraged to "guess the first of these locations that came to [their] mind" if they could not identify the target location.

2.3.3. Visual backward masking identification task

The stimuli for the identification task were the same as those in the location task, with the exception that the mask duration was lengthened to 27 ms to produce a "high-energy mask"—as the mask duration was twice the length of the target duration (13 ms). A longer ISI was added to the identification condition, as the sustained (P) channels are thought to have a longer latency than the transient (M) channels emphasized in the location task (Green et al., 1994). This resulted in five ISIs: 13, 27, 40, 80, and 93 ms, which each consisted of 16 trials. The ISIs and background colors were presented in a counterbalanced order.

After each trial, the participant was asked to state aloud which letter (S, C, O, or Q) appeared before the mask. The four letters were placed on a large card in front of the participant to remind them of the choices. Participants were encouraged to "guess the first of the

four letters that came to [their] mind" if they could not identify the target location. The principle investigator entered the participant's stated answer using a numeric keypad.

In both task conditions, targets and locations were selected in a block-randomized manner, with the constraint that the same variable (target and location) could not be presented in succession. In addition, to reduce the influence of practice effects, the task condition (location or identification) was presented in a counterbalanced order and the background color condition was presented in a counterbalanced order within each task condition.

3. Results

3.1. Demographic data

Demographic data (see Table 1) were analyzed using Pearson chi-square, Mann–Whitney *U*-, and *t*-tests, as appropriate for data distribution. Although there was no statistically significant difference between the groups on age, gender, state anxiety, and visual acuity, the relatives group contained 64% minorities while the control group contained 15% minorities. In addition, the estimated IQ and socio-economic status were statistically higher in the control group as compared to the relatives group.

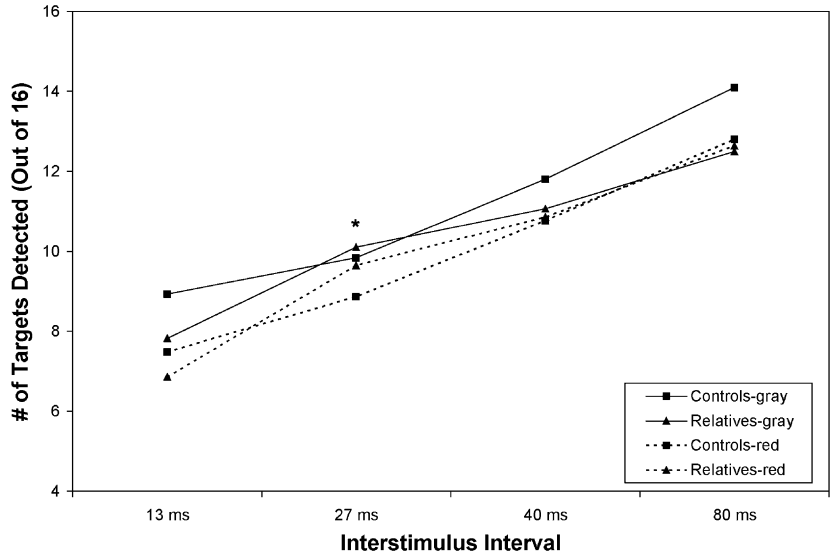
3.2. Location condition—effect of a red background

As accuracy scores were not normally distributed, a Wilcoxon Signed Ranks Test was used to examine performance between groups, which revealed that the groups did not differ in performance at any ISI within the red background condition (see Table 2). A related-sample Wilcoxon Signed Ranks Test was used within each group to examine accuracy change with background color. After adjusting for multiple comparisons, analysis of accuracy in the control group revealed a statistically significant decrease in accuracy with the red compared to neutral background in two ISIs, while displaying a trend toward decreased accuracy with a red background in the other two ISIs (see Table 2). In contrast, analysis of accuracy in the relatives group did not approach statistical significance within any ISI.

Table 2
Backward masking performance on the location condition

ISI (ms)	Group	Background color	Number correct (out of 16) Mean ± SD	z^a	p^a	z^b	p^b	z^c	p^c
13	controls	gray	8.94 ± 2.97	1.12	ns	2.54	0.01 *	0.18	ns
		red	7.48 ± 3.44	0.66	ns				
13	relatives	gray	7.82 ± 4.66			1.37	ns		
		red	6.86 ± 3.33						
27	controls	gray	9.84 ± 4.71	0.19	ns	1.72	0.09	0.39	ns
		red	8.87 ± 3.96	0.88	ns				
27	relatives	gray	10.11 ± 4.57			0.82	ns		
		red	9.64 ± 4.34						
40	controls	gray	11.81 ± 4.28	0.73	ns	2.26	0.02	1.30	ns
		red	10.77 ± 4.40	0.14	ns				
40	relatives	gray	11.07 ± 4.72			0.28	ns		
		red	10.86 ± 4.28						
80	controls	gray	14.10 ± 3.58	1.39	ns	3.08	0.002 *	2.77	0.006 *
		red	12.81 ± 3.51	0.18	ns				
80	relatives	gray	12.50 ± 4.54			0.46	ns		
		red	12.64 ± 4.03						

[a] Wilcoxon Signed Ranks Test comparing groups on accuracy.
[b] Within-group Wilcoxon Signed Ranks Test for change in performance due to color of background.
[c] Wilcoxon Signed Ranks Test comparing groups for change in performance due to color of background.
* Statistically significant with Bonferroni-corrected alpha level of 0.01.



* Repeated-measures ANOVA suggested a group difference in the quadratic shape of performance across ISIs with the gray background ($F(1,57) = 3.44$, $p = .07$).

Fig. 1. Performance on the location condition of backward masking by group and background color.

To further examine this group difference, change scores were created by subtracting the accuracy with the gray background from the accuracy with the red background. After correcting for multiple comparisons, analysis of the change scores revealed that the group difference on accuracy change with a red background was statistically significant at only the 80 ms ISI (see Fig. 2 and Table 2). A related-sample Wilcoxon Signed Ranks Test showed that at the 80 ms ISI, the controls displayed decreased accuracy with a red background, while the relatives showed no change (see Table 2).

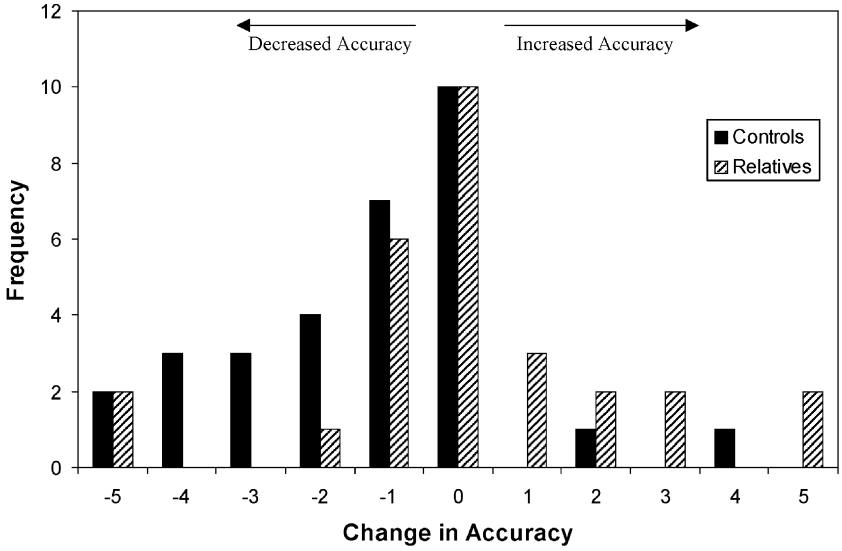


Fig. 2. Change in accuracy with a red background compared to a neutral background with the 80 ms ISI on the location condition.

3.3. Location condition with a neutral background

Accuracy scores were not normally distributed and thus were compared between groups using an independent-sample Wilcoxon Signed Ranks test. The groups did not display a statistically significant difference in accuracy within any of the four ISIs examined (see Table 2). Exploratory examination with a repeated-measures ANOVA revealed a strong linear (monotonic) relationship between ISI and accuracy, with accuracy improving with increasing ISI [$F(1,57) = 110.0$, $p < 0.001$], but did not suggest any non-linear (non-monotonic) relationship between ISI and accuracy (see Fig. 1). This exploratory examination also suggested a group difference in the quadratic (but not linear) shape of performance across ISIs on the gray background [$F(1,57) = 3.44$, $p = 0.07$], which appears to be due to the shape of the profile surrounding the 27 ms interstimulus interval (see Fig. 1). However, the examination with ANOVA must be interpreted with caution, as the data were not normally distributed in two (80 and 93 ms) of the four ISIs.

3.4. Identification condition—effect of a red background

Accuracy score were normally distributed across all ISIs and an independent sample *t*-test was used to examine group differences in accuracy with the red background, which revealed no difference between groups at any ISI (see Table 3 and Fig. 3). The difference between groups on the shape of the accuracy by ISI function found with the gray background appears preserved on visual inspection of Fig. 3 with the red background, but no longer approaches statistical significance [$F(1,57) = 1.93$]. A repeated-measures analysis of variance was conducted to examine the effect of change in background color on accuracy, using both color and ISI as repeated measures and group as a between-group measure. The main effect of color was not statistically significant, but did display a tendency for the red background to decrease accuracy [$F(1,57) = 2.73$, $p = 0.10$] (see Fig. 3). The interaction of color by group was not statistically significant [$F(1,57) = 0.003$].

Table 3
Backward masking performance on the identification condition

ISI (ms)	Group	Background color	Number correct (out of 16) Mean ± SD	t^a	p^a	t^b	p^b	F^c	p^c
13	controls	gray	4.35 ± 2.03	0.66	ns	0.40	ns	0.49	ns
		red	4.19 ± 1.97	0.12	ns				
13	relatives	gray	4.04 ± 1.67			0.62	ns		
		red	4.25 ± 1.74						
27	controls	gray	5.19 ± 1.68	0.76	ns	0.54	ns	1.81	ns
		red	4.94 ± 2.25	1.07	ns				
27	relatives	gray	4.82 ± 2.07			1.34	ns		
		red	5.50 ± 1.75						
40	controls	gray	6.84 ± 2.42	0.24	ns	0.91	ns	0.08	ns
		red	6.35 ± 2.63	0.05	ns				
40	relatives	gray	6.64 ± 3.68			0.39	ns		
		red	6.39 ± 3.12						
80	controls	gray	9.16 ± 2.98	0.06	ns	0.31	ns	0.95	ns
		red	8.97 ± 3.69	0.86	ns				
80	relatives	gray	9.11 ± 3.78			2.04	0.05		
		red	8.14 ± 3.71						
93	controls	gray	9.90 ± 2.66	0.46	ns	0.69	ns	1.38	ns
		red	9.58 ± 3.49	1.12	ns				
93	relatives	gray	9.46 ± 4.34			3.11	0.004 *		
		red	8.46 ± 4.19						

[a] Independent-sample *t*-test on accuracy between groups.
[b] Within-group repeated measures *t*-test on change in performance due to color of background.
[c] Repeated-measures ANOVA with color as the repeated measure and group as the between-group measure.
* Statistically significant with Bonferroni-corrected alpha level of 0.01.

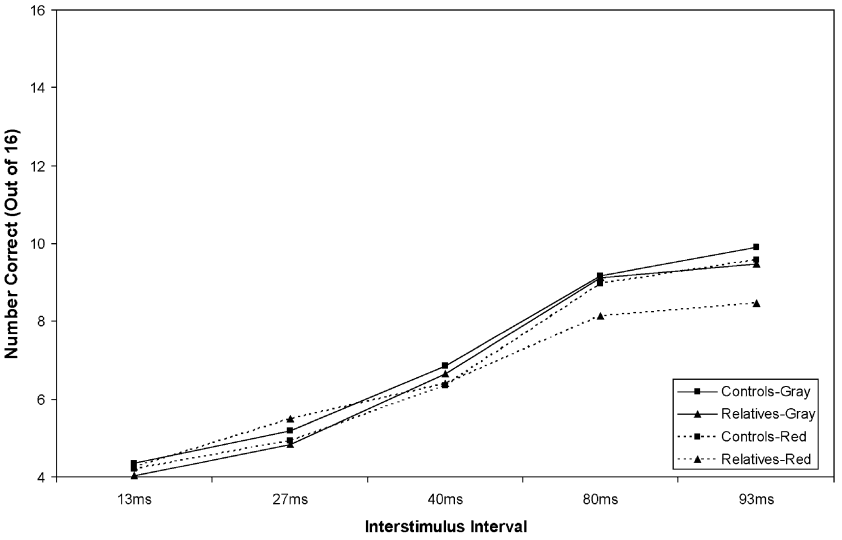


Fig. 3. Performance on the identification condition of backward masking by group and background color.

Exploratory examination for both linear and non-linear trends with univariate *F*-tests revealed a statistically significant linear interaction of color and ISI [$F(1,57)=4.36$, $p=0.04$] and a trend for a linear interaction of group by color by ISI [$F(1,57)=3.38$, $p=0.07$] (see Fig. 3). Further exploratory analysis examined the effect of color on performance within each ISI and group independently using a repeated-measures *t*-test. This analysis revealed that color did not affect performance in controls at any ISI, but decreased performance in relatives only during the 93 ms ISI (see Table 3). However, a repeated-measure ANOVA at the 93 ms ISI (and all other ISIs) failed to reveal statistically significant group differences in performance change between the background color conditions (see Table 3).

3.5. Identification condition with a neutral background

Accuracy scores were normally distributed across all ISIs and were analyzed using a repeated-measures analysis of variance design with ISI as a repeated measure and group as a between-subjects factor. The main effect for ISI was statistically significant, as accuracy improved across groups as the length of the ISI increased [$F(4,228)=67.14$, $p<0.001$]. A univariate *F* test revealed both linear [$F(1,57)=131.5$, $p<0.001$] and cubic components [$F(1,57)=18.2$, $p<0.001$] for this effect (see Fig. 3). There was no statistically significant main effect for accuracy differences between groups after collapsing across ISIs [$F(1,57)=0.27$]. In addition, there were no group differences in the linear pattern of performance across ISIs [$F(4,228)=0.07$] and there was no evidence of non-linear trends for group differences in performance. Exploratory examination of group differences in performance within each ISI using an independent sample *t*-test revealed no statistically significant group differences within any ISI (see Table 3 and Fig. 3).

4. Discussion

Results support the notion, purported by others, that persons with a genetic loading for schizophrenia have a hyperactive magnocellular pathway. The ability to accurately determine an object's location is dependent on adequate functioning of the magnocellular visual pathway (Breitmeyer and Ganz, 1976; Livingstone and Hubel, 1987) and the color red has been shown to suppress magnocellular functioning (Kruger, 1977; Schiller et al., 1990). Thus, it is reasonable to predict that accuracy on the location condition of backward masking would be impaired in healthy individuals when it is presented on a diffuse red background.

Results support this prediction, as healthy controls displayed a marked decrease in accuracy on the location condition with the red compared to a neutral background. Data from the relatives confirmed the a priori hypothesis of no change in performance between the red and neutral backgrounds. As the relatives are thought to have an overactive magnocellular visual pathway, and red suppresses this pathway, it is reasonable that the color red decreases the activity in their pathway to a relatively normal level, resulting in either no change or improvement in accuracy. Although the current study cannot directly address this issue, it is possible that due to genetic loading for schizophrenia, the relatives have a smaller number of M pathway cells in the retina that are inhibited by red light. A functional magnetic imaging study is underway to explore these possibilities.

Unexpectedly, there was no indication of a group difference in backward masking performance with a neutral background in either the identification or the location condition, which is consistent with one study finding a similar null finding (Lieb et al., 1996), but inconsistent with two other studies, which reported decreased accuracy in a group of relatives of persons with schizophrenia (Green et al., 1997; Keri et al., 2001). While the null finding in the Lieb study may be accounted for by a small sample size, restriction in age, and inclusion of only children of persons with schizophrenia, these factors are unlikely to explain the null finding in the present study. Therefore, it is possible that altered performance on visual background masking is a relatively weak and inconsistent biobehavioral marker of schizophrenia genes in first-degree relatives. It is hoped that additional independent studies may clarify this matter.

It is not clear why the relatives showed a trend towards a difference in the quadratic (non-monotonic) shape of the performance profile across the ISIs of the gray background in the location condition. However, such an oscillation of performance over increasing ISIs has been proposed to reflect an underlying oscillation of neural firing in the P pathway as it interacts with the M pathway during backward masking (Purushothaman et al., 2000). One study found that persons with schizophrenia failed to show such an oscillation in performance, as, unlike controls, they failed to display a non-linear improvement in accuracy at a stimulus-onset asynchrony (SOA) of 30 ms (length of target duration plus ISI) relative to the SOA before (20 ms) and after (50 ms) (Green et al., 1999), a finding also reported indirectly by others (Cadenhead et al., 1998).

The present study did not measure a SOA of 30 ms and did not find such a non-linear spike in performance in controls at the nearest SOAs measured (26 and 40 ms) during any condition measured (see Figs. 1 and 3). However, in both the red and gray background conditions of the location task, relatives showed a spike in performance at the 40 ms SOA (27 ms ISI plus 13 ms target) (see Fig. 1). In the identification task, the relatives, like the controls, did not show the spike at the 27 ms ISI with the gray background, but displayed the spike only with the red background (see Fig. 3). Considering the theory of an oscillating P pathway, these results, taken together with previous results in persons with schizophrenia, are consistent with either a change in the frequency of oscillation of the P pathway or a change in the speed of the M pathway related to genetic loading for schizophrenia. Considering that in the identification condition, the relatives only showed the spike at the 27 ms ISI with the red background and that the red background primarily effects the M pathway, it seems probable that the later explanation—that the speed of the M pathway is effected by genetic loading for schizophrenia—best explains the results.

Examining biobehavioral characteristics in healthy first-degree relatives of persons with schizophrenia is advantageous because unique factors found in these individuals may offer insight into genetic expression in schizophrenia without confounds such as neuroleptic exposure, duration of hospitalization, and active symptom effects (Adler et al., 1999; Weinberger, 1999). This insight may lead to identification of members of an affected family that are likely carrying one or more genes associated with schizophrenia in the absence of frank psychopathology. The identification of such ‘‘silent carriers’’ would add statistical power to genetic linkage studies, thereby increasing the probability that the genes responsible for the disorder will be discovered (Adler et al., 1999; Freedman et al., 1999).

This study was limited by the reliance on the refresh rate of a computer monitor for stimuli presentation intervals, which limited analysis of masking functions over very brief ISIs (e.g., less than 13 ms) and limited the interval for stimulus presentation. This limitation

may explain the inability to detect group differences in the neutral background condition, as one of the (two) studies detecting such differences used stimuli presentation intervals that were less than the 13 ms used in the current study (Green et al., 1997). In addition, although considerable efforts were made to standardize the placement of participants relative to the computer monitor, a chin rest was not used, which may have increased the error variance of accuracy scores.

In summary, this study used a novel technique to investigate abnormal functioning of the magnocellular system in persons with genetic loading for schizophrenia by using the color red to suppress magnocellular activity. While controls displayed impaired performance on a magnocellular-reliant task with a red background, relatives did not show such impairment. As the diffuse red background suppresses the magnocellular pathway and relatives are thought to have too much of this activity, the data is consistent with the notion that the color red decreased the relatives' overactive magnocellular activity to a relatively normal level, but decreased the controls' normal activity to a hypoactive level. This is particularly interesting, as the groups did not differ in their performance on the neutral background, suggesting that the use of the diffuse red background may be more sensitive to visual processing unique to genetic loading for schizophrenia.

Acknowledgements

The authors would like to thank Dr. Sharon Esposito and Advantage Behavioral Health Systems (Athens, GA) for help recruiting the relatives, Greg Strauss and Melissa Shalango for help with data collection and entry, Dr. Michael Green and Dr. Bruno G. Breitmeyer for advice on task construction, and the Georgia Gerontology Consortium for grant support.

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