

Testing Sensory and Cognitive Explanations of the Antisaccade Deficit in Schizophrenia

Carly J. Leonard
University of California, Davis

Benjamin M. Robinson, Samuel T. Kaiser,
and Britta Hahn
University of Maryland School of Medicine

Clara McClenon
University of California, Davis

Alex N. Harvey
University of Maryland School of Medicine

Steven J. Luck
University of California, Davis

James M. Gold
University of Maryland School of Medicine

Recent research has suggested that people with schizophrenia (PSZ) have sensory deficits, especially in the magnocellular pathway, and this has led to the proposal that dysfunctional sensory processing may underlie higher-order cognitive deficits. Here we test the hypothesis that the antisaccade deficit in PSZ reflects dysfunctional magnocellular processing rather than impaired cognitive processing, as indexed by working memory capacity. This is a plausible hypothesis because oculomotor regions have direct magnocellular inputs, and the stimuli used in most antisaccade tasks strongly activate the magnocellular visual pathway. In the current study, we examined both prosaccade and antisaccade performance in PSZ ($N = 22$) and matched healthy control subjects (HCS; $N = 22$) with Gabor stimuli designed to preferentially activate the magnocellular pathway, the parvocellular pathway, or both pathways. We also measured working memory capacity. PSZ exhibited impaired antisaccade performance relative to HCS across stimulus types, with impairment even for stimuli that minimized magnocellular activation. Although both sensory thresholds and working memory capacity were impaired in PSZ, only working memory capacity was correlated with antisaccade accuracy, consistent with a cognitive rather than sensory origin for the antisaccade deficit.

Keywords: antisaccade, eye movements, magnocellular pathway, schizophrenia, working memory

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Impaired cognitive abilities are a core feature of schizophrenia and one of the best predictors of long-term outcome (Green,

Kern, & Heaton, 2004). A growing body of research shows that people with schizophrenia (PSZ) also have impairments in low-level sensory processing, including evidence of a relationship between visual perceptual ability, social perception, and functional outcome (Sergi, Rassovsky, Nuechterlein, & Green, 2006). One line of research has focused on the more specific hypothesis that PSZ have a selective deficit in the magnocellular pathway (Butler et al., 2007; Butler et al., 2005). Although this hypothesis is controversial (Skottun & Skoyles, 2007), it is considered viable by many researchers (e.g., Bedwell et al., 2013; Coleman et al., 2009). Some researchers have further proposed that magnocellular sensory deficits propagate forward to impair some aspects of higher-level cognition and functioning (e.g., Butler et al., 2009; Javitt, 2009; Leitman et al., 2010; Martínez et al., 2012). However, other researchers have argued that deficits in higher-level cognitive processes that involve prefrontal functioning are the predominant source of impairment in many tasks (Barch et al., 2001; Lesh, Niendam, Minzenberg, & Carter, 2011). It is likely that both sensory and cognitive deficits play important roles in schizophrenia, and it is important to understand exactly what these roles are in a variety of domains. The present study therefore sought to determine the role of magnocellular sensory deficits in one com-

Carly J. Leonard, Center for Mind & Brain and Department of Psychology, University of California, Davis; Benjamin M. Robinson, Samuel T. Kaiser, and Britta Hahn, Maryland Psychiatric Research Center, University of Maryland School of Medicine; Clara McClenon, Center for Mind & Brain and Department of Psychology, University of California, Davis; Alex N. Harvey, Maryland Psychiatric Research Center, University of Maryland School of Medicine; Steven J. Luck, Center for Mind & Brain and Department of Psychology, University of California, Davis; James M. Gold, Maryland Psychiatric Research Center, University of Maryland School of Medicine.

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Correspondence concerning this article should be addressed to Carly J. Leonard, Center for Mind and Brain, University of California, Davis, 267 Cousteau Place, Davis, CA 95618. E-mail: cjleonard@ucdavis.edu

monly used cognitive control paradigm, the *antisaccade* task (Hallett, 1978).

In the antisaccade task, an object appears on one side of the screen, and the participant is instructed to make a saccade directly to the opposite side of the screen. PSZ are impaired in this task, with little or no deficit in the *prosaccade* task, in which a saccade must be made directly to the target. This has been widely studied in PSZ (e.g., Camchong, Dyckman, Austin, Clementz, & McDowell, 2008; Everling & Fischer, 1998), and has been attributed to dysfunctional prefrontal control processes (McDowell et al., 2002; Fukushima et al., 1988; Hutton & Ettinger, 2006; Klein, Heinks, Andresen, Berg, & Moritz, 2000; Manoach et al., 2002; Radant et al., 2010; Radant et al., 2007; Sereno & Holzman, 1995). However, abnormalities in visual processing in the magnocellular pathway could also potentially lead to impaired antisaccade performance.

The magnocellular pathway begins with parasol ganglion cells in the retina, which provide a major input to the superior colliculus (Crook et al., 2008), a structure ultimately responsible for saccade generation (White & Munoz, 2011). Magnocellular inputs also provide significant input to the dorsal stream (Merigan & Maunsell, 1993), which plays a key role in attention and eye movements. In contrast, the parvocellular pathway, which begins with midget ganglion cells in the retina, has little or no direct projection to the dorsal pathway (Merigan & Maunsell, 1993) or the superior colliculus (Tailby, Cheong, Pietersen, Solomon, & Martin, 2012). Some mixing of these two pathways begins in area V1 (Sincich & Horton, 2005), and the ventral stream receives strong inputs from both the magnocellular and parvocellular pathways (Merigan & Maunsell, 1993). Although parvocellular information can ultimately reach saccadic control systems, it does not play the same prominent role in rapid oculomotor control. Magnocellular information has faster access to oculomotor systems than does parvocellular information (White, Boehnke, Marino, Itti, & Munoz, 2009), and contributes to the earliest responses in the dorsal stream (Bisley, Krishna, & Goldberg, 2004). Note that a third and less prominent pathway, the koniocellular pathway (Hendry & Reid, 2000), will be considered in the Discussion.

Prior research has not assessed the possible contribution of atypical magnocellular sensory processing to the antisaccade deficit in PSZ. In many studies, PSZ exhibit both reduced behavioral sensitivity and reduced sensory responses in cortex for stimuli that are processed by the magnocellular pathway (Butler et al., 2005; Butler et al., 2007; Martínez et al., 2008; but see Skottun & Skoyles, 2007). This type of impairment would not be expected to directly produce an exaggerated antisaccade deficit. However, seemingly contradictory research has shown that visual masks that activate the magnocellular pathway lead to exaggerated impairments in target detection in PSZ (Butler et al., 2003; Cadenhead, Serper, & Braff, 1998; Green, Nuechterlein, & Mintz, 1994; Schechter, Butler, Silipo, Zemon, & Javitt, 2003; Slaghuis & Curran, 1999). One potential explanation of these apparently conflicting results is that the magnocellular signals may be weakened in early sensory processing, but to compensate for the decreased strength, these signals may be given greater weight in higher levels of the system. Thus, the signals would be of poor quality but would nonetheless have an exaggerated impact on behavioral performance in some tasks. Correct antisaccade performance requires active inhibition of stimulus-driven magnocellular activity (Ander-

son, Husain, & Sumner, 2008), and a dysregulated weighting of magnocellular input could cause an increased tendency to move the eyes toward rather than away from the target.

Consistent with this hypothesis, previous research from our group has shown that PSZ exhibit increased attentional capture to an irrelevant distractor, but only when this distractor is visible to the magnocellular pathway (Fuller et al., 2007; Leonard, Robinson, Hahn, Gold, & Luck, under review). Thus, we hypothesized that the antisaccade deficit in PSZ may be present only for stimuli that are easily visible by the magnocellular pathway. Antisaccade tasks typically involve high-contrast luminance onsets that strongly activate both the parvocellular and magnocellular pathways because they contain information across a broad range of spatial frequencies. In the current study, we designed a Gabor target that activated both pathways and was roughly comparable in terms of spatial frequency content to what has been used in most other antisaccade studies. We also designed Gabor targets that preferentially activated either the magnocellular pathway or the parvocellular pathway.

Most theories of antisaccade deficit in PSZ propose that dysfunctional prefrontal control processes are at the root of this deficit (Hutton & Ettinger, 2006; McDowell et al., 2002), consistent with the prominent proposal that cognitive impairments stem from impairments in prefrontal functioning (Barch et al., 2001; Weinberger, Berman, & Zec, 1986). To contrast the explanatory power of low-level sensory functioning to explain the antisaccade deficit, we also examined correlations between antisaccade performance and working memory capacity, which is known to rely on prefrontal functioning (McNab & Klingberg, 2008). We have previously shown that performance in this type of working memory task is not associated with sensory dysfunction in PSZ (Gold et al., 2010; Leonard et al., 2013). Lower working memory capacity has been associated with poorer antisaccade performance in healthy individuals (Kane, Bleckley, Conway, & Engle, 2001; Unsworth, Schrock, & Engle, 2004). A relationship of working memory capacity to antisaccade performance in PSZ would provide evidence supporting a higher-level locus of impairment for the antisaccade deficit.

To test this hypothesis, stimulus properties were varied to manipulate the degree of magnocellular involvement. If the antisaccade deficit is a downstream consequence of impaired magnocellular sensory processing, then it should be present primarily when the stimuli activate the magnocellular pathway, and it should be uncorrelated with working memory capacity. If the antisaccade deficit instead reflects impaired cognitive abilities, then it should be present even for stimuli that primarily activate the parvocellular pathway, and it should be correlated with working memory capacity. If both sensory and cognitive factors contribute to the antisaccade deficit, then the deficit should be present for all of our stimulus types but should be larger for the stimuli that preferentially activate the magnocellular pathway.

Method

Participants

Twenty-five people who met the criteria for schizophrenia (PSZ) and 24 healthy controls (HCS) took part in the experiment. One HCS failed to understand the antisaccade instructions and was

excluded. One additional HCS and three PSZ who performed below criterion on a sensory thresholding task (described below) were also excluded. The clinical description below and demographic summary in Table 1 pertain to the remaining 22 PSZ and 22 HCS. This protocol was approved by the Institutional Review Board at the University of Maryland School of Medicine and all participants gave written informed consent before taking part in this study.

The diagnosis was based on the standard operational criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision (*DSM-IV-TR*). A best estimate approach was used to establish diagnosis by combining material from past medical records, collateral informants (when available), and the results of the Structured Clinical Interview for *DSM-IV-TR* Axis I disorders (SCID-I). Final diagnosis was reached at a consensus conference. The PSZ were all clinically stable outpatients who had been receiving the same medications, at the same dose, for at least 4 weeks before participation. All PSZ received antipsychotic medication: three were treated with typical and 19 with atypical antipsychotics. Nine additionally received anxiolytic medication and 15 antidepressant medication. Two in the PSZ group were treated with a mood stabilizer, two with zolpidem as a sleep aid, one with modafinil for excessive sleepiness, and one with benzotropine as an anti-Parkinsonian drug.

Random digit dialing was used to recruit HCS, who were screened using the (SCID-I; First, Spitzer, Miriam, & Williams, 2002); and the SCID for Axis II Personality Disorders (SCID-IV; Pfohl, Blum, & Zimmerman, 1995). HCS had no current diagnosis of any Axis I disorder or Axis II schizophrenia spectrum disorder, and denied a lifetime history of psychosis or family history of psychotic disorders in first-degree relatives.

Demographic information is summarized in Table 1. No significant differences were found between groups in age, race, gender, parental education, or handedness. Years of education was lower for PSZ, presumably because disease onset limits education attainment.

Stimuli and Equipment

The stimuli were presented in a dimly lit room on a 17" gamma-corrected CRT monitor (60 Hz). Participants sat with head fixed in a chin/forehead rest at 70 cm from the monitor. A tabletop Eyelink 1000 system (SR Research Ltd., Mississauga, Ontario) recorded eye movements.

Following the approach used by Butler, Javitt, and their colleagues to show magnocellular processing deficits in PSZ (Butler et al., 2007; Butler et al., 2005; Martínez et al., 2012), three different types of Gabor patches were used as targets (see Figure 1). Each patch was a vertical sine-wave grating multiplied by a circular 2-D Gaussian envelope (standard deviation = 0.4°). The *magno-biased stimulus* had a spatial frequency of 1 cycle/ $^\circ$ and 10% Michelson contrast. Parvocellular neurons in the lateral geniculate nucleus (LGN) typically have a very low response rate at this contrast level (Tootell, Hamilton, & Switkes, 1988) and at this low spatial frequency (Derrington & Lennie, 1984), so this stimulus should be primarily processed by the magnocellular system. The *parvo-biased stimulus* had a spatial frequency of 8 cycles/ $^\circ$ and 100% contrast. At the eccentricity used (9°), this spatial frequency elicits a large response in parvocellular LGN cells but virtually no response in magnocellular LGN cells (Kaplan & Shapley, 1982). The *magno + parvo stimulus* had a spatial frequency of 1 cycle/ $^\circ$ and 100% contrast, which should drive both pathways.

Task and Procedure

Each trial began once the participant achieved stable fixation for 250–350 ms. The fixation point then disappeared, and simultaneously a Gabor patch target appeared 9° to the left or right of fixation for 1000 ms. Participants were instructed either to make a speeded saccade toward the target (prosaccade task) or to the opposite side of the screen (antisaccade task). A variable blank intertrial interval (1000–2000 ms) followed target offset.

Participants completed 3 antisaccade blocks and 3 prosaccade blocks, each containing 20 randomly intermixed trials for each stimulus type (magno-biased, parvo-biased, and magno + parvo). Prosaccade and antisaccade blocks alternated, with the initial block type randomized. Ten practice trials were completed before each block with the opportunity for repetition.

To demonstrate that all stimulus types could be reliably detected, participants completed a perceptual threshold task similar to that used by Butler, Javitt, and colleagues (Butler et al., 2005). Using the QUEST adaptive psychometric procedure (Watson & Pelli, 1983), we measured the contrast at which a Gabor patch of 1 cycle/ $^\circ$ or 8 cycles/ $^\circ$ was detectable 85% of the time. On each trial, a stimulus appeared for 200 ms at one of the two locations used in the main task. Participants reported the stimulus location

Table 1
Demographic Features of Sample (SD = Standard Deviation)

Demographic feature	HCS group		PSZ group		Comparison		
	Mean	SD	Mean	SD	Test-Stat	df	p
Age	28.9	5.9	30.9	7.2	$t = 0.99$	42	0.32
Education (yrs.)	15.0	2.0	13.2	1.8	$t = 3.1$	42	<0.01
Parental education (yrs.) ^a	14.9	2.1	14.6	2.2	$t = 0.45$	41	0.66
Male/Female	16:6		16:6		$\chi^2 = 0$	1	1
Race (AA:W:O) ^b	7:15:0		8:13:1		$\chi^2 = 1.2$	2	0.54
Chlorpromazine equivalents	—		540.5 284.3				

^a Average of mother's and father's years of education, when both available. Data were unavailable from one from the PSZ group. ^b AA = African American, W = White, O = Other.

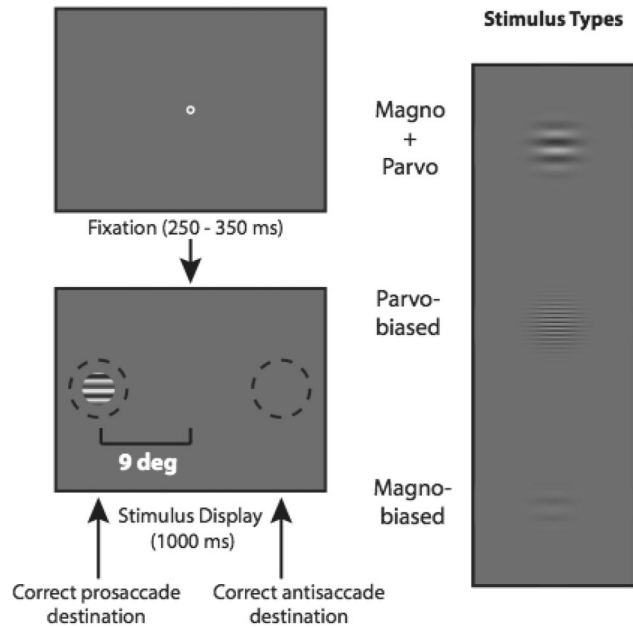


Figure 1. Stimuli and task. At trial start, fixation at the center was required for 250–350 ms before the target was presented. The fixation point offset simultaneously with the appearance of the target. Three types of Gabor patches, shown at the right, were used as targets. Target type and side were randomly intermixed. Participants were told to move their eyes to the target location in the prosaccade task and to the opposite location in the antisaccade task.

(left or right) with no time pressure. The two spatial frequencies and two locations were randomly intermixed in a block of 80 trials.

Participants were excluded if their detection threshold at 85% accuracy was $\geq 85\%$ of either of the contrasts used in the main task (i.e., $\geq 85\%$ contrast for the 8 cycle/° Gabor or $\geq 8.5\%$ contrast for the 1 cycle/° Gabor). Accordingly, three PSZ and one HCS were excluded from all analyses, although the results were significant without exclusion.

Recording Methods and Analyses

Eye position was recorded from the right eye at 2000 Hz. Saccades were defined using a minimum velocity threshold of 30°/s and a minimum acceleration threshold of 9500°/s. Saccade endpoint was the average location during the subsequent period of fixation. The first saccade of each trial was analyzed, and trials were excluded if not initiated within 750 ms after stimulus onset or if landing off screen (approximately 5% of trials). Following previous research (e.g., Radant et al., 2007; Sereno & Holzman, 1995), trials in which the first saccade amplitude was less than half of target eccentricity were excluded from the primary analysis, with accuracy quantified as the percentage of remaining trials on which the first saccade landed on the correct side of the screen. Analysis of hypometric saccades across stimulus conditions can be found in the Supplementary Information. Saccadic latencies were calculated only for correct trials.

Working Memory Task

Most participants (21 of 22 PSZ and 19 of 22 HCS) also completed a 60-trial change localization task that provides a reliable estimate of visual working memory capacity (Gold et al., 2006; Johnson et al., 2013; Kyllingsbaek & Bundesen, 2009). In this task each trial consisted of an array of four colored squares, presented for 100 ms, followed by a 900-ms delay and then a test array (see Johnson et al., 2013). The sample and test arrays were identical except for the color of one square, and the task was to indicate which square had changed. Working memory capacity (K) for each participant was estimated by multiplying the proportion correct by the number of objects in the array (four).

Results

Saccade Accuracy

For all stimulus types, both PSZ and HCS exhibited near-ceiling accuracy in the prosaccade task and lower accuracy in the antisaccade task (Figure 2A and 2B). This was confirmed by a significant main effect of task, $F(1, 42) = 65.7, p < .01$, in an ANOVA with factors of group, stimulus type, and task. Antisaccade accuracy was much lower in PSZ than in HCS (Figure 2B), as confirmed by a significant group \times task interaction, $F(1, 42) = 9.0, p < .01$. There was no significant main effect of stimulus type on accuracy, $F(2, 84) = 2.2, p = .11$. In the antisaccade but not the prosaccade task, accuracy was slightly higher for parvo-biased and

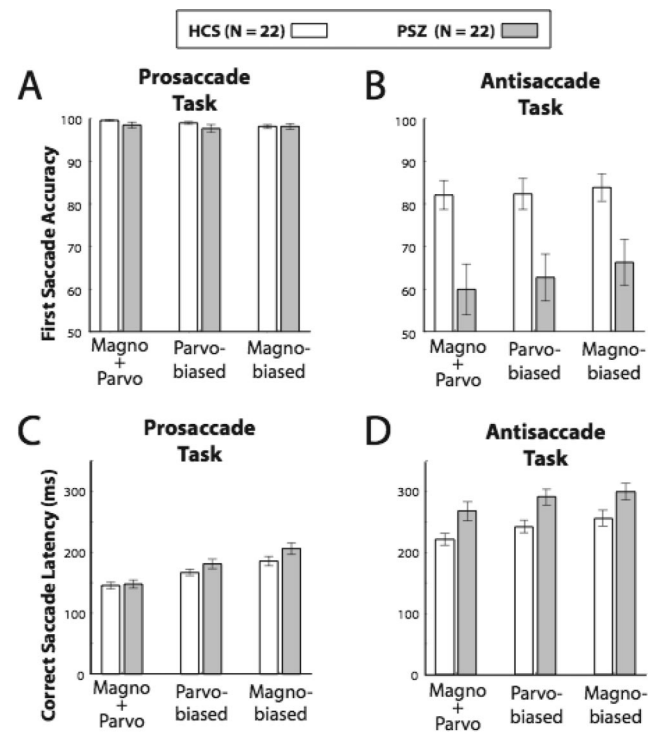


Figure 2. Performance accuracy (top row) and saccadic latency (bottom row) for the first saccade in the prosaccade and antisaccade tasks across stimulus types, excluding trials with saccades that landed within 4.5° of fixation.

magno-biased stimuli than for magno + parvo stimuli, leading to a significant interaction between stimulus type and task across all participants, $F(2, 84) = 4.5, p = .01$.

The antisaccade deficit in PSZ relative to HCS (Figure 2B) was numerically largest for the magno + parvo stimuli (Cohen's $d = 0.98$), slightly smaller for the parvo-biased stimuli ($d = 0.89$), and slightly smaller still for the magno-biased stimuli ($d = 0.84$). However, neither the stimulus type \times group interaction nor the stimulus type \times group \times task interaction was significant, $F(2, 84) = 1.7, p = .19$ and $F(2, 84) = 0.62, p = .54$, respectively. Moreover, the nonsignificant numerical trend was in the direction of a larger antisaccade deficit for the parvo-biased stimuli than for the magno-biased stimuli. Thus, there was no suggestion that the antisaccade deficit might be eliminated or substantially reduced for stimuli that do not activate the magnocellular pathway (i.e., the parvo-biased stimuli).

Separate ANOVAs were performed on the prosaccade and antisaccade accuracy data. In the prosaccade task, there were no significant main effects (stimulus type: $F(2, 84) = 2.5, p = .09$; group: $F(1, 42) = 1.5, p = .25$) and no group \times stimulus type interaction, $F(2, 84) = 1.4, p = .25$. PSZ performed lower than HCS in the antisaccade task, supported by a significant main effect of group, $F(1, 42) = 9.8, p < .01$. The lower error rate for the parvo-biased and magno-biased stimuli as compared with the magno + parvo stimuli led to a significant main effect of stimulus type, $F(2, 84) = 3.5, p = .04$. There was no interaction of group with stimulus type, $F(2, 84) = 1.1, p = .34$. Thus, although we had the statistical power to detect slight differences in antisaccade accuracy across the different stimulus types, these differences did not vary across groups, even though PSZ exhibited a robust antisaccade deficit relative to HCS.

The key question is whether PSZ exhibit a substantial antisaccade deficit for stimuli that produce little or no activation of the magnocellular pathway (i.e., the parvo-biased stimuli). We therefore conducted a separate analysis that focused solely on the parvo-biased stimuli. For these stimuli, prosaccade accuracy was near ceiling in both PSZ and HCS, but antisaccade accuracy was impaired by 20% in PSZ relative to HCS. In a two-way ANOVA with factors of group and task, this antisaccade deficit led to a significant group \times task interaction, $F(1, 42) = 7.7, p < .01$. Follow-up comparisons showed that accuracy was impaired in PSZ relative to HCS in the antisaccade task, $t(42) = 3.0, p < .01$, but not in the prosaccade task, $t(42) = 1.3, p = .18$. Thus, PSZ exhibited a robust antisaccade deficit for stimuli that should have produced minimal magnocellular activation.

Saccadic Latency on Correct Trials

Saccade latencies were generally slower in PSZ than in HCS (group main effect: $F(1, 42) = 4.9, p = .03$) and slower in the antisaccade task than in the prosaccade task (task main effect: $F(1, 42) = 130.1, p < .01$). The slowing in the antisaccade condition was more prominent in PSZ, although the group \times task interaction did not reach significance, $F(1, 42) = 3.6, p = 0.06$. Overall, saccade latencies were fastest for magno + parvo targets, slower for parvo-biased targets, and slower still for magno-biased targets (see Figure 2C and 2D). Accordingly, there was a main effect of stimulus type, $F(2, 84) = 150.0, p < .01$, but there was no significant group \times stimulus type interaction, $F(2, 84) = 1.9, p =$

.16 or group \times stimulus type \times task interaction, $F(2, 84) = 2.2, p = .12$. Thus, the stimuli varied in salience, but neither antisaccade costs per se, nor the antisaccade deficit in PSZ were significantly impacted by stimulus type.

As with accuracy, the key question is whether PSZ exhibited a substantial antisaccade deficit for the parvo-biased stimuli. A separate analysis for the parvo-biased stimuli with factors of group and task yielded a significant group \times task interaction, $F(1, 42) = 3.9, p = .05$. Saccade latencies were slowed by 45 ms in PSZ relative to HCS in the antisaccade task, a significant difference, $t(42) = 2.6, p = .02$. However, PSZ were slowed by only 14 ms relative to HCS in the prosaccade task, which was not a significant difference, $t(42) = 1.48, p = .15$. This provides further evidence that an antisaccade deficit can be observed in PSZ with stimuli that are largely invisible to the magnocellular pathway.

Correlations With Working Memory Capacity

Visual working memory capacity is reduced in PSZ (Gold et al., 2010; Leonard et al., 2013), and it is possible that both this and deficits in antisaccade performance are manifestations of PFC dysfunction in PSZ. Visual working memory capacity (K) estimates were available for 21 of 22 PSZ and 19 of 22 HCS. As expected, HCS had significantly higher mean K scores than PSZ (3.2 vs. 2.6; $t(38) = 3.8, p < .01$).

Figure 3 shows scatterplots of the correlation between K and saccade performance (averaged across stimulus types). Prosaccade accuracy was near ceiling for both groups and did not significantly correlate with K. Antisaccade accuracy was positively correlated with K in PSZ, with higher K values associated with higher antisaccade accuracy. This correlation was not significant in HCS, possibly because of restricted ranges for both values. The strong correlation between K and antisaccade accuracy in PSZ suggests that the antisaccade deficit in PSZ is related to deficits in cognitive processes such as working memory.

In HCS, higher K values were correlated with slower saccadic latencies in both the prosaccade and antisaccade tasks. However, this relationship was absent in PSZ. The correlations significantly differed between groups for both the prosaccade condition ($z = 3.14, p < .01, 2$ -tailed) and the antisaccade condition ($z = 2.32, p = .02, 2$ -tailed). This may indicate that HCS with high K slowed their saccadic responses to avoid errors, whereas PSZ were slow irrespective of K. This dissociation is consistent with previous research showing that visual working memory correlations in PSZ are divergent from those in HCS (Leonard et al., 2013).

Sensory Thresholds

PSZ performed more poorly than HCS in the sensory threshold task for both low (PSZ threshold = 3.2%, HCS threshold = 2.6%, $t(42) = 2.5, p = .01$) and high spatial frequencies (PSZ threshold = 39.8%, HCS threshold = 24.7%, $t(42) = 2.3, p = .03$). Elevated thresholds for high spatial frequencies can arise from uncorrected accommodation problems (owing, e.g., to out-of-date eyeglass prescriptions). Indeed, Snellen acuity was significantly correlated with high spatial frequency threshold in PSZ ($\rho = -0.48, p = .03$) but not in HCS ($\rho = -0.19, p = .45$). Snellen acuity was not correlated with low spatial frequency thresholds in either PSZ ($\rho = 0.06, p = .78$) or HCS ($\rho = -0.06,$

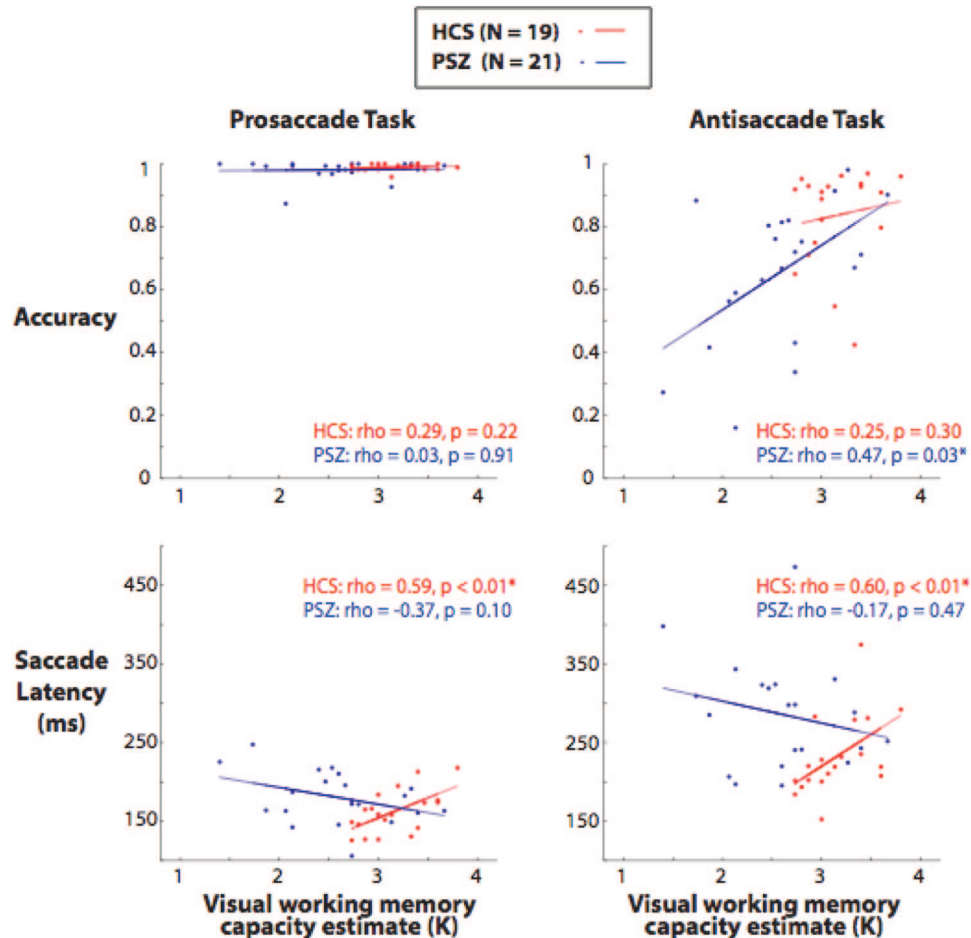


Figure 3. Scatterplots of correlations between visual working memory capacity estimate (K) and overall task performance (Spearman's rho and significance values shown).

$p = .81$). This pattern may indicate that uncorrected optical problems explain the elevated high spatial frequency thresholds in PSZ, although we cannot rule out a neural impairment.

To determine whether the observed sensory deficits in PSZ could explain saccade performance, we assessed correlations between thresholds and saccade performance in the 21 PSZ and 19 HCS included in the working memory analyses. Critically, there were no significant correlations between saccadic accuracy and either low or high spatial frequency thresholds in either group (all $\rho < 0.22$ with p s > 0.35 , with the exception of high spatial frequency in HCS for the antisaccade condition, $\rho = -0.4, p = .09$). Most importantly, there was no significant relationship between low spatial frequency threshold and antisaccade accuracy in either HCS ($\rho = 0.18, p = .47$) or PSZ ($\rho = -0.21, p = .36$). Additionally, there was no significant correlation between high spatial frequency threshold and saccadic latency for either group. In both groups, low spatial frequency threshold tended to be positively associated with both prosaccade and antisaccade latency, indicating that participants who had better perceptual abilities for low spatial frequencies made faster eye movements. However, this correlation reached significance only for prosaccade latencies in HCS ($\rho = 0.55, p = .01$). There was no corresponding

correlation for low-spatial frequency and prosaccade latency in PSZ ($\rho = 0.11, p = .63$). The correlation of antisaccade latency and low frequency threshold did not reach significance for either HCS ($\rho = 0.41, p = .08$) or PSZ ($\rho = 0.38, p = .09$).

Direct comparison in PSZ shows that the correlation between working memory capacity and antisaccade accuracy was significantly stronger than the correlation between low-spatial frequency threshold (a proxy for magnocellular functioning) and antisaccade accuracy ($z = 2.17, p = .03$, two-tailed). Overall these results suggest that, in PSZ, individual variation in working memory performance explains antisaccade deficits better than does individual variation in sensory deficits.

Medication Analyses

To assess possible antipsychotic medication effects, chlorpromazine equivalents (see Andreasen, Pressler, Nopoulos, Miller, & Ho, 2010) were correlated with performance measures in the saccade tasks. There were no correlations with either saccadic accuracy (prosaccade $\rho = -0.22, p = .32$; antisaccade $\rho = -0.09, p = .70$) or saccadic latency (prosaccade $\rho = -0.13, p = .55$; antisaccade: $\rho = -0.17, p = .44$). No correlations approached

significance for any stimulus type. Thus, saccade performance does not appear to have been impacted by antipsychotic medication, consistent with prior evidence (Hutton & Ettinger, 2006). We also examined correlations between negative symptom severity (using the SANS total score) and positive symptoms (using the psychosis factor score from the BPRS) with antisaccade performance. Neither correlation approached significance (both p s >0.6). There were also no significant correlation between K and BPRS ($p = .7$). For the SANS total measure, there was a nonsignificant trend for a negative correlation with working memory, such that higher K was associated with less severe negative symptoms ($\rho = -0.33$, $p = .14$).

Discussion

The present results provide evidence suggesting that one key measure of cognitive impairment in PSZ—the antisaccade deficit—is not a downstream consequence of abnormalities in magnocellular sensory processing. Instead, the results are consistent with a locus of impairment that is related to higher cognitive functioning as measured by working memory capacity. Magnocellular sensory deficits may contribute to other aspects of cognition (Butler et al., 2009; Sergi et al., 2006); however, the present observation provides an important limit on the range of cognitive impairments that can be attributed to magnocellular sensory dysfunction.

The key finding in the current study was that a robust antisaccade deficit was present in PSZ for the parvo-biased stimuli, which were designed to minimize magnocellular involvement in stimulus processing. That is, because the magnocellular system should have been largely unresponsive to these stimuli, PSZ should not have suffered any ill effects of abnormal magnocellular processing. The finding that parvo-biased stimuli produce a robust antisaccade deficit—well within the typical range observed in PSZ (Hutton & Ettinger, 2006)—provides evidence against a magnocellular explanation of this deficit.

This conclusion is further supported by the finding that the antisaccade deficit for the parvo-biased stimuli was similar in magnitude to that observed for both magno + parvo stimuli, which activated both pathways, and for magno-biased stimuli. This is consistent with previous evidence that attentional control mechanisms in healthy individuals operate equivalently for stimuli that do and do not activate the magnocellular system (Leonard & Luck, 2011). We found significantly impaired sensory thresholds for low spatial frequency stimuli in PSZ that could not be explained by uncorrected optical problems, consistent with previous reports of impaired magnocellular processing. However, this impairment was not associated with the antisaccade accuracy deficit in PSZ.

Previous research suggests that early sensory processes (Devrim-Üçok, Keskin-Ergen, & Üçok, 2008) and perceptual functioning (Uhlhaas, Phillips, & Silverstein, 2005) may be more impaired during the acute illness phase. Thus, it is possible that an exaggerated antisaccade deficit would have been observed for the magno-biased stimuli if we had tested acute rather than chronic patients. However, we did find significant impairment in sensory thresholds in PSZ compared to HCS in our sample. Moreover, the present results demonstrate that a substantial antisaccade deficit can be obtained with parvo-biased stimuli, which rules out the possibility that this deficit can be largely explained by magnocellular sensory abnormalities.

Might some other, as-yet-unspecified sensory impairment explain the antisaccade deficit in PSZ? Although difficult to completely rule out a generic hypothesis of this sort, the correlation between antisaccade accuracy and visual working memory capacity indicates that at least a portion of the deficit is reflective of higher-level cognitive dysfunction. Some working memory deficits may be a consequence of impaired perceptual processing (e.g., Haenschel et al., 2007), but we have previously shown that the impaired capacity exhibited by PSZ in the type of working memory task used in the present study is not a result of impaired low-level sensory processing (Gold et al., 2010; Leonard et al., 2013). Thus, the correlation between this measure of working memory capacity and antisaccade performance most likely reflects the role of higher cognitive factors in the antisaccade deficit.

The koniocellular pathway—a smaller and physiologically more heterogeneous source of visual information (Hendry & Reid, 2000)—is difficult to isolate psychophysically and may have been responsive to all three of our stimulus types. However, this does not impact our main conclusion, which is that the antisaccade deficit is present in PSZ even for stimuli that produce little or no response in the magnocellular pathway.

Our three stimulus types were designed to selectively activate the magnocellular and parvocellular pathways, which led to differences in prosaccade latencies across stimulus types in both HCS and PSZ. This suggests that these stimulus types differed in the speed of the feedforward sweep of processing that enables detection and saccade production. Antisaccade error rates are typically increased by manipulations that shorten prosaccade latencies (Hutton & Ettinger, 2006), and there was a numerical trend for this relationship in the current results. That is, prosaccade latencies were fastest for the magno + parvo stimuli and slowest for the magno-biased stimuli, and antisaccade error rates tended to be largest for the magno + parvo stimuli and smallest for the magno-biased stimuli. This pattern is exactly what would be predicted if a stimulus with a faster speed of detection required greater recruitment of cognitive control to overcome reflexive orienting.

Together, the effects of our stimulus manipulations and the correlations with working memory capacity but not perceptual thresholds support the idea that the antisaccade deficit in PSZ does not arise from impaired magnocellular sensory processing, and is more closely tied to higher-level cognitive control. However, this does not imply that magnocellular processing is unimpaired in PSZ. Indeed we found increased perceptual thresholds for magno-biased stimuli, although this impairment was not related to antisaccade accuracy. Sensory deficits may contribute to other higher-order cognitive deficits, as has been suggested by several studies (Butler et al., 2009; Sergi et al., 2006).

Understanding the degree to which sensory versus higher-level control deficits contribute to broad impairment in schizophrenia can help guide development of future pharmacological and cognitive remediation treatments, as these two accounts implicate different mechanisms that likely require different approaches (Adcock et al., 2009; Wykes & Spaulding, 2011). For example, a strategy that targets magnocellular sensory functioning is likely to impact a specific cognitive impairment only to the extent that this specific cognitive impairment is secondary to magnocellular dysfunction. Thus, we would not expect magnocellular-specific sensory training to ameliorate deficits related to the antisaccade deficit in PSZ. However, recent research suggested that auditory training

can impact higher-level cognitive abilities (Fisher, Holland, Subramaniam, & Vinogradov, 2010). It is important to note that the training protocol in this study involved many higher-level abilities as well, and that it is extremely difficult to design a “pure” sensory training regimen that does not involve working memory, sustained attention, and task maintenance. Thus, although the effects of sensory training on cognitive performance can potentially help establish the causal role of sensory deficits in impaired cognition, great care is needed to rule out alternative explanations.

As research continues to explore the relationship between sensory and cognitive processing in both typical and atypical populations, a distinction should be made between correlations resulting from the content of sensory representations and correlations resulting from the effects of attention and cognitive control on sensory processing. In terms of content, improvements in sensory processing will have downstream benefits for higher-level processing to the extent that downstream processes are limited by sensory quality (Norman & Bobrow, 1975). That is, small changes in sensory quality may have a big impact on downstream processes in some situations (e.g., understanding speech in a noisy environment) but not in others (e.g., determining whether a nearby traffic light is red or green on a clear day). Attentional processes are known to have a large impact on sensory responses (Kastner, Pinsk, De Weerd, Desimone, & Ungerleider, 1999; Luck, Chelazzi, Hillyard, & Desimone, 1997), which raises the possibility that impairments in top-down processes could lead to a correlation between sensory processing and cognitive performance as well. Thus, there is a complicated relationship between sensory processing and higher-level task performance that may result in correlations in some situations but not in others.

There are important findings showing that both lower level sensory processing as well as higher order cognitive control processes are impaired in schizophrenia. A major challenge facing the field is to carefully evaluate the role that each of these forms of impairment plays in the genesis of the cardinal cognitive impairments in schizophrenia. Programmatic work is needed to clarify how these contributions ultimately lead to impairments in episodic memory, set shifting, and aspects of social cognition so that treatment approaches that can improve day-to-day functioning are targeted appropriately.

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