NeuroImage: Clinical 2 (2013) 8–16

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Impaired magnocellular/dorsal stream activation predicts impaired reading ability in schizophrenia ☆

Antígona Martínez [a,c,*], Nadine Revheim [a], Pamela D. Butler [a,b], David N. Guilfoyle [a], Elisa C. Dias [a], Daniel C. Javitt [a,b]

[a] Nathan Kline Institute for Psychiatric Research, USA
[b] New York University Langone School of Medicine, USA
[c] University of California, San Diego, USA

ARTICLE INFO

Article history:
Received 7 June 2012
Received in revised form 1 September 2012
Accepted 5 September 2012
Available online 14 September 2012

Keywords:
Reading
fMRI
Magnocellular
Schizophrenia

ABSTRACT

In healthy humans, passage reading depends upon a critical organizing role played by the magnocellular/dorsal visual pathway. In a recent study, we found a significant correlation between orthographic reading deficits in schizophrenia and deficits in contrast sensitivity to low spatial frequency stimuli, suggesting an underlying magnocellular processing abnormality. The interrelationship between magnocellular dysfunction and passage reading impairments in schizophrenia was investigated in 21 patients with schizophrenia and 17 healthy control volunteers using behavioral and functional MRI (fMRI) based measures. fMRI activation patterns during passage- and single-word reading were evaluated in relation to cortical areas with differential sensitivity to low versus high spatial frequency cortical regions indentified using a phase-encoded fMRI paradigm.

On average, patients with schizophrenia read at the 6th grade level, despite completion of more than 12 years of education and estimated normal pre-morbid IQ. Schizophrenia patients also showed significantly impaired contrast sensitivity to low spatial frequencies and abnormal neural activity in response to stimulation with low spatial frequencies, consistent with dysfunction of magnocellular processing. Further, these magnocellular deficits were predictive of poor performance on a standardized psychoeducational test of passage reading. These findings suggest that reading is an important index of cognitive dysfunction in schizophrenia and highlight the contribution of magnocellular dysfunction to overall cognitive impairments in schizophrenia.

1. Introduction

Schizophrenia (SZ) is associated with cognitive deficits that represent a core feature of the disorder and are primary predictors of impaired long-term functional outcome. Traditional studies of cognitive dysfunction have focused on higher order processes such as attention, executive processing or working memory (e.g. Goldman-Rakic, 1994). More recent studies, however, point to significant deficits in sensory processing as well, consistent with models that posit distributed neurochemical deficits in schizophrenia (reviewed in Javitt, 2009).

In the visual system of SZ patients, sensory processing deficits are most pronounced within the magnocellular pathway which projects preferentially to the dorsal visual stream. Behaviorally, impaired magnocellular functioning has been demonstrated in backward masking (Green et al., 1994; Schechter et al., 2003), motion processing (Brittain et al., 2010; Kim et al., 2006) and contrast sensitivity paradigms (Butler et al., 2001), among others. Physiologically, deficits have been observed using steady-state (Butler et al., 2001, 2005; Krishnan et al., 2005) and transient (Butler et al., 2007; Schechter et al., 2005) event-related potentials (ERPs), and with functional neuroimaging (fMRI) measures (Martinez et al., 2011, 2008). In addition, deficits in processes thought to depend upon intact magnocellular/dorsal stream input have also been documented in SZ including perceptual closure (Doniger et al., 2002; Sehatpour et al., 2010), face emotion recognition (Butler et al., 2009), visual continuous performance tasks (Dias et al., 2011) and selective attention to low spatial frequencies (LSF) (Martinez et al., 2011). On the neurochemical level, deficits in magnocellular processing have been linked to impaired functioning of N-methyl-D-aspartate (NMDA)-type glutamate receptors (Butler et al., 2005; Javitt, 2009, 2010).

One cognitive process that is widely considered to depend upon intact magnocellular/dorsal stream activity is reading (Kevan and Pammer, 2008; Levy et al., 2010; Pammer et al., 2006; Vidyasagar and Pammer, 1999). Though seemingly automatic, reading involves

* Corresponding author at: Nathan Kline Institute for Psychiatric Research, 140 Old Orangeburg Rd, Orangeburg, NY 10962, USA. Tel.: +1 845 398 5497; fax: +1 845 398 6545.
E-mail address: martinez@nki.rfmh.org (A. Martínez).

2213-1582/$ – see front matter © 2012 The Authors. Published by Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.nicl.2012.09.006

complex coordination of processes involved in the integration of orthographic, phonological, and lexical/semantic features of words. Neurobiologically, the reading system includes a frontal system as well as two posterior components, a ventral (occipitotemporal) system thought to be involved in mapping orthographic lexical stimuli onto their phonological representations and a dorsal (temporoparietal) system involved in sublexical analysis of word stimuli (i.e., mapping of letters onto their sounds as well as other analytical aspects of reading including semantic analysis) (Howard et al., 1992; Pugh et al., 2000; Rumsey et al., 1997; Sandak et al., 2004; Shaywitz and Shaywitz, 2008; Shaywitz et al., 2002). Both of these streams share early visual feature analysis in the occipital cortex. Functional neuroimaging studies indicate that this network of interacting cortical areas is engaged when skilled readers read isolated words, reading sentences/passages for meaning results in more widespread activity in regions including the posterior superior and middle temporal gyri as well as portions of the parietal lobes (reviewed in Rimrodt et al., 2009).

In contrast to reading single words, passage reading relies on the ability to smoothly sweep attention across the written page and select words and their features based on their spatial location (Pammer et al., 2006; Vidyasagar and Pammer, 2009). This ability is largely mediated by cortical areas in the dorsal visual stream which receive strong magnocellular input. Accordingly, it has been proposed that impairment anywhere along the dorsal pathway can cause an inability to move the focus of attention along the length of each word and thus lead to poor reading performance (Pammer et al., 2006; Vidyasagar and Pammer, 2009). This theory provides a plausible mechanism for the role of the magnocellular pathway in passage reading and is consistent with the view that the dorsal pathway identifies and selects relevant regions of space to be then passed on to the ventral system for more detailed analysis thus providing "framing" input for higher-order functions (Schroeder et al., 1998; Vidyasagar and Pammer, 2009).

Impaired magnocellular/dorsal functioning has been associated with reading deficits in developmental dyslexia (Chase and Stein, 2003; Demb et al., 1998a, 1998b; Stein, 2001). For example, several studies have reported that dyslexics perform poorly on psychophysical tasks such as motion discrimination and contrast detection which require intact functioning of the magnocellular pathway (Cornelissen et al., 1995; Demb et al., 1998a; Wilmer et al., 2004). Additionally, dyslexic individuals show diminished neural activity in brain regions known to receive strong magnocellular input (Demb et al., 1997, 1998b). Significant correlations between individual reading ability and neural activity within these brain regions have been reported (Demb et al., 1997), supporting the hypothesis that magnocellular pathway integrity is critical for normal reading.

Single word reading has been studied in individuals with SZ; it has been reported to be largely unaffected when compared to other cognitive deficits (Dalby and Williams, 1986; Kremen et al., 1996) and relatively preserved in geriatric patients with lifelong chronic SZ (Harvey et al., 2002). In contrast to single-word reading, studies that have investigated passage reading abilities have reported deficits in patients with SZ (Fuller et al., 2002; Hayes and O'Grady, 2003; Revheim et al., 2006). For example, in a recent study, we evaluated passage reading in SZ patients and demonstrated significant impairments in orthographic reading (Revheim et al., 2006). These deficits correlated significantly with deficits in impaired contrast sensitivity to LSF stimuli, suggesting an underlying magnocellular processing abnormality. The present study further investigates impairments in passage reading in SZ in relation to magnocellular/dorsal stream dysfunction. Specifically, we assess fMRI activation patterns during passage reading in SZ patients, relative to healthy control subjects, and compare these to activation patterns during single word reading.

Activations are evaluated in relation to cortical areas with differential sensitivity to LSF versus high spatial frequency (HSF) regions indentified using a phase-encoded fMRI paradigm described previously (Martinez et al., 2008). We hypothesized that passage reading in control subjects would be associated with increased activation within LSF-sensitive, dorsal stream visual regions relative to single word reading, and that deficits in passage reading in SZ would be associated with differentially reduced activation of these same LSF-sensitive brain regions. In addition, we hypothesized that both impaired reading and impaired activation by LSF stimuli would be associated with deficient contrast sensitivity to low, but not high, spatial frequencies, as in our previous study (Revheim et al., 2006).

2. Materials and methods

2.1. Participants

Twenty one patients with schizophrenia or schizoaffective disorder ($n=5$) (20 males) and 17 healthy control volunteers (15 males) signed written informed consent to participate in the behavioral portions of the study. A subset of these participants (11 patients, 11 controls) took part in a single fMRI scanning session involving modified versions of the reading tests described below. Patients were recruited from outpatient and chronic inpatient clinics in the New York City area. At the time of testing ten of the patients were inpatients. All participants had normal or corrected-to-normal visual acuity (20/30 or better on the Logarithmic Visual Acuity Chart, Precision Vision, LaSalle, IL). Individuals with a history of neurological impairment, mental retardation, color vision deficits, or current alcohol or drug abuse (<1 month) or substance dependence (<6 months) were excluded. On average, patients had been ill for 18.5 years prior to testing. All were on a stable dose of antipsychotic medication (1314.1 +/− 973.5 chlorpromazine equivalents/d).

Overall, patient and control subject groups did not significantly differ in age, gender, or handedness. Hollingshead parental socioeconomic status (SES) also did not significantly differ between groups (Table 1). Participant SES, however, was significantly lower in SZ patients compared to control subjects ($p<.0001$), as was the difference between participant and parental SES ($p=.0004$). Quick IQ score, which assesses verbal IQ, was significantly lower in patients than controls ($p=.001$), but was nonetheless close to the population average of 100 even for patients.

2.2. Symptom and neuropsychological measures

Symptoms for all subjects were assessed using the Positive and Negative Symptom Scale (PANSS) (New York: PANSS Institute). General

Table 1
Demographics.

Measure	Control		Patient		t	df	p	Effect size (d)
	Mean	SD	Mean	SD				
Demographics								
Age	32.7	11.0	39.4	10.8	1.89	36	.07	−.6
IQ	106.4	10.4	97.3	8.6	2.91	35	.007	1.1
Education (years)	16.1	2.4	12.4	2.3	4.79	36	<.001	1.6
Parental socioeconomic status (SES)	43.1	12.3	47.6	27.4	.63	35	.53	−.2
Participant socioeconomic status (SES)	50.5	11.0	26.3	10.4	6.86	35	<.0001	2.3
SES difference (participant–parent)	7.5	11.9	−21.3	28.1	3.85	35	<.001	1.4

Table 2
Reading, contrast sensitivity, and neuropsychological test scores.

Measure	Controls (n = 17)		Patients (n = 21)		t	df	p	Effect size (d)
	Mean	SD	Mean	SD				
Reading (Gray Oral Reading Test, GORT)								
Fluency (standard score)	14.2	2.2	3.7	4.4	8.94	36	<.0001	3.2
Fluency (grade equivalent)[a]	12.8	0.0	6.0	2.9	9.63	36	<.0001	4.7
Comprehension (standard score)	9.1	1.9	5.1	2.7	5.17	36	<.0001	1.7
Comprehension (grade equivalent)	11.5	1.6	6.2	3.8	5.38	36	<.0001	2.0
Summary score (Oral Reading Quotient)	71.4	19.3	9.3	25.5	8.28	36	.000	2.8
Visual contrast sensitivity (CS)								
Low spatial frequency (LSF, .5–2 cpd)	132.6	38.3	79.4	35.1	4.29	33	.000	1.5
High spatial frequency (HSF, 4–10 cpd)	53.9	34.7	34.0	15.6	2.24	33	.03	0.8
General measures								
Wechsler adult intelligence scale III-Processing Speed Index (WAIS3-PSI)	99.9	19.5	82.2	10.0	3.09	24	.005	1.2
Wechsler memory scale III Working memory index (WMS3-WMI)	102.8	9.1	88.8	20.5	1.84	26	.077	1.0

[a] Grade equivalent scores are capped at grade 12.8, leading to lack of variance on this measure for controls.

neuropsychological function was assessed using the WAIS-III (Wechsler, 1997) processing speed index (PSI), perceptual organization index (POI) and working memory index (WMI) (Table 2). In all the above tests, index scores were calculated from the sum of the pertinent age-adjusted scaled scores based on raw scores for each subtest as found in the respective manual. Neuropsychological measures were not available from four SZ patients.

2.3. General statistical analyses

Between group statistics were performed using Student's t-tests, univariate or repeated measures analysis of variance (ANOVA). Correlation coefficients (r) between measures were assessed using linear regression with all variables entered simultaneously. Effect sizes (d) were calculated as the mean divided by the average standard deviation and interpreted according to the convention of Cohen with 0.2, 0.5 and 0.8 reflecting thresholds for small, medium and large effects, respectively. Statistics were performed using SPSS 18.0 (SPSS, Inc. Chicago, IL) and were two-tailed with preset level for significance of $p<.05$.

2.4. Behavioral reading measures

Two standardized psychoeducational reading tests were administered to all subjects. These tests assessed single word reading and passage reading. The tests were administered in a well-lit/quiet room according to specified directions. Participants were given multiple opportunities for rest periods. Scoring was performed by hand or computer software.

Single word reading was assessed with the Wide Range Achievement Test 3rd Edition, (WRAT3, San Antonio, TX: The Psychological Corporation, 2001), which measures basic word-reading skill in the absence of demands on comprehension. Raw scores from the WRAT3 were converted into standard scores using age-related norms with a mean of 100 and a standard deviation (SD) of 15. Passage reading abilities were assessed with the Gray Oral Reading Test (GORT-4) (Austin, TX: Pro-Ed, 2001), which measures oral reading skills. Individuals read aloud up to 14 stories and answered multiple-choice questions that followed. The GORT-4 test results in five separate scores: a) Rate (the amount of time taken to read the story); b) Accuracy (the ability to pronounce each word correctly); c) Fluency (Rate + Accuracy); and d) Comprehension (the accuracy of answers to the multiple-choice questions). GORT-4 scores are reported as standard scores with a mean of 10 and a SD of 3. An overall reading ability score, the Oral Reading Quotient (ORQ), with a mean of 100 and SD of 15, combines the fluency and comprehension scores. The ORQ was used in all subsequent statistical analyses of GORT-4 scores. Statistical analyses of within- and between-group performance (patients versus controls) on WRAT3 and ORQ scores were carried out using ANOVA with the standardized score from each reading test as the dependent variable.

2.5. Contrast sensitivity

Functioning of the magnocellular visual pathway was assessed by deriving contrast sensitivity (CS) functions using previously described methods (see Butler et al., 2005 for details). Briefly, horizontal sine-wave gratings consisting of 0.5, 1, 2, 4, 7 or 10 cycles per degree (cpd) were delivered one at a time in random order to the left or right side of a computer screen. On each trial, the grating was presented for 32 ms and the subjects' task was to indicate the side of the screen that the grating appeared in. An up-down transform response method was used to obtain contrast thresholds with a criterion of 70.7% correct responses for each spatial frequency. The mean of 10 reversals was used to obtain thresholds.

The data were analyzed in terms of CS values, which is the reciprocal of the detection threshold. To reduce the number of comparisons, data were averaged separately for LSF (0.5, 1, 2 cpd) and HSF (4, 7, 10 cpd) SF stimuli. Group differences in CS were assessed in a repeated measures ANOVA with a between subject factor of Group (patients, controls) and a within subjects factor of spatial frequency (LSF, HSF). The relationship between reading deficits and CS was evaluated across both groups of subjects using multiple regression with factors of group and CS scores. CS data were not available from three SZ patients and three control subjects.

2.6. fMRI tasks

Modified versions of the GORT-4 and WRAT3 reading tests were administered to subjects inside the scanner during separate functional MRI (fMRI) scans. During the fMRI, subjects silently read passages (as in GORT-4) or single words (as in WRAT-3) presented via MR-compatible liquid crystal display goggles (Resonance Technology Inc., Northridge, CA). In both cases, 30-second blocks of each reading task were alternated with blocks of rest (fixation only) lasting 20 s. A single scan consisted of six blocks of the reading task (words or passages) and six blocks of rest. To ensure task compliance, subjects were asked to answer a few brief questions at the end of each scan regarding the content of the paragraphs read or, in the case of the single-word task, to state whether a list of specific words were presented during the scan. In particular, questions about the reading passages ('yes–no' format) were presented to patients as a validity check for their adherence to the demand characteristics of the reading tasks while being scanned. The questions elicited recognition of passage details rather than pure recall because recognition of verbal materials is less

impaired compared to recall in SZ (Aleman et al., 1999). The accuracy of the responses was assessed by the examiner in the context of the imaging session, (i.e., while the patient was still lying in the scanner before emerging). The examiner determined that all patients were able to answer questions accurately using this validity check, therefore, it was determined that all the patients complied with the expectation to read the passages as directed while being scanned. Answering questions or reading aloud while in the scanner would have precluded data collection that required patients to be quiescent; therefore, this behavioral data was used to bridge and 'infer' that task adherence during scanning was appropriate.

2.7. fMRI data acquisition and analyses

Echo-planar T2*-weighted images (EPIs; TR = 2 s; TE = 38 ms; flip angle = 90°; voxel size = 4 mm^3; matrix size 64×64) were acquired on a 3 T MRRS (formerly SMIS, Guildford, UK) head-only MRI system housed at the Nathan Kline Institute Center for Advanced Brain Imaging. During each run, 154 volumes were acquired on each of the 32 contiguous slices in the axial plane. The first four volumes from each run were discarded prior to all analyses to allow for stabilization of the blood oxygen level dependent (BOLD) signal. For anatomical localization of functional data, high-resolution (1 mm^3) images of the entire brain were acquired from each subject, using a standard MPRAGE sequence (TR = 11.6 ms; TE = 4.9 ms, flip angle = 8°; effective inversion time = 1.1 s; matrix size 256×256). The fMRI data were analyzed with the AFNI software package (Cox, 1996).

Prior to statistical testing the EPI images from each scan were realigned to the first included volume, linearly de-trended and slice-time corrected. Individual subject data were statistically analyzed using a general linear model (GLM). For each subject, the fMRI time series associated with each reading task was fit with a regressor representing the timing of the reading task. Motion parameter estimates were also included in the GLM as covariates. The resulting regression coefficients for each reading condition were normalized and converted to percent BOLD signal change. Individual subject maps of percent signal change were then co-registered with each individuals' high-resolution anatomical images and projected into Tailarach coordinate space before being spatially smoothed with a Gaussian kernel of 4 mm FWHM. These signal change maps were used subsequently in repeated measures ANOVAs to test for group differences, as described below.

To assess the relationship between sensory visual processing and reading, between-group statistical analyses were carried out within cortical regions of interest (ROIs) delineated according to their relative sensitivity to low and high spatial frequencies. The procedures described in Martinez et al. (2008) were used to define spatial frequency sensitivity in each participant. In short, high-contrast sinusoidal gradients slowly and monotonically increasing in SF content (0.2 to 4.9 cpd) were used to elicit phasic responses in early visual cortex. The phase of the fMRI response at each voxel was estimated using functions implemented in the 3ddelay algorithm included in AFNI. Across all subjects, cortical areas with phase values representing preferential responses to SF's ranging from 0.2 to 1.5 cpd were averaged together to create the ROI for LSF. Similarly, cortical areas responding preferentially to frequencies in the 2.5–4.9 cpd range formed the averaged HSF ROI.

For each reading task, the mean percent signal change was calculated individually within the ROIs for LSF and HSF and entered into repeated measures ANOVA with factors ROI (LSF, HSF) and Group (patients, controls). Significance levels and minimum cluster sizes were calculated using Monte Carlo simulations. In all cases, only voxels with uncorrected p-values<0.005 (corresponding to p<.01, corrected for multiple comparisons) and belonging to nearest-neighbor clusters of 11 or more voxels, survived the final threshold.

Finally, the relationship between neural activity associated with reading and behavioral measures of reading ability (assessed outside the scanner) was evaluated within the cortical region encompassed by the ROIs for LSF and HSF. Specifically, voxelwise correlations were carried out using individual subjects' mean fMRI percent signal change values during passage and single-word reading and individual scores on the GORT-4 and WRAT3 tests which were administered prior to scanning.

3. Results

3.1. Reading performance and correlation with CS

3.1.1. Reading

Patients with SZ read at the 6th grade level, despite completion of an average of 12.4 years of education and despite having estimated normal pre-morbid IQ relative to the population mean ($t(19) = -1.70$, $p = .110$) (Table 1). Overall, SZ patients performed significantly worse than control subjects on standardized tests of both passage (GORT-4) and single word (WRAT3) reading ($F(1,36) = 79.37$, $p < .0001$; see Fig. 1A). The degree of reading impairment in patients, however, was significantly larger for passage than word reading, as evidenced by a highly significant Group (patients, controls)×Test (GORT, WRAT) ($F(1,36) = 34.29$, $p = 10^{-6}$) interaction. Within the GORT test, deficits in mechanical aspects of reading (rate, accuracy, fluency) were significantly greater than deficits in comprehension, as reflected in a Group×Factor (fluency/rate/comprehension) interaction ($F(1,36) = 30.6$, $p < .0001$) (Table 2).

Finally, differences in reading between groups remained strongly significant even following covariation for standardized measures of general cognitive impairment (PSI, WMI) ($F(1,21) = 20.8$, $p < .0001$) as did the Group×Test (GORT/WRAT) interaction ($F(1,21) = 12.7$, $p = .002$). Furthermore, across groups, lower scores on the GORT test were significantly predictive of achieved socioeconomic status (SES) ($r = .42$, $p = .01$) but not with general intelligence (PSI) ($r = .25$, $p = .24$).

3.1.2. Contrast sensitivity

Compared to control subjects, SZ patients showed reduced CS for both low (0.5–2 cpd) and high (4–10 cpd) ($F(1,33) = 15.6$, $p = .0004$) spatial frequencies. The impairment in CS was significantly greater, however, at low SF (Table 2), as reflected in a significant Group×SF interaction ($F(1,33) = 9.11$; $p = .005$). Consistent with our prior report (Revheim et al., 2006), simultaneous linear regression showed significant independent contributions of Group (partial $r = 0.71$, $p = .001$) and CS at LSF (partial $r = 0.48$, $p = .007$) to impaired passage reading, whereas the correlation between reading and CS at HSF was not significant (partial $r = .08$, $p = 0.7$). Further, a significant relationship between passage reading (GORT scores) and CS to LSF ($r = 0.50$, $p = .035$) but not HSF ($r = -0.1$, $p = 0.7$) stimuli was observed even if the correlations were confined to patients alone (Fig. 1B). This correlation between passage reading and CS to LSF approached significance when considering only control subjects ($r = 0.47$, $p = .076$). In contrast, no significant correlations were observed between single word (WRAT) reading and CS to either LSF (partial $r = 0.31$, $p = 0.09$) or HSF (partial $r = -0.12$, $p = 0.5$) stimuli. Finally, CS at LSF was not correlated with individual IQ scores ($r = 0.11$, $p = 0.82$) (Fig. 1C).

3.2. fMRI results

3.2.1. SF sensitivity

As in our previous report (Martinez et al., 2008), SZ patients showed reduced activation within LSF-sensitive areas ($F(1,20) = 20.51$, $p < .001$) along with a significant correlation between the magnitude of the activations elicited by LSF stimuli and individual CS to LSF's (1 cpd) ($r = .68$, $p = .03$).

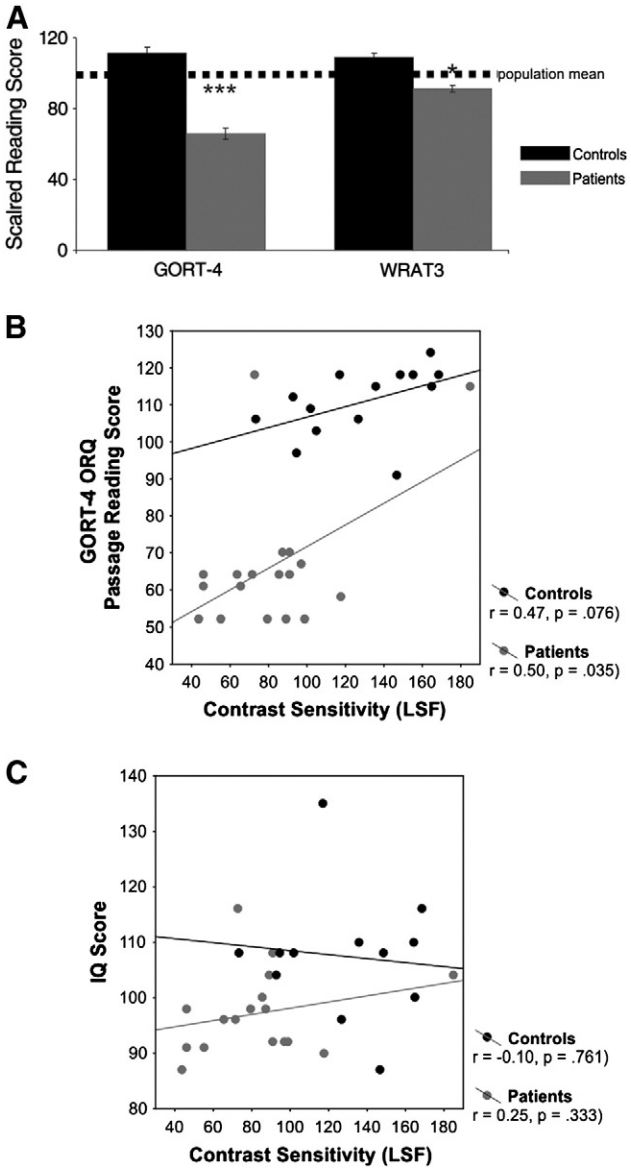

Fig. 1. Standardized (scaled) reading scores and their correlation with contrast sensitivity. (A) Compared to control subjects, SZ patients scored significantly lower on both passage reading (GORT-4; left bars) and single word reading (WRAT3; right bars) measures. Nonetheless, patients' degree of reading impairment was greater for passage reading. (** = p<.0001; * = p<.001). Dotted line represents standardized population mean score of 100 for both tests. (B) Contrast sensitivity (CS) at low spatial frequency (LSF, 0.5–2 cpd) was significantly correlated with individual passage reading scores (GORT-ORQ). The correlation was significant across patients and controls (r = .70, p<.0001) and for SZ patients alone. Within-group correlations are plotted individually for patients (gray dots and gray regression line) and controls (black dots and black regression line). CS thresholds for high spatial frequencies were not significantly correlated with passage reading scores. (C) Across patients and controls, CS at LSF did not correlate with individual IQ scores (r = 0.11, p = 0.82) nor did these two measures correlate within subject groups. Data is shown as in panel B for SZ patients (gray) and controls (black).

3.2.2. Reading tasks

Group differences in fMRI activation during single word and passage reading were evaluated within the ROIs for HSF and LSF shown in Fig. 2A. For both reading tasks (single word and passage reading), an analysis of variance (ANOVA) consisting of Group (patients, controls) × ROI (LSF, HSF) was performed to investigate the relative activation of LSF- versus HSF-sensitive regions across groups. Follow-up t-tests were carried out within each ROI to assess between-group differences.

3.2.2.1. Single word reading. The most prominent group difference during single word reading was located in medial occipital cortex within the lingual gyrus of both hemispheres and belonging to the ROI for HSFs. A portion of the posterior fusiform gyrus belonging to the LSF ROI was also significantly different in patients versus controls. Follow up t-tests revealed that in both ROIs the group difference was due to greater activation in SZ patients compared to controls (t(20) = 2.12, p<.04; HSF t(20) = 2.50, p<.02; LSF) (Fig. 2B, C). No other significant main effects or interactions were obtained during single word reading.

3.2.2.2. Passage reading. Compared to control subjects, SZ patients showed significantly reduced levels of activation, overall, during passage reading (F(1,20) = 16.79, p<.001). These group differences were largest in the ROI for LSF (Group × ROI interaction: F(1,20) = 16.54; p<.001) and were localized in the bilateral middle occipital gyrus (MOG), posterior portions of the superior temporal gyrus (STG) of the right hemisphere (RH) and the middle temporal gyrus (MTG) of both hemispheres (Fig. 2B, C). No group differences were obtained within the ROI for HSF.

3.2.3. Comparison between single word and passage reading

A 3-way analysis was conducted with both Task (passage, single words) and ROI (HSF, LSF) as within-subject factors and Group as a between-subject factor. As expected, there was a significant Group × Task interaction reflecting greater activation reductions for patients in the passage, compared to single word reading task (F(1,20) = 20.18; p<.001). In addition, a significant ROI × Group interaction indicated that, across tasks, patients had significantly reduced activations in LSF regions (F(1,20) = 18.81; p<.001). Finally, a significant three-way (Task × ROI × Group) interaction was obtained, reflecting the fact that the most pronounced between-group differences occurred within the LSF ROI during the passage reading task (F(1,20) = 5.51; p<.03). Cortical areas showing this significant 3-way interaction were localized in the MTG of the LH and RH and the fusiform gyrus of the LH (Fig. 3A).

3.2.4. Correlation between fMRI and behavioral measures

Subjects' scores on the passage (GORT) and single word (WRAT) reading tests, administered outside the scanner, were correlated with individual functional activation maps during word and passage reading. Significant correlations were obtained with passage reading scores only. Specifically, across subjects, higher GORT scores were associated with increased activation in the MOG of the LH and RH and in the MTG of the right hemisphere (r = 0.71, p = .01; SZ alone r = 0.76). Both the MOG and MTG regions were contained within the ROI for low spatial frequencies (Fig. 3B, C).

3.3. Correlations with symptoms and outcome

Patients showed significantly reduced individual achievement (SES) relative to parents (t(20) = 3.41, p = .003) as well as to control subjects (t(40) = 6.81, p<.0001). In contrast, parental SES was similar across groups (t(39) = .4, p = .68) and control subjects showed slightly higher SES compared to their parents (t(19) = 1.93, p = .07). Patients' reduced achievement correlated significantly with individual passage reading scores (GORT) (r = .42, p<.01), but not with other neuropsychological measures such as PSI (r = . 25, p = .24) or WMI (r = −.02, p = .93). Antipsychotic dose (CPZ) was inversely correlated with passage reading scores (r = −.56, p = .008) such that the higher the dose the lower the score. Similar correlations were observed for PSI (r = −.58, n = 17, p = .015) and WMI (r = −.59, p = .008).

4. Discussion

Cognitive deficits in schizophrenia have traditionally been attributed to impaired functioning of high-order brain regions (Callicott et al., 2003; Cohen and Servan-Schreiber, 1992; Goldman-Rakic, 1994). Over

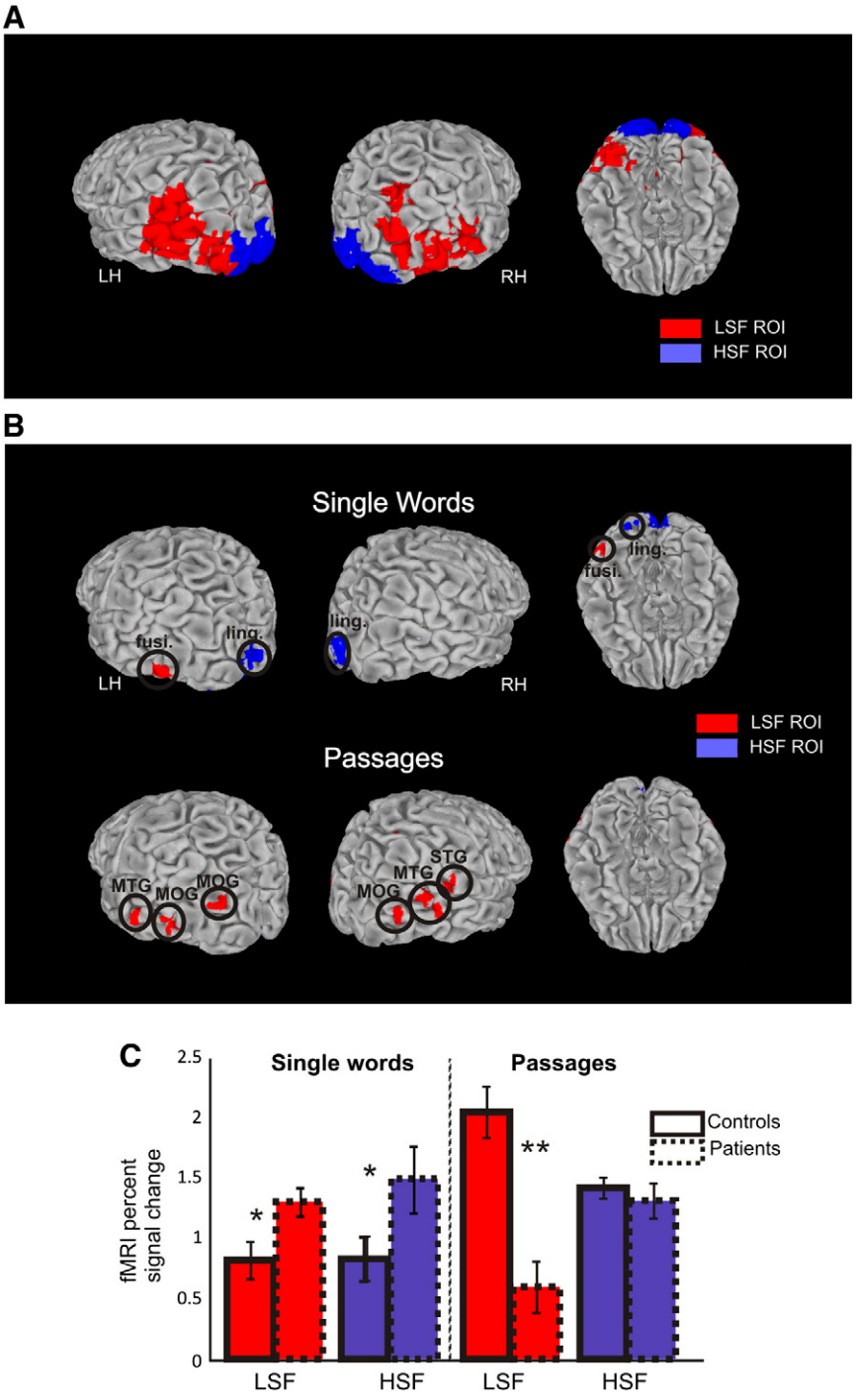

Fig. 2. Differences during single word and passage reading within regions of interest defined by differential spatial frequency sensitivity. (A) Cortical areas with preferential responsivity to spatial frequencies in the low (0.2–1.5 cpd) or high (2.5–4.9) range were identified as in Martinez et al. (2008). The resulting mean activations made up the regions of interest (ROI) for high (HSF; blue regions) and low (LSF; red regions) spatial frequencies. The ROIs are shown superimposed on the rendered cortical surface (left; LH, right; RH and ventral views) of a standardized brain. High spatial frequencies activated more posterior and medial portions of occipital cortex whereas LSF activations extended anteriorly and dorsally into temporal and parietal cortices. (B) Cortical areas showing significant group differences during single word (top row) and passage (bottom row) reading are shown colored according to the ROI (HSF, blue; LSF, red) in which they were contained. For single word reading, group differences were localized bilaterally in the lingual gyrus within the HSF ROI and in the fusiform gyrus of the LH contained in the ROI for LSF. In all cases, these differences were due to significantly greater fMRI activation in SZ patients compared to controls (see (C) left panel, below). In contrast, group differences during passage reading were localized exclusively within the ROI for LSF in bilateral middle temporal (MTG) and middle occipital (MOG) gyri and in the superior temporal gyrus (STG) of the RH and these group differences were driven by greater activation in controls compared to SZ patients (see (C) right panel, below). (C) Mean percent signal change for voxels in each ROI is shown for controls (dark red/blue bars) and patients (light red/blue bars) during single word (left) and passage (right) reading tasks. Error bars are standard error of the mean.

recent years, however, there has been increasing appreciation of the role of sensory dysfunction in the disorder. In particular, deficits in magnocellular/dorsal stream visual function have been documented using behavioral (Butler et al., 2001; Slaghuis, 1998), neurophysiological (Butler et al., 2007, 2001, 2002, 2005; Schechter et al., 2005) and fMRI-based approaches (Martinez et al., 2011, 2008).

The magnocellular/dorsal visual system plays an important role in normal reading (Kevan and Pammer, 2008; Levy et al., 2010; Pammer

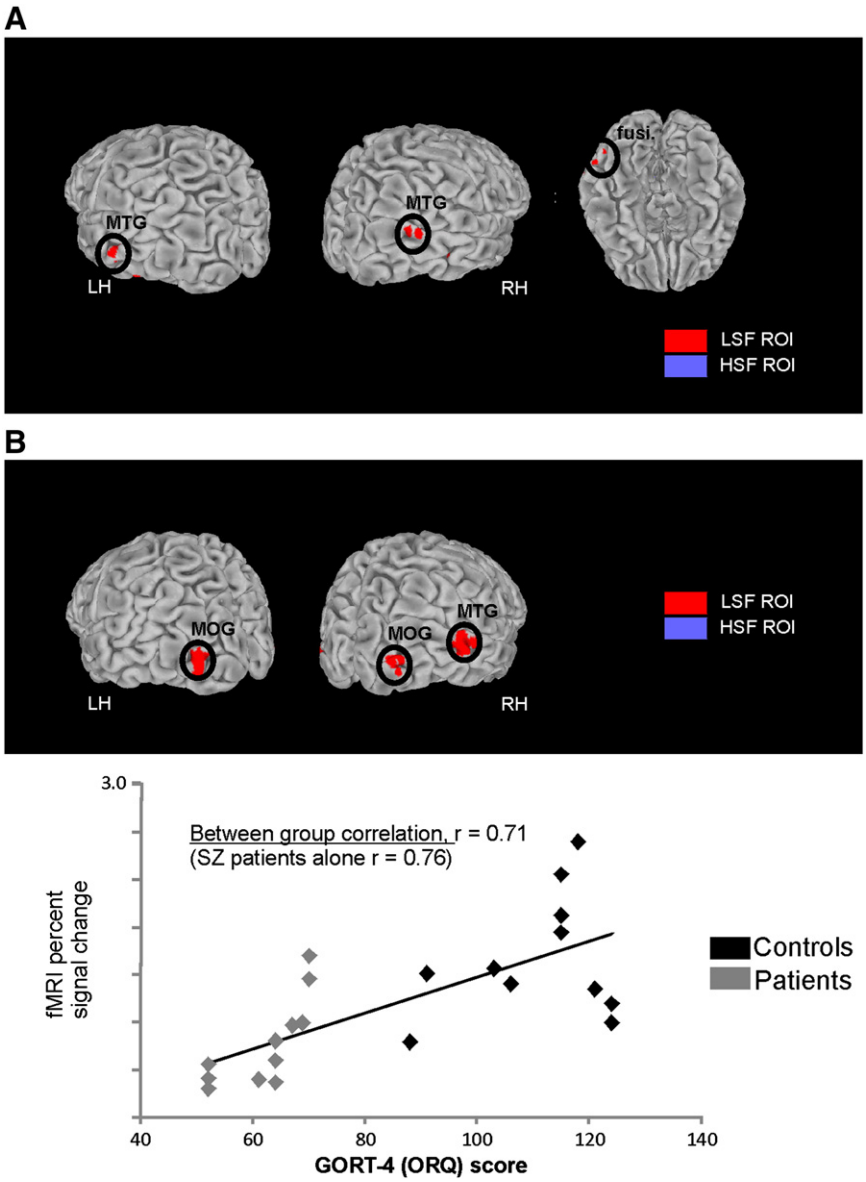

Fig. 3. Interaction between subject group, ROI and reading task and correlation with standardized reading scores (GORT-4). (A) Between-group differences were significantly greater during passage reading, especially within cortical areas in the ROI for LSF. This led to a significant 3-way interaction between Group (patients, controls), ROI (HSF, LSF) and Task (single word, passage reading) within bilateral MTG and in the fusiform gyrus of the LH (B). Better performance on the GORT-4 (ORQ) test (administered outside the scanner) was associated with increased activation (percent signal change) during passage reading. This significant correlation was observed within regions contained in the ROI for LSF (coded red), specifically, in bilateral MOG and the MTG of the right hemisphere. Individual mean percent signal change values (averaged across both ROIs) and GORT-4 scores are shown in bottom panel. The regression line depicts the positive correlation across both groups ($r = 0.71$). Control subjects are shown in black, SZ patients in gray. The correlation was also significant when tested within SZ patients only ($r = 0.76$). Single word reading scores on the standardized WRAT-3 test were not significantly correlated with fMRI activation during either reading task.

et al., 2006; Vidyasagar and Pammer, 1999) and it has been suggested that magnocellular processing deficits may underlie impairments in developmental dyslexia (Chase and Stein, 2003; Demb et al., 1998a, 1998b). Given well-documented magnocellular dysfunction in SZ, a strong forward prediction is that patients with SZ should show reading deficits commensurate with their magnocellular/dorsal stream dysfunction, providing a critical test both of sensory theories of SZ as well as magnocellular theories of reading.

Until recently, reading was considered a relatively intact function in SZ based largely on studies using single-word reading measures such as the Wide Range Achievement Test (WRAT) and the Wechsler Test of Adult Reading (WTAR) (San Antonio, TX: The Psychological Corporation, 2001). Such measures are sensitive to the acquisition of language skills during childhood and adolescence and thus are good measures of reading difficulty in developmental dyslexia. However, in disorders such as schizophrenia, where cognitive deficits may develop during late adolescence or early adulthood, such tests may be sensitive primarily to pre-morbid rather than current functional level.

In the present study, we found that SZ patients have pronounced impairments in orthographic reading ability which remained significant even following covariation for more general cognitive dysfunction and which strongly predicted overall psychosocial dysfunction. Moreover, during passage reading, patients showed significant hypoactivation of LSF-sensitive regions of cortex despite preserved or even increased activation of HSF-responsive regions. Finally, reading deficits (assessed using standardized tests outside the scanner) correlated specifically

with reduced fMRI activation of LSF-responsive cortical regions providing convergent support for magnocellular involvement in both the pathophysiology of SZ and in the neurobiology of passage reading in general.

The WAIS3-PSI and WMS3-WMI were obtained as measures of global cognitive function and SES, which measures education and present occupational function, was used as a global outcome measure. The magnitude of the deficit shown by patients in both PSI and WMI was consistent with other reports of neurocognitive functioning (Bilder et al., 2000; Saykin et al., 1994). Deficits in reading, in contrast, were significantly larger in effect size ($d = 2.8$) and between-group differences remained significant even following covariation for between-group differences in PSI or WMI.

The finding that SZ patients' reading deficits, but not deficits in other neuropsychological functions, were correlated with reductions in SES supports data from follow-back studies indicating that reading ability in individuals who go on to develop SZ begins to degenerate even prior to illness onset. In particular, follow-back studies have shown reduced reading and language ability between the 8th and 11th grades in SZ (Fuller et al., 2002; Ho et al., 2005) as well as increased risk for SZ among adolescents with poor reading, versus arithmetic, ability at age 16 (Weiser et al., 2007).

Behaviorally, patients performed significantly worse than controls on measures of both single-word (WRAT3) and passage (GORT-4) reading. However, passage reading abilities were impaired in SZ patients to a significantly greater extent compared to single word reading. Furthermore, poor performance on the passage reading test correlated significantly with CS deficits (higher thresholds) at low, but not high, SF, suggesting that impaired functioning of the magnocellular visual pathway contributes, at least partly, to this reading impairment (Revheim et al., 2006). Furthermore, impaired CS at LSF was not associated with lower IQ in SZ, further indicating that passage reading deficits are due to dysfunctional magnocellular functioning and not to generalized, non-specific, performance deficits.

Consistent with our psychophysical findings, during passage reading SZ patients showed significantly reduced activation in regions of visual cortex with preferential sensitivity to LSF's. In contrast, patients showed significantly increased activation in both LSF- and HSF-sensitive cortical regions during single word reading. These regions of increased activity included an area of the left fusiform gyrus corresponding anatomically to the visual word form area (VWFA). The VWFA has been implicated in numerous studies as especially responsive to single words (reviewed in Wandell, 2011).

The increased activation shown by patients during single-word reading suggests that physiological dysfunction within the early visual system may lead to hyper-responsiveness to HSF information during naturalistic tasks such as single-word reading. We have previously observed similar compensatory increases in cortical responses to HSF stimuli during passive viewing (Martinez et al., 2008) and active attention (Martinez et al., 2011) paradigms. Moreover, compensatory patterns of hyperactivation within cortical reading areas, including the VWFA, have also been reported in children with developmental dyslexia (Shaywitz et al., 2002).

Finally, diminished activation within LSF-sensitive regions of visual cortex correlated with impaired reading ability both across- and within-groups. Previous brain imaging studies of developmental dyslexia have also reported under-activation within these cortical areas during reading tasks (Howard et al., 1992; Paulesu et al., 2001; Rumsey et al., 1997; Shaywitz et al., 2002). The present findings thus provide convergent evidence for the role of the magnocellular/dorsal stream system in reading, in general, and novel evidence of a role for magnocellular/dorsal stream dysfunction in reading impairments in schizophrenia.

In summary, dysfunction of early visual function, especially involving the magnocellular/dorsal stream pathway, is a well-replicated finding in schizophrenia. We hypothesized that patients with SZ would show deficits in passage reading ability since this process is known to depend upon intact function of the magnocellular visual system. Consistent with our prior research, SZ patients showed significant differential deficits in passage, relative to single-word, reading, accompanied by diminished activation of dorsal stream, LSF-sensitive, visual brain regions. In addition to supporting distributed neurochemical models of SZ, the present study highlights the consequences of early, sensory-level dysfunction to processes related to activities of daily function. It should be pointed out, however, that the patients in the present study, were relatively chronic and showed relatively poor outcome, with only about half the subjects recruited from an ambulatory clinic. Future studies should address the degree to which similar deficits are observed earlier in the course of the illness and among higher functioning patient populations. Nonetheless, the data reported here suggests that passage reading may represent an important index of cognitive dysfunction in schizophrenia, and that fMRI of LSF brain regions during passage reading may be useful in assessing the contribution of magnocellular/dorsal stream dysfunction to reading disorders in general, and, in particular, may assist in early detection of individuals showing initial signs of schizophrenia.

Acknowledgments

We thank Gail Silipo for her assistance. This work was supported by grants from the NIMH, R21MH075849, R24MH082790 and P50MH86385.

References

Aleman, A., Hijman, R., de Haan, E.H., Kahn, R.S., 1999. Memory impairment in schizophrenia: a meta-analysis. The American Journal of Psychiatry 156, 1358–1366.
Bilder, R.M., Goldman, R.S., Robinson, D., Reiter, G., Bell, L., Bates, J.A., Pappadopulos, E., Willson, D.F., Alvir, J.M., Woerner, M.G., Geisler, S., Kane, J.M., Lieberman, J.A., 2000. Neuropsychology of first-episode schizophrenia: initial characterization and clinical correlates. The American Journal of Psychiatry 157, 549–559.
Brittain, P.J., Surguladze, S., McKendrick, A.M., Ffytche, D.H., 2010. Backward and forward visual masking in schizophrenia and its relation to global motion and global form perception. Schizophrenia Research 124, 134–141.
Butler, P.D., Schechter, I., Zemon, V., Schwartz, S.G., Greenstein, V.C., Gordon, J., Schroeder, C.E., Javitt, D.C., 2001. Dysfunction of early stage visual processing in schizophrenia. The American Journal of Psychiatry 158, 1126–1133.
Butler, P.D., Schechter, I., Zemon, V., Schwartz, S.G., Greenstein, V.C., Gordon, J., Schroeder, C.E., Javitt, D.C., 2002. Early-stage vision and schizophrenia. The American Journal of Psychiatry 159, 678–679.
Butler, P.D., Zemon, V., Schechter, I., Saperstein, A.M., Hoptman, M.J., Lim, K.O., Revheim, N., Silipo, G., Javitt, D.C., 2005. Early-stage visual processing and cortical amplification deficits in schizophrenia. Archives of General Psychiatry 62, 495–504.
Butler, P.D., Martinez, A., Foxe, J.J., Kim, D., Zemon, V., Silipo, G., Mahoney, J., Shpaner, M., Jalbrzikowski, M., Javitt, D.C., 2007. Subcortical visual dysfunction in schizophrenia drives secondary cortical impairments. Brain 130, 417–430.
Butler, P.D., Abeles, I.Y., Weiskopf, N.G., Tambini, A., Jalbrzikowski, M., Legatt, M.E., Zemon, V., Loughead, J., Gur, R.C., Javitt, D.C., 2009. Sensory contributions to impaired emotion processing in schizophrenia. Schizophrenia Bulletin 35, 1095–1107.
Callicott, J.H., Mattay, V.S., Verchinski, B.A., Marenco, S., Egan, M.F., Weinberger, D.R., 2003. Complexity of prefrontal cortical dysfunction in schizophrenia: more than up or down. The American Journal of Psychiatry 160, 2209–2215.
Chase, C., Stein, J., 2003. Visual magnocellular deficits in dyslexia. Brain 126, E2 (author reply E3).
Cohen, J.D., Servan-Schreiber, D., 1992. Context, cortex, and dopamine: a connectionist approach to behavior and biology in schizophrenia. Psychological Review 99, 45–77.
Cornelissen, P., Richardson, A., Mason, A., Fowler, S., Stein, J., 1995. Contrast sensitivity and coherent motion detection measured at photopic luminance levels in dyslexics and controls. Vision Research 35, 1483–1494.
Cox, R.W., 1996. AFNI — software for analysis and visualization of functional magnetic resonance neuroimages. Computers and Biomedical Research 29, 162–173.
Dalby, J.T., Williams, R., 1986. Preserved reading and spelling ability in psychotic disorders. Psychological Medicine 16, 171–175.
Demb, J.B., Boynton, G.M., Heeger, D.J., 1997. Brain activity in visual cortex predicts individual differences in reading performance. Proceedings of the National Academy of Sciences of the United States of America 94, 13363–13366.
Demb, J.B., Boynton, G.M., Best, M., Heeger, D.J., 1998a. Psychophysical evidence for a magnocellular pathway deficit in dyslexia. Vision Research 38, 1555–1559.
Demb, J.B., Boynton, G.M., Heeger, D.J., 1998b. Functional magnetic resonance imaging of early visual pathways in dyslexia. Journal of Neuroscience 18, 6939–6951.
Dias, E.C., Butler, P.D., Hoptman, M.J., Javitt, D.C., 2011. Early sensory contributions to contextual encoding deficits in schizophrenia. Archives of General Psychiatry 68 (7), 654–664.

Doniger, G.M., Foxe, J.J., Murray, M.M., Higgins, B.A., Javitt, D.C., 2002. Impaired visual object recognition and dorsal/ventral stream interaction in schizophrenia. Archives of General Psychiatry 59, 1011–1020.
Fuller, R., Nopoulos, P., Arndt, S., O'Leary, D., Ho, B.C., Andreasen, N.C., 2002. Longitudinal assessment of premorbid cognitive functioning in patients with schizophrenia through examination of standardized scholastic test performance. The American Journal of Psychiatry 159, 1183–1189.
Goldman-Rakic, P.S., 1994. Working memory dysfunction in schizophrenia. The Journal of Neuropsychiatry and Clinical Neurosciences 6, 348–357.
Green, M.F., Nuechterlein, K.H., Mintz, J., 1994. Backward masking in schizophrenia and mania. II. Specifying the visual channels. Archives of General Psychiatry 51, 945–951.
Harvey, P.D., Moriarty, P.J., Bowie, C., Friedman, J.I., Parrella, M., White, L., Davis, K.L., 2002. Cortical and subcortical cognitive deficits in schizophrenia: convergence of classifications based on language and memory skill areas. Journal of Clinical and Experimental Neuropsychology 24, 55–66.
Hayes, R.L., O'Grady, B.M., 2003. Do people with schizophrenia comprehend what they read? Schizophrenia Bulletin 29, 499–507.
Ho, B.C., Andreasen, N.C., Nopoulos, P., Fuller, R., Arndt, S., Cadoret, R.J., 2005. Secondary prevention of schizophrenia: utility of standardized scholastic tests in early identification. Annals of Clinical Psychiatry 17, 11–18.
Howard, D., Patterson, K., Wise, R., Brown, W.D., Friston, K., Weiller, C., Frackowiak, R., 1992. The cortical localization of the lexicons. Positron emission tomography evidence. Brain 115 (Pt 6), 1769–1782.
Javitt, D.C., 2009. When doors of perception close: bottom-up models of disrupted cognition in schizophrenia. Annual Review of Clinical Psychology 5, 249–275.
Javitt, D.C., 2010. Glutamatergic theories of schizophrenia. The Israel Journal of Psychiatry and Related Sciences 47, 4–16.
Kevan, A., Pammer, K., 2008. Making the link between dorsal stream sensitivity and reading. NeuroReport 19, 467–470.
Kim, D., Wylie, G., Pasternak, R., Butler, P.D., Javitt, D.C., 2006. Magnocellular contributions to impaired motion processing in schizophrenia. Schizophrenia Research 82, 1–8.
Kremen, W.S., Seidman, l.J., Faraone, S.V., Pepple, J.R., Lyons, M.J., Tsuang, M.T., 1996. The "3 Rs" and neuropsychological function in schizophrenia: an empirical test of the matching fallacy. Neuropsychology 10, 22–31.
Krishnan, G.P., Vohs, J.L., Hetrick, W.P., Carroll, C.A., Shekhar, A., Bockbrader, M.A., O'Donnell, B.F., 2005. Steady state visual evoked potential abnormalities in schizophrenia. Clinical Neurophysiology 116, 614–624.
Levy, T., Walsh, V., Lavidor, M., 2010. Dorsal stream modulation of visual word recognition in skilled readers. Vision Research 50, 883–888.
Martinez, A., Hillyard, S.A., Dias, E.C., Hagler Jr., D.J., Butler, P.D., Guilfoyle, D.N., Jalbrzikowski, M., Silipo, G., Javitt, D.C., 2008. Magnocellular pathway impairment in schizophrenia: evidence from functional magnetic resonance imaging. Journal of Neuroscience 28, 7492–7500.
Martinez, A., Hillyard, S.A., Bickel, S., Butler, P.D., Javitt, D.C., 2011. Consequences of magnocellular dysfunction on processing attended information in schizophrenia. Cerebral Cortex 22 (6), 1282–1293.
Pammer, K., Hansen, P., Holliday, I., Cornelissen, P., 2006. Attentional shifting and the role of the dorsal pathway in visual word recognition. Neuropsychologia 44, 2926–2936.
Paulesu, E., Demonet, J.F., Fazio, F., McCrory, E., Chanoine, V., Brunswick, N., Cappa, S.F., Cossu, G., Habib, M., Frith, C.D., Frith, U., 2001. Dyslexia: cultural diversity and biological unity. Science 291, 2165–2167.
Pugh, K.R., Mencl, W.E., Jenner, A.R., Katz, L., Frost, S.J., Lee, J.R., Shaywitz, S.E., Shaywitz, B.A., 2000. Functional neuroimaging studies of reading and reading disability (developmental dyslexia). Mental Retardation and Developmental Disabilities Research Reviews 6, 207–213.
Revheim, N., Butler, P.D., Schechter, I., Jalbrzikowski, M., Silipo, G., Javitt, D.C., 2006. Reading impairment and visual processing deficits in schizophrenia. Schizophrenia Research 87, 238–245.
Rimrodt, S.L., Clements-Stephens, A.M., Pugh, K.R., Courtney, S.M., Gaur, P., Pekar, J.J., Cutting, L.E., 2009. Functional MRI of sentence comprehension in children with dyslexia: beyond word recognition. Cerebral Cortex 19, 402–413.
Rumsey, J.M., Nace, K., Donohue, B., Wise, D., Maisog, J.M., Andreason, P., 1997. A positron emission tomographic study of impaired word recognition and phonological processing in dyslexic men. Archives of Neurology 54, 562–573.
Sandak, R., Mencl, W.E., Frost, S.J., Rueckl, J.G., Katz, L., Moore, D.L., Mason, S.A., Fulbright, R.K., Constable, R.T., Pugh, K.R., 2004. The neurobiology of adaptive learning in reading: a contrast of different training conditions. Cognitive, Affective, & Behavioral Neuroscience 4, 67–88.
Saykin, A.J., Shtasel, D.L., Gur, R.E., Kester, D.B., Mozley, L.H., Stafiniak, P., Gur, R.C., 1994. Neuropsychological deficits in neuroleptic naive patients with first-episode schizophrenia. Archives of General Psychiatry 51, 124–131.
Schechter, I., Butler, P.D., Silipo, G., Zemon, V., Javitt, D.C., 2003. Magnocellular and parvocellular contributions to backward masking dysfunction in schizophrenia. Schizophrenia Research 64, 91–101.
Schechter, I., Butler, P.D., Zemon, V.M., Revheim, N., Saperstein, A.M., Jalbrzikowski, M., Pasternak, R., Silipo, G., Javitt, D.C., 2005. Impairments in generation of early-stage transient visual evoked potentials to magno- and parvocellular-selective stimuli in schizophrenia. Clinical Neurophysiology 116, 2204–2215.
Schroeder, C.E., Mehta, A.D., Givre, S.J., 1998. A spatiotemporal profile of visual system activation revealed by current source density analysis in the awake macaque. Cerebral Cortex 8, 575–592.
Sehatpour, P., Dias, E.C., Butler, P.D., Revheim, N., Guilfoyle, D.N., Foxe, J.J., Javitt, D.C., 2010. Impaired visual object processing across an occipital–frontal–hippocampal brain network in schizophrenia: an integrated neuroimaging study. Archives of General Psychiatry 67, 772–782.
Shaywitz, S.E., Shaywitz, B.A., 2008. Paying attention to reading: the neurobiology of reading and dyslexia. Development and Psychopathology 20, 1329–1349.
Shaywitz, B.A., Shaywitz, S.E., Pugh, K.R., Mencl, W.E., Fulbright, R.K., Skudlarski, P., Constable, R.T., Marchione, K.E., Fletcher, J.M., Lyon, G.R., Gore, J.C., 2002. Disruption of posterior brain systems for reading in children with developmental dyslexia. Biological Psychiatry 52, 101–110.
Slaghuis, W.L., 1998. Contrast sensitivity for stationary and drifting spatial frequency gratings in positive- and negative-symptom schizophrenia. Journal of Abnormal Psychology 107, 49–62.
Stein, J., 2001. The magnocellular theory of developmental dyslexia. Dyslexia 7, 12–36.
Vidyasagar, T.R., Pammer, K., 1999. Impaired visual search in dyslexia relates to the role of the magnocellular pathway in attention. NeuroReport 10, 1283–1287.
Vidyasagar, T.R., Pammer, K., 2009. Dyslexia: a deficit in visuo-spatial attention, not in phonological processing. Trends in Cognitive Sciences 14.
Wandell, B.A., 2011. The neurobiological basis of seeing words. Annals of the New York Academy of Sciences 1224, 63–80.
Wechsler, D., 1997. WAIS-III Administration and Scoring Manual. The Psychological Corporation, San Antonio, TX.
Weiser, M., Reichenberg, A., Rabinowitz, J., Nahon, D., Kravitz, E., Lubin, G., Knobler, H.Y., Davidson, M., Noy, S., 2007. Impaired reading comprehension and mathematical abilities in male adolescents with average or above general intellectual abilities are associated with comorbid and future psychopathology. The Journal of Nervous and Mental Disease 195, 883–890.
Wilmer, J.B., Richardson, A.J., Chen, Y., Stein, J.F., 2004. Two visual motion processing deficits in developmental dyslexia associated with different reading skills deficits. Journal of Cognitive Neuroscience 16, 528–540.