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Reduced functional connectivity in a right-hemisphere network for volitional ocular motor control in schizophrenia

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Patients with schizophrenia consistently show deficient performance on tasks requiring volitional saccades. We previously reported reduced fractional anisotropy in the white matter underlying right dorsal anterior cingulate cortex in schizophrenia, which, along with lower fractional anisotropy in the right frontal eye field and posterior parietal cortex, predicted longer latencies of volitional saccades. This suggests that reduced microstructural integrity of dorsal anterior cingulate cortex white matter disrupts connectivity in the right hemisphere-dominant network for spatial attention and volitional ocular motor control. To test this hypothesis, we examined functional connectivity of the cingulate eye field component of this network, which is located in dorsal anterior cingulate cortex, during a task comprising volitional prosaccades and antisaccades. In patients with schizophrenia, we expected to find reduced functional connectivity, specifically in the right hemisphere, which predicted prolonged saccadic latency. Twenty-seven medicated schizophrenia outpatients and 21 demographically matched healthy controls performed volitional saccades during functional magnetic resonance imaging. Based on task-related activation, seed regions in the right and left cingulate eye field were defined. In both groups, the right and left cingulate eye field showed positive correlations with the ocular motor network and negative correlations with the default network. Patients showed reduced positive functional connectivity of the cingulate eye field, specifically in the right hemisphere. Negative functional connectivity of the right cingulate eye field predicted faster saccades, but these relations differed by group, and were only present in controls. This pattern of relations suggests that the coordination of activity between ocular motor and default networks is important for efficient task performance and is disrupted in schizophrenia. Along with prior observations of reduced white matter microstructural integrity (fractional anisotropy) in schizophrenia, the present finding of reduced functional connectivity suggests that functional and structural abnormalities of the right cingulate eye field disrupt connectivity in the network for spatial attention and volitional ocular motor control. These abnormalities may contribute to deficits in overcoming prepotency in the service of directing eye gaze and attention to the parts of the environment that are the most behaviourally relevant.

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Abbreviations: CEF = cingulate eye field; fMRI = functional magnetic resonance imaging; FSL = Functional MRI of the Brain Software Library; MNI = Montreal Neurological Institute

Introduction

Patients with schizophrenia consistently show performance deficits on tasks requiring volitional saccades (Manoach *et al*., 2002; Calkins *et al*., 2003; Harris *et al*., 2006; Radant *et al*., 2007) that are associated with abnormal activation of the anterior cingulate cortex (Crawford *et al*., 1996; Camchong *et al*., 2008; Polli *et al*., 2008). The anterior cingulate cortex is a large and heterogeneous region that can be partitioned on the basis of cytoarchitecture, function and both structural and functional connectivity (Devinsky *et al*., 1995; Bush *et al*., 2000; Koski and Paus, 2000; Margulies *et al*., 2007). Here, we focus on the dorsal anterior cingulate cortex, which is structurally (Pandya *et al*., 1981; Morecraft *et al*., 1993) and functionally (Koski and Paus, 2000; Margulies *et al*., 2007) connected to premotor, motor and ocular motor regions, consistent with its putative role in providing top-down control of motor (Miller and Cohen, 2001) and ocular motor (Johnston *et al*., 2007) responses. More specifically, the posterior part of the dorsal anterior cingulate cortex has been labelled the cingulate eye field (CEF) based on its involvement in tasks requiring volitional saccadic control (Paus *et al*., 1993; Gaymard *et al*., 1998; Pierrot-Deseilligny *et al*., 2004). In monkeys, stimulation of the dorsal bank of cingulate sulcus, ventral to the supplementary eye field, evokes saccades (Mitz and Godschalk, 1989). In humans, lesions of the posterior dorsal anterior cingulate cortex increase antisaccade errors (Milea *et al*., 2003) and prolong the latencies of both prosaccades and antisaccades (Gaymard *et al*., 1998).

Using diffusion tensor imaging, Manoach *et al*. (2007*a*) reported reduced microstructural integrity, measured as fractional anisotropy, of the white matter underlying the dorsal anterior cingulate cortex of the right hemisphere in schizophrenia, which, along with lower fractional anisotropy in the white matter underlying the right frontal eye field and the right posterior parietal cortex, predicted longer latencies of volitional saccades. These three regions comprise the key cortical components of a right hemisphere dominant network for the spatial distribution of attention and eye gaze (Mesulam, 1981, 1990; Gitelman *et al*., 1999), which are tightly linked (Klein and McCormick, 1989; Corbetta and Shulman, 2002; Hunt and Kingstone, 2003; Moore *et al*., 2003). These findings support the hypothesis that in schizophrenia, anterior cingulate cortex abnormalities compromise the function of the distributed network critical for spatial attention and volitional ocular motor control. Here, to evaluate this hypothesis further, we examined functional MRI (fMRI) measurements of functional connectivity of the CEF during the performance of volitional saccades in individuals with schizophrenia compared with healthy controls. Functional connectivity MRI (Biswal *et al*., 1995; Fox and Raichle, 2007; Van Dijk *et al*., in press) has proven to be a powerful method for evaluating network dysfunction in neuropsychiatric disorders (Buckner *et al*., 2008; Greicius, 2008; Calhoun *et al*., 2009). We hypothesized that patients with schizophrenia would show reduced functional connectivity, specifically of the right CEF, during saccadic performance and that this would be associated with prolonged saccadic latencies.

Methods

Participants

The schizophrenia sample comprised 27 out-patients recruited from an urban community mental health centre. Twenty-five had been maintained on stable doses of a variety of anti-psychotic medications for at least 6 weeks; 24 took atypical agents (risperidone, aripiprazole, clozapine, olazapine and quetiapine) and one took prolixin. Two patients had discontinued their anti-psychotic medications at least 6 weeks prior to the study. No patient took anti-cholinergic medications and nine took diverse adjunctive medications for anxiety, agitation and/or concurrent mood disturbance. Diagnosis was confirmed with the Structured Clinical Interview in the Diagnostic and Statistical Manual of Mental Disorders (SCI-DSM)-IV (First *et al*., 1997). Clinical status was characterized with the Brief Psychiatric Rating Scale (Overall and Gorham, 1962), the Positive and Negative Syndrome Scale (Kay *et al*., 1987) and the Scale for the Assessment of Negative Symptoms (Andreasen, 1983). (Table 1 provides demographic information and clinical ratings.) Twenty-one healthy control participants, screened to exclude those with a personal history of mental illness (SCIDSM-Non-patient edition, First *et al*., 2002) or a family history of schizophrenia spectrum disorders, were recruited from the community with poster and website advertisements.

Participants were screened to exclude substance abuse or dependence within the past 6 months, a history of head injury resulting in a sustained loss of consciousness and/or cognitive sequelae, neurological illness, and any disorder affecting cerebral metabolism. Groups did not differ in age, gender, handedness as measured by the modified Edinburgh Handedness Inventory (Oldfield, 1971; White and Ashton, 1976), or parental education. The study was approved by the Partners Human Research Committee and the Central Office Research Review Committee of the Massachusetts Department of Mental Health. All participants gave written informed consent after the experimental procedures had been fully explained.

Saccadic paradigm

The paradigm consisted of a pseudorandom series of prosaccades and antisaccades. Prosaccades are the prepotent response of looking towards a suddenly appearing visual stimulus, while antisaccades require inhibition of the prepotent prosaccade and the generation of the novel behaviour of looking in the opposite direction (Hallett, 1978). Since prosaccade and antisaccade trials were inter-mixed and both required participants to respond according to an instructional cue, both trial types required volitional saccades.

Prior to scanning, the task was explained and participants practiced in a mock scanner. Participants were encouraged to respond as quickly and accurately as possible. In addition to a base rate of pay, they received 5 cents for each correct response, an incentive intended to enhance attention and motivation. Each run of the task consisted of a

Table 1 Means, standard deviations, and group comparisons of demographic data and rating scale scores for patients

Participant characteristics	Healthy controls ($n=21$)	Schizophrenia patients ($n=27$)	t	P
Age	33 ± 11	36 ± 13	1.05	0.30
Sex	13M/8F	20M/7F	$\phi=0.81$	0.37
Handedness (Edinburgh)	82 ± 38	71 ± 48	0.85	0.40
Parental education	15 ± 3	14 ± 3	1.14	0.26
			Level of severity	
Age of onset		24 ± 6		
Length of illness (years)		12 ± 11		
BPRS		16 ± 8	Minimal	
PANSS positive		14 ± 5	Mild	
PANSS negative		16 ± 6	Mild	
SANS		32 ± 17	Questionable	

BPRS = Brief Psychiatric Rating Scale; PANSS = Positive and Negative Syndrome Scale; SANS = Scale for the Assessment of Negative Symptoms.

pseudorandom sequence of prosaccade and antisaccade trials that were balanced for right and left movements. Figure 1 provides a graphic depiction of the task and a description of task parameters. Randomly inter-leaved with the saccadic trials were intervals of fixation lasting 2, 4 or 6 s. The fixation trials provided a baseline for analyses of task-related activation and their variable length introduced 'temporal jitter', which optimizes the analysis of rapid presentation event-related fMRI designs (Buckner *et al*., 1998; Burock and Dale, 2000; Miezin *et al*., 2000). Participants performed six runs of the task, each lasting 5 min 22 s, with short rests between runs. The total experiment lasted about 40 min and generated a total of 211 prosaccade trials, 211 antisaccade trials and 80 fixation intervals.

Stimulus display and eye tracking

Displays of the eye movement task were generated using the Vision Shell programming platform, and back-projected with a Sharp XG-2000 colour LCD projector (Osaka, Japan) onto a screen at the rear of the bore that was viewed by the participant via a mirror on the head coil. Vision Shell triggered the scanner to begin acquiring data. The ISCAN fMRI Remote Eye Tracking Laboratory (ISCAN, Burlington, MA, USA) was used to sample eye position at a rate of 60 Hz during scanning. Stimuli presented by Vision Shell were digitally encoded and relayed to ISCAN as triggers that were inserted into the eye position recordings.

Eye position data were scored in MATLAB (Mathworks, Natick, MA, USA) using a partially automated programme that determined the directional accuracy of each saccade with respect to the required response and the latency from target onset. Saccades were identified as horizontal eye movements with velocities exceeding 47°/s. The onset of a saccade was defined as the point at which the velocity of the eye movement first exceeded 31°/s. Only trials with saccades in the desired direction and latencies over 130 ms were considered correct, and only correct saccades were included in the latency analyses. The cutoff of 130 ms excluded anticipatory saccades, which are executed too quickly to be a valid response to the appearance of the target (Fischer and Breitmeyer, 1987). Error rate and latency of correct trials were compared using repeated measures ANOVA with factors for group (schizophrenia, control), condition, (antisaccade, prosaccade) and their interaction. Error rate was logit transformed in all analyses.

Image acquisition

Images were acquired with a 3.0T Siemens Trio whole body high-speed imaging device equipped for echo planar imaging (Siemens Medical Systems, Erlangen, Germany). Head stabilization was achieved with cushioning, and all participants wore earplugs (29 dB rating) to attenuate noise. Automated shimming procedures were performed and scout images were obtained. Two high-resolution structural images were acquired in the sagittal plane using a high resolution 3D magnetization prepared rapid gradient echo sequence (repetition time, 2530 ms; echo spacing, 7.25 ms; echo time, 3 ms; flip angle 7°; field of view, 256 mm; matrix, 256 × 256) with an in-plane resolution of 1 and 1.3 mm slice thickness. T_1- and T_2-weighted structural images, with the same slice specifications as the blood oxygen level dependent scans, were obtained to assist in registering functional and structural images.

Functional images were collected using a gradient echo T_2^*-weighted sequence (repetition time/echo time/Flip = 2000 ms/30 ms/90°; field of view, 200 mm; matrix, 64 × 64). Twenty contiguous horizontal slices, parallel to the inter-commissural plane (voxel size: 3.13 × 3.13 × 5 mm), were acquired inter-leaved. The functional sequences included prospective acquisition correction for head motion (Thesen *et al*., 2000). Prospective acquisition correction adjusts slice position and orientation in real time during data acquisition to reduce motion-induced effects on magnetization history.

Analyses of functional data

Motion correction

Functional scans were corrected retrospectively for motion using the Analysis of Functional NeuroImages algorithm (Cox and Jesmanowicz, 1999).

CEF seed region definition

We defined the CEF using both Montreal Neurological Institute (MNI) anatomical criteria for anterior cingulate cortex and fMRI activation during the performance of volitional saccades. In the averaged functional data of all participants, unbiased to participant group, we computed the contrast of all correct trials versus fixation at 4 s, which is the time of peak ocular motor response (Polli *et al*., 2005). This analysis was conducted using FreeSurfer Functional Analysis Stream software (Burock and Dale, 2000). Motion-corrected functional scans were intensity normalized, and smoothed using a 3D 8 mm full width at half maximum Gaussian kernel. For each participant, finite impulse response estimates (Burock and Dale, 2000; Miezin *et al*., 2000) of the event-related haemodynamic responses were calculated for four trial types (correct and error prosaccades and antisaccades) at 12 time points with an interval of 2 s (corresponding to the repetition time), ranging from 4 s before the start of a trial to 18 s after the start.

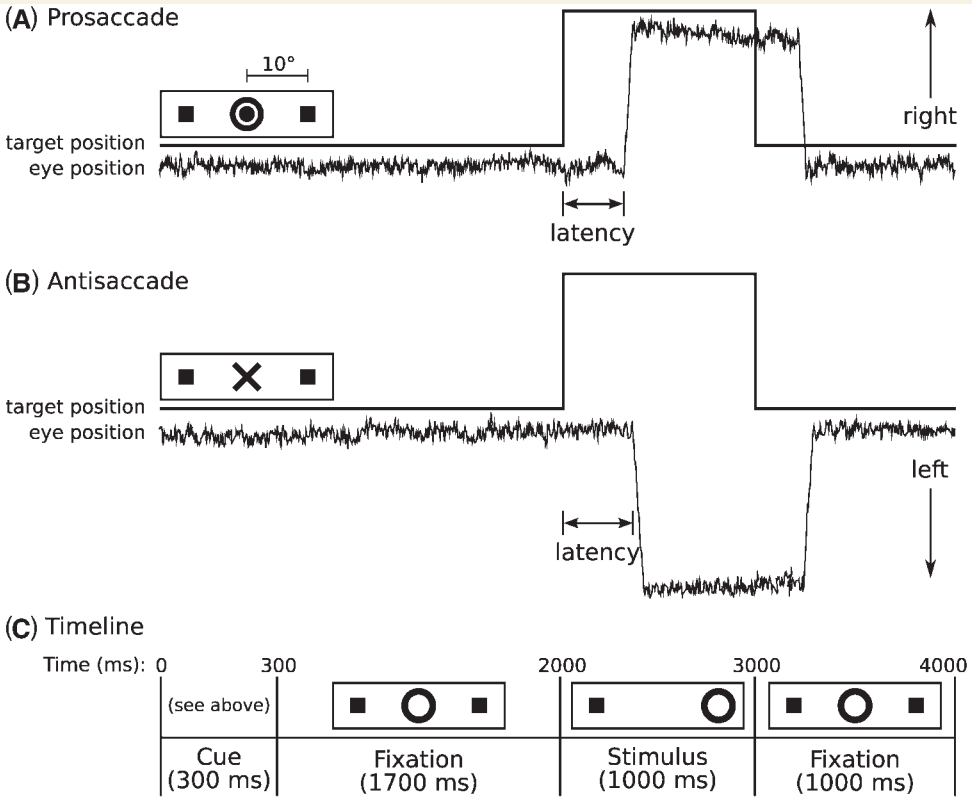

Figure 1 Saccadic paradigm with idealized eye position traces. Saccadic trials lasted 4000 ms and began with an instructional cue at the centre of the screen. For half of the participants, orange concentric rings were the cue for a prosaccade trial (**A**) and a blue cross was the cue for an antisaccade trial (**B**). These cues were reversed for the rest of the participants. The cue was flanked horizontally by two small green squares of 0.2° width that marked the potential locations of stimulus appearance, 10° left and right of centre. These squares remained on the screen for the duration of each run. (**C**) At 300 ms, the instructional cue was replaced by a green fixation ring at the centre of the screen, of 0.4° diameter and luminance of 20 cd/m^2. After 1700 ms, the ring shifted to one of the two target locations, right or left, with equal probability. This was the stimulus to which the participant responded by either making a saccade to it (prosaccade) or to the square on the opposite side (anti saccade). The green ring remained in the peripheral location for 1000 ms and then returned to the centre, where participants were also to return their gaze for 1000 ms before the start of the next trial. Fixation intervals were simply a continuation of the fixation display that constituted the final second of the previous saccadic trial.

To obtain estimates of the haemodynamic responses in the averaged group data, individual contrast images were registered to the MNI152 atlas with the Functional MRI of the Brain Software Library (FSL; www.fmrib.ox.ac.uk/fsl) using the same registration matrix as the functional connectivity analysis, and activation was examined using a random effects model. As in prior studies of this paradigm (Polli *et al*., 2005; Manoach *et al*., 2007*b*), we observed significant task-related activation in dorsal anterior cingulate cortex at 4 s (corrected for multiple comparisons based on 10 000 Monte Carlo simulations of synthesized white Gaussian noise using a *P*-value of $\leqslant 0.05$ and the smoothing, resampling and averaging parameters of the functional analyses). Right and left CEF seed regions were defined as spheres of 4 mm radius around the peak voxels (Fig. 2).

Functional connectivity pre-processing

The motion corrected functional scans were registered to the MNI152 atlas (Collins *et al*., 1994) using FSL. Additional pre-processing steps, described in previous reports (Fox *et al*., 2005; Vincent *et al*., 2006; Van Dijk *et al*., in press), were: (i) spatial smoothing using a Gaussian kernel of 6 mm full-width at half-maximum; (ii) temporal filtering ($0.009\,\text{Hz} < f < 0.08\,\text{Hz}$); (iii) removal of spurious or non-specific sources of variance by regression of the following variables: (a) the six movement parameters computed by rigid body translation and rotation in preprocessing, (b) the mean whole brain signal, (c) the mean signal within the lateral ventricles and (d) the mean signal within a deep white matter region of interest. The first temporal derivatives of these regressors were included in the linear model to account for the time-shifted versions of spurious variance. Regression of each of these signals was computed simultaneously and the residual time course was retained for the correlation analysis.

Functional connectivity analysis

Blood oxygen level dependent time courses of the right and left CEF seed regions were based on the average signal across voxels. A Pearson correlation map was created for the time course of each seed region and all of the other voxels in the brain. To avoid auto-correlation, a sphere of 10 mm radius around the voxel at the centre of the seed was excluded from analysis. The correlation map of each participant was converted to a map of *z*-scores using a Fisher's *z* transform (Vincent *et al*., 2006).

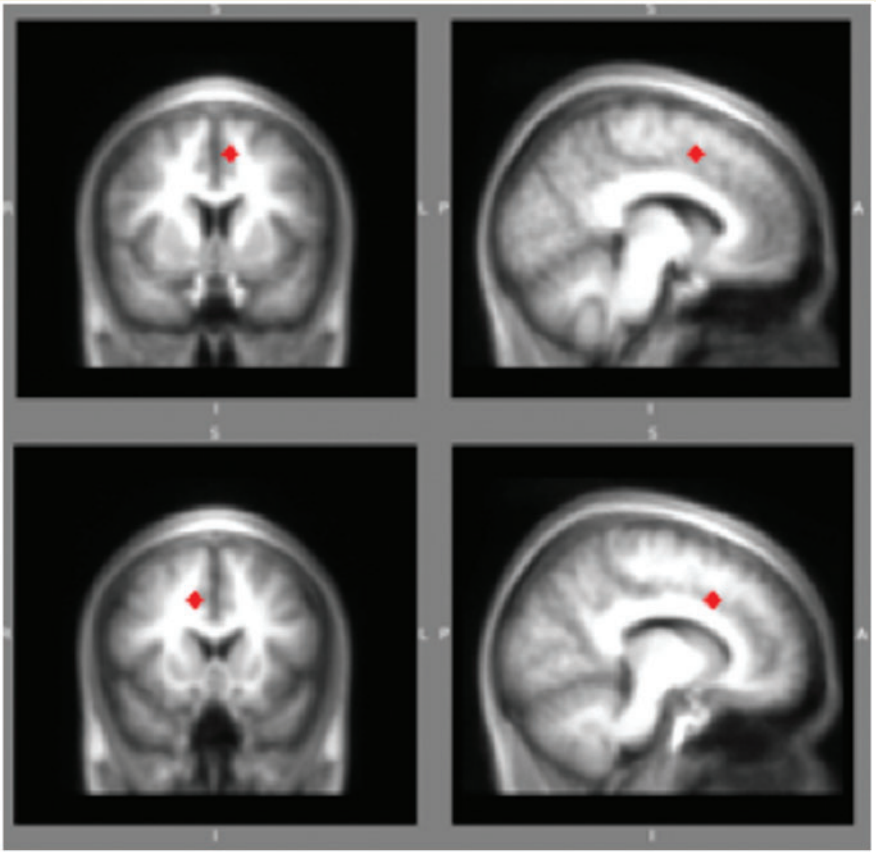

Figure 2 CEF seed regions displayed on coronal and sagittal views of the averaged structural MRI image of study participants registered to the MNI152 atlas (Collins *et al*., 1994). Top row = left CEF: Brodmann's area 24, –8, 8, 50; bottom row = right CEF, Brodmann's area 32, 12, 16, 38.

We first examined positive and negative CEF functional connectivity in the averaged data of all participants using a false discovery rate threshold of $P<0.001$. Based on this analysis, we created four masks: positive and negative functional connectivity for the right and left CEF. For each participant, we derived a single value for each mask by averaging the *z*-scores for the correlation coefficients across all the voxels in the mask. Using these 'global functional connectivity' values, we compared groups using repeated measures ANOVAs with factors of group, hemisphere and their interaction.

To determine whether there were regionally specific group differences in functional connectivity, we also compared groups at each voxel in the brain. The group difference map was thresholded at $P<0.001$ and a cluster-wise threshold of $P<0.05$ was used to control for multiple comparisons.

Correlations of CEF functional connectivity with saccadic latency

The association between CEF functional connectivity and saccadic latency, adjusting both variables for age, was investigated using multiple regression analyses. For these regressions, global functional connectivity (see above) was the dependent variable and saccadic latency and age were covariates. An interaction term (latency by group) was included in the model to test whether the slope of the relation differed by group. The mean latency of correct prosaccades or antisaccades was the covariate of interest. Age was regarded as a potential confound given the documented relation of age with decreased functional connectivity (Andrews-Hanna *et al*., 2007; Damoiseaux *et al*., 2007; Sambataro *et al*., 2008) and increased saccadic latency (Munoz *et al*., 1998).

Effect of anti-psychotic medications

To estimate the effect of medication on functional connectivity and to determine whether group differences and correlations with behaviour remained significant when this effect was statistically controlled, we regressed functional connectivity measures on anti-psychotic medication dose as measured by chlorpromazine equivalent (Woods, 2003) for each mask. We adjusted the estimates of functional connectivity by subtracting the product of the slope of the regression and chlorpromazine equivalent from activation for each region of interest in each participant with schizophrenia. These adjusted functional connectivity measures for patients and the original measures for controls were entered into the group comparison and correlation analyses described above.

Results

Saccadic performance

Two controls and one patient were missing latency data due to technical problems). The groups did not differ significantly in the

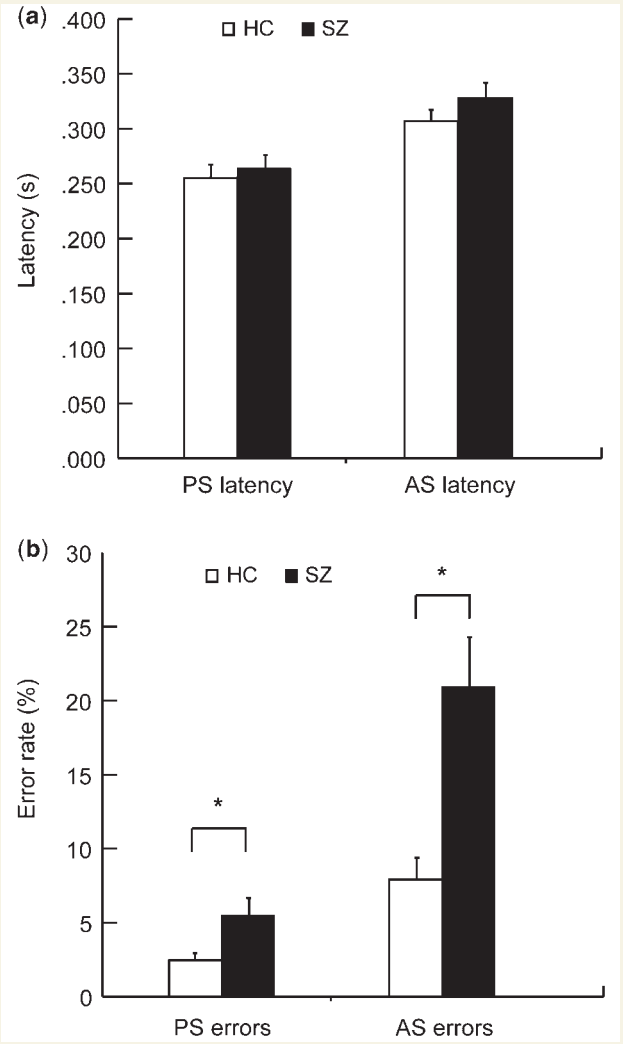

Figure 3 Bar graphs of performance by group and task measured as mean and standard errors of (**A**) latency of correct saccades and (**B**) error rate. HC = healthy controls; SZ = schizophrenia; PS = prosaccade; AS = antisaccade. Asterisks denote statistical significance.

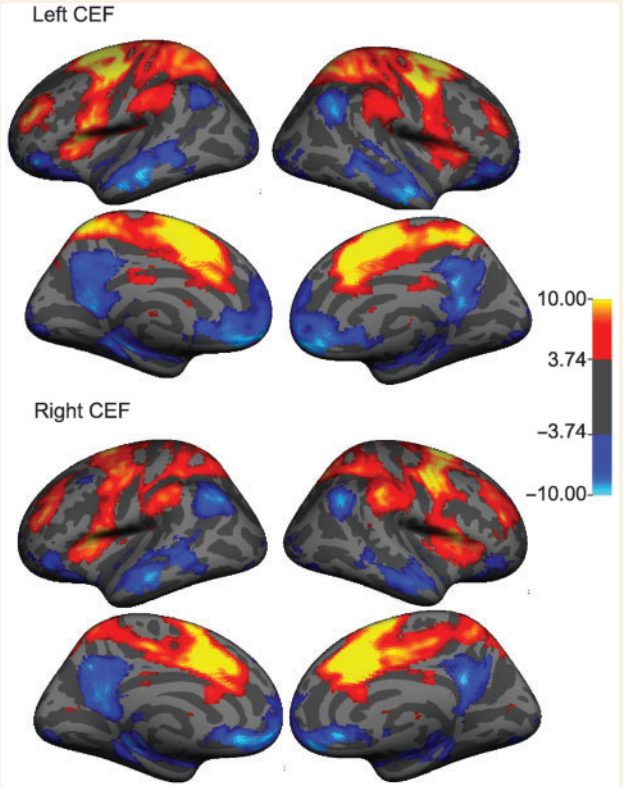

Figure 4 Regions showing significant (false-discovery rate corrected $P < 0.001$) positive and negative functional connectivity with left and right CEF in the combined group data displayed on the lateral and medial inflated cortical surfaces.

latency of correct saccades [$F(1,42) = 0.80$, $P = 0.38$], regardless of the task [Group × Task: $F(1,42) = 1.89$, $P = 0.18$] (Fig. 3). Participants with schizophrenia made significantly more errors than controls [$F(1,46) = 12.55$, $P = 0.001$], and compared with controls, they made disproportionately more errors on antisaccade than prosaccade trials [Group × Task: $F(1,46) = 7.19$, $P = 0.01$; antisaccade: $t(46) = 3.31$, $P = 0.002$; prosaccade: $t(46) = 2.30$, $P = 0.03$].

Functional connectivity

CEF functional connectivity in the combined groups

Positive correlations

Positive functional connectivity was similar for the right and left CEFs (Fig. 4). For both seeds, the strongest correlation was with the homologous region of the other hemisphere, as in a previous study (Margulies *et al.*, 2007). Significant correlations were also observed bilaterally in premotor and ocular motor regions, including the frontal and supplementary eye fields, posterior parietal cortex, supplementary motor area and pre-supplementary motor area. Additional regions showing correlations were bilateral dorsolateral prefrontal cortex and anterior insula (see Supplementary Table S1 for a complete list of regions).

Negative correlations

The right and left CEF were both negatively correlated with regions that comprise the default network (Shulman *et al.*, 1997; Gusnard *et al.*, 2001; Mazoyer *et al.*, 2001; Raichle *et al.*, 2001; Buckner *et al.*, 2008) including: the ventromedial prefrontal cortex, rostral anterior cingulate cortex, posterior cingulate gyrus, angular gyrus and superior temporal sulcus and gyrus. Negative correlations, given our pre-processing step of whole brain signal regression, must be interpreted with caution (see Discussion section, Chang and Glover, 2009; Murphy *et al.*, 2009).

Group comparisons of CEF functional connectivity

Positive global functional connectivity

The main effects of group [$F(1,46) = 1.29$, $P = 0.26$] and hemisphere [$F(1,46) = 2.96$, $P = 0.09$] were not significant, but there was a significant group by hemisphere interaction [Fig. 4A; $F(1,46) = 5.92$, $P = 0.02$]. As predicted, compared with controls, patients showed reduced positive functional connectivity

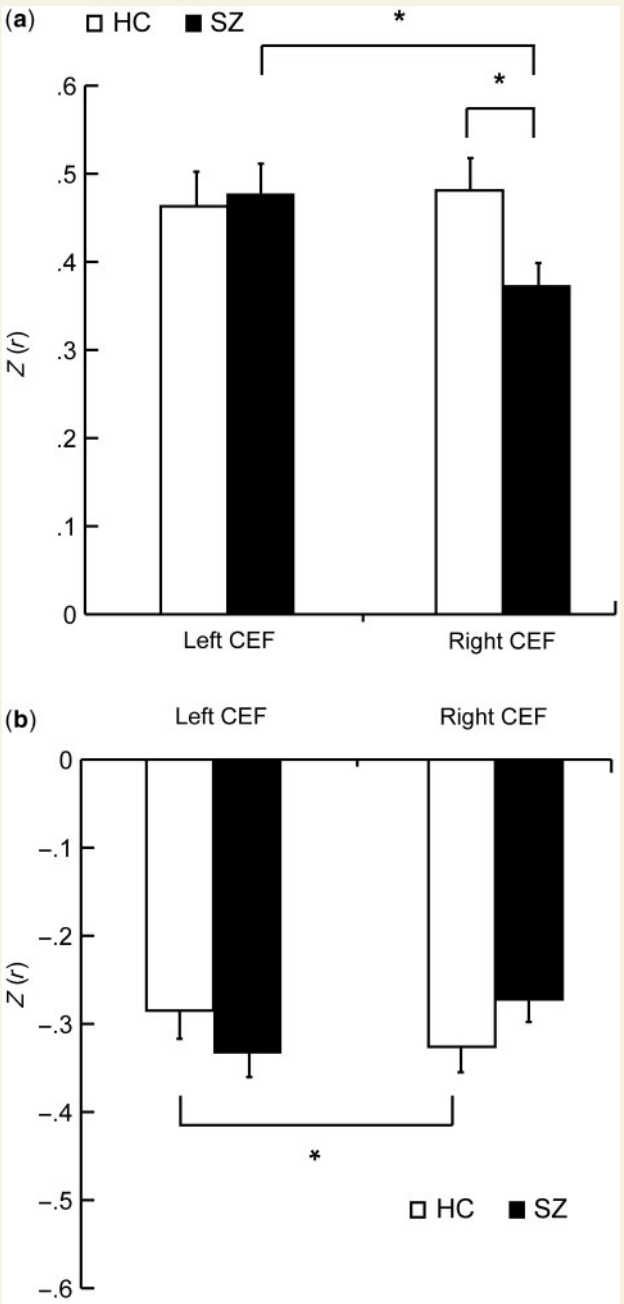

Figure 5 Bar graphs of (**A**) positive functional connectivity and (**B**) negative functional connectivity divided by group and hemisphere. Correlations are expressed as *z*-scores with standard error bars. HC = healthy controls; SZ = schizophrenia. Asterisks denote statistical significance.

specifically of the right CEF [$t(46) = 2.44$, $P = 0.02$; left: $t(46) = 0.25$, $P = 0.80$; Fig. 5a]. In addition, patients showed significant leftward asymmetry of functional connectivity [$t(26) = 2.78$, $P = 0.01$], while controls showed no significant asymmetry [$t(20) = -0.57$, $P = 0.57$].

Negative global functional connectivity

Neither the main effect of group [$F(1,46) = 0.006$, $P = 0.94$] nor hemisphere [$F(1,46) = 0.24$, $P = 0.63$] was significant, but the group by hemisphere interaction was [$F(1,46) = 6.57$, $P = 0.01$], reflecting the different patterns of hemispheric asymmetry by group (Fig. 5b). As was the case with positive functional connectivity, patients showed a trend to leftward asymmetry of negative functional connectivity [trend: $t(26) = -1.92$, $P = 0.06$]. In contrast, controls showed a significant rightward asymmetry of negative functional connectivity [$t(20) = 2.24$, $P = 0.03$]. The groups did not differ significantly, however, in negative functional connectivity in either hemisphere [right: $t(46) = 1.42$, $P = 0.16$; left: $t(46) = 1.15$, $P = 0.25$].

Regionally specific group differences in functional connectivity

Relative to controls, patients showed significantly reduced functional connectivity of the right CEF with the left thalamus, right pre-supplementary motor area and right anterior insula (Fig. 6 and Table 2). There were no significant group differences in the functional connectivity of the left CEF.

Relations of global CEF functional connectivity with saccadic latency

Positive functional connectivity did not correlate with saccadic latency in the combined group (all P's > 0.3). However, greater negative functional connectivity of the right CEF predicted faster prosaccade and antisaccade latencies (Table 3 and Fig. 7). These relations differed by group, significantly for prosaccades, and at a trend level for antisaccades (Table 3). These group differences reflected that controls showed strong and significant relations (P's $\leqslant 0.01$), while in patients the slopes of the relations were essentially flat.

On an exploratory basis, we also examined the correlations of CEF functional connectivity with error rate. Neither positive nor negative CEF functional connectivity significantly correlated with either antisaccade or prosaccade error rate in the combined group.

Control analyses with functional connectivity measurements adjusted for chloropromazine equivalent

In patients, chloropromazine equivalent was not significantly related to functional connectivity in any mask (all P's $\geqslant 0.42$). Adjusting functional connectivity measurements for chloropromazine equivalents in patients did not substantially alter the findings of either the group comparisons or the correlations with behaviour (i.e. all significant findings remained). That the findings were unchanged reflects that the slopes of the relations of functional connectivity measurements to chloropromazine equivalent were all very low ($<10^{-4}$), and consequently the adjusted functional connectivity values were very close to the original ones.

Discussion

Compared with controls, patients with schizophrenia showed reduced positive functional connectivity of the CEF, specifically in the right hemisphere, during the performance of volitional saccades. In both groups, the CEFs showed positive functional connectivity with premotor and ocular motor regions, including the frontal eye field and the posterior parietal cortex. This pattern of connectivity is similar to that observed in a previous study that placed seeds in posterior dorsal anterior cingulate cortex

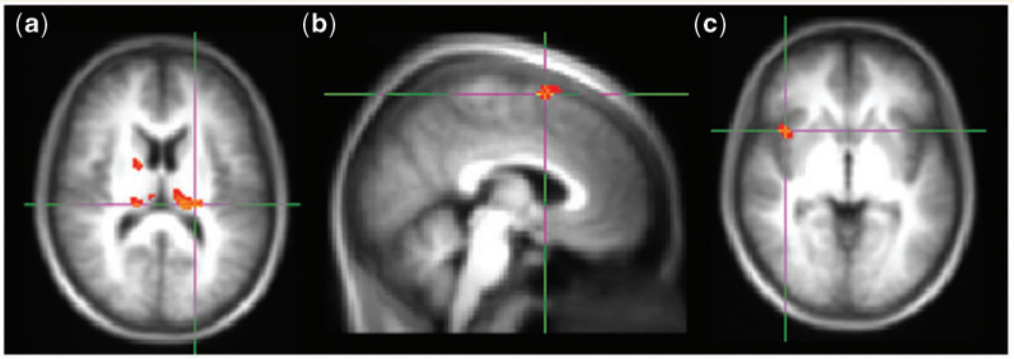

Figure 6 Statistical maps of regionally specific group differences in the positive functional connectivity of the right CEF displayed on the averaged structural MRI image of study participants registered to the MNI152 atlas (Collins *et al*., 1994). Schizophrenia participants showed reduced functional connectivity in the (a) left thalamus, (b) right pre-supplementary motor area (SMA), and (c) right anterior insula.

Table 2 Regionally specific group differences in the functional connectivity of right CEF

Structures	Brodmann's area	Peak coordinates			Peak *t*	Cluster size	CWP	HC FC values	SZ FC values
Left thalamus	Pulvinar	−22	−26	14	4.76	103	0.006	0.046 ± .035	−0.018 ± .053
Right pre-SMA	6	4	8	66	4.56	84	0.012	0.219 ± .093	0.103 ± .112
Right insula	13	42	14	−2	3.84	54	0.037	0.220 ± .115	0.079 ± .100

SMA = supplementary motor area; CWP = cluster-wise probability level; HC = healthy controls; SZ = schizophrenia; FC = functional connectivity. Cluster size is expressed as the number of voxels.

(Margulies *et al*., 2007), and is consistent with the putative role of this region in providing top-down control of structures generating ocular motor responses (Johnston *et al*., 2007). Dorsal anterior cingulate cortex, the frontal eye field and posterior parietal cortex are the key cortical components of the right hemisphere dominant network for spatial attention (Mesulam, 1981, 1990; Gitelman *et al*., 1999) and volitional ocular motor control, which are tightly linked (Klein and McCormick, 1989; Corbetta and Shulman, 2002; Hunt and Kingstone, 2003; Moore *et al*., 2003), with the paralimbic anterior cingulate cortex providing a map of motivational salience. In schizophrenia, reduced connectivity of this network might compromise inter-regional communication and thereby contribute to deficits on tasks requiring volitional ocular motor control, a consistent finding in the schizophrenia literature (Gooding and Basso, 2008). The finding of a selective reduction of right CEF positive functional connectivity complements our prior observation of reduced microstructural integrity of the white matter underlying the right dorsal anterior cingulate cortex (Manoach *et al*., 2007*a*). Together, these findings, along with those of prior studies showing abnormal dorsal anterior cingulate cortex activation during volitional saccades in schizophrenia (Crawford *et al*., 1996; Camchong *et al*., 2008; Polli *et al*., 2008), suggest that functional and structural abnormalities of the right CEF disrupt connectivity and function in the network for spatial attention and volitional ocular motor control in schizophrenia.

Unlike the other cortical components of the ocular motor network (i.e. frontal, parietal, and supplementary eye fields, McDowell and Clementz, 2001), there is abundant evidence of structural abnormalities of the anterior cingulate cortex in schizophrenia. In addition to grey matter reductions (Ohnuma *et al*., 1997; Goldstein *et al*., 1999; Sigmundsson *et al*., 2001; Suzuki *et al*., 2002; Kuperberg *et al*., 2003; Ha *et al*., 2004; Yamasue *et al*., 2004; Mitelman *et al*., 2005), there are reports of reduced fractional anisotropy of the cingulum bundle (Agartz *et al*., 2001; Ardekani *et al*., 2003; although for negative reports see, Buchsbaum *et al*., 1998; Foong *et al*., 2002; Burns *et al*., 2003; Kubicki *et al*., 2003; Sun *et al*., 2003; Wang *et al*., 2004; Hao *et al*., 2006), and volume reductions in the white matter underlying anterior cingulate cortex (McDonald *et al*., 2005; Mitelman *et al*., 2005). There is histopathological evidence of disturbances in micro- and macrocircuitry that might alter communication between the anterior cingulate cortex and connected regions (Benes, 1993, 2000). The anterior cingulate cortex is comprised of several subregions with distinct cytoarchitecture, patterns of connectivity and contributions to cognition (Devinsky *et al*., 1995; Bush *et al*., 1998; 2000; Whalen *et al*., 1998; Margulies *et al*., 2007). Dorsal anterior cingulate cortex contributes to the performance volitional saccades in healthy individuals (Polli *et al*., 2005), while showing abnormal activity in patients with schizophrenia (Polli *et al*., 2008) and their unaffected relatives (Camchong *et al*., 2008). The present findings add to this

Table 3 Regression analyses of negative CEF connectivity on saccadic latency with the interaction term of latency by group, and within group regressions

Region of interest	Latency		Latency by group		Within group			
					Controls		Patients	
	t	*P*	*t*	*P*	*t*	*P*	*t*	*P*
Left CEF								
AS latency	1.23	0.22	−0.83	0.40	1.39	0.18	.45	0.65
PS latency	1.79	0.08	−1.56	0.12	2.07	0.054	−0.14	0.88
Right CEF								
AS latency	2.22	0.03*	−1.76	0.08	2.76	0.01*	−0.33	0.74
PS latency	2.86	0.006*	−2.11	0.04*	3.87	0.001*	0.36	0.72

CEF = cingulate eye field; AS = antisaccade; PS = prosaccade; *$P < 0.05$.

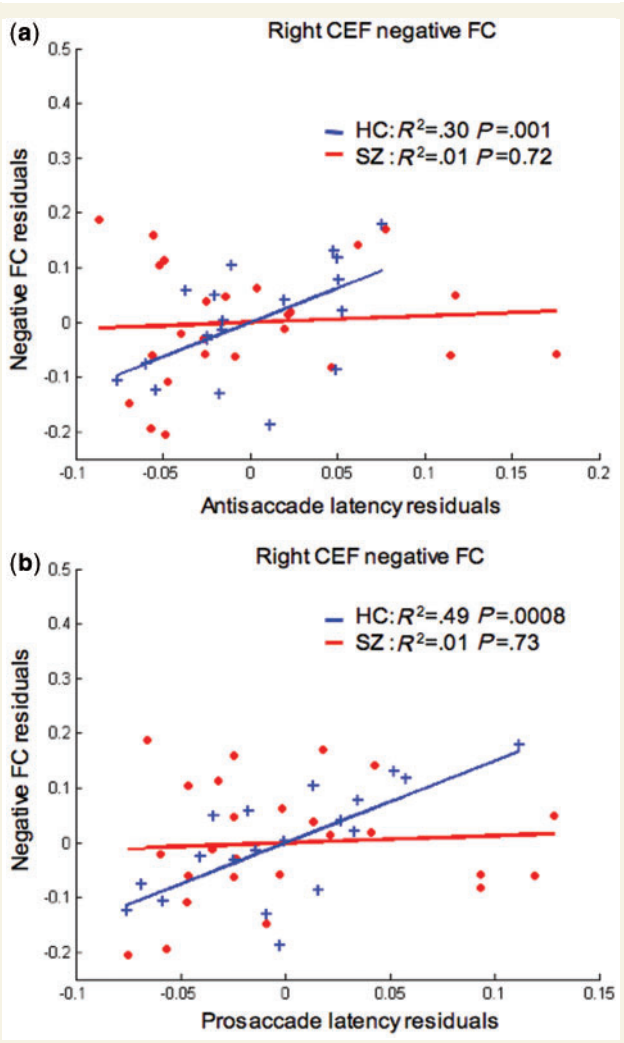

Figure 7 Scatter plots of the age-corrected regressions of negative functional connectivity (FC) of the right cingulate eye field on (**A**) antisaccade latency and (**B**) prosaccade latency by group. Regression lines are given for controls (HC) and patients (SZ) separately. Only for controls is negative functional connectivity of the right CEF related to saccadic latency.

literature by demonstrating a specifically localized and lateralized abnormality of anterior cingulate cortex functional connectivity which, along with the prior diffusion tensor imaging findings (Manoach *et al*., 2007*a*), suggests functional and structural dysconnectivity in a distributed network for spatial attention and volitional ocular motor control.

The reductions of right CEF functional connectivity in schizophrenia were most pronounced in the left thalamus, right pre-supplementary motor area and right anterior insula. The thalamus did not show significant functional connectivity with CEF in the combined group data, but is known to project to dorsal anterior cingulate cortex (Vogt *et al*., 1979). The pre-supplementary motor area and anterior insula, which both showed positive functional connectivity with CEF in the combined group data, receive projections from the dorsal anterior cingulate cortex (Pandya *et al*., 1981; Morecraft *et al*., 1993). Anterior insula and dorsal anterior cingulate cortices are hypothesized to be components of a right hemisphere dominant network that re-orients attention to behaviourally relevant events (Corbetta and Shulman, 2002). The pre-supplementary motor area, which borders the supplementary eye field and CEFs (Nachev *et al*., 2008), is thought to contribute to volitional ocular motor control. Activation of the pre-supplementary motor area has been associated with volitional rather than exogenously generated action (Nachev *et al*., 2008) and with switching responses during eye movement paradigms (Isoda and Hikosaka, 2007). It shows greater preparatory activation in response to cues to perform an antisaccade compared with prosaccade (Curtis and D'Esposito, 2003) and right pre-supplementary motor area has been shown to have greater functional connectivity with the frontal eye field during the performance of antisaccades compared with prosaccades (Miller *et al*., 2005). Based on this evidence, the pre-supplementary motor area is theorized to interact with ocular motor structures to establish a preparatory set when higher level cognitive control is required (Curtis and D'Esposito, 2003; Miller *et al*., 2005). Thus, reduced connectivity between the right CEF and both the right anterior insula and right pre-supplementary motor area in schizophrenia may contribute to poorer performance on tasks that require one to reorient spatial attention and eye gaze volitionally.

In our prior diffusion tensor imaging study, reduced fractional anisotropy underlying the dorsal anterior cingulate cortex, as well as lower fractional anisotropy in frontal eye field, and posterior parietal cortex of the right hemisphere predicted longer latencies of volitional saccades in schizophrenia (Manoach *et al*., 2007*a*). These relations suggest that abnormally reduced microstructural integrity of the white matter underlying dorsal anterior cingulate cortex in schizophrenia compromised network connectivity, thereby contributing to slower performance of volitional saccades. Based on this finding, we predicted that reduced positive functional connectivity of the right CEF in schizophrenia would also be associated with prolonged saccadic latencies. This prediction was not borne out. Instead, negative functional connectivity (i.e. anti-correlations) of the right CEF predicted faster latencies of both prosaccades and antisaccades, but this relation differed by group and was only present in controls. Since the negative mask primarily comprised default network regions, this relation may reflect a reciprocal relationship between activation in the ocular motor and default networks that optimizes performance. This interpretation is compatible with the current theory of default network function and with activation findings using a range of cognitive tasks, including the saccadic paradigm of the present study.

Default network regions commonly show deactivation during task performance (Shulman *et al*., 1997; Binder *et al*., 1999; Mazoyer *et al*., 2001; Raichle *et al*., 2001; Buckner *et al*., 2008). Using the same saccadic paradigm employed here, we previously reported that correct antisaccade trials were accompanied by task-induced deactivation of default network regions and error trials were marked by a failure of task-induced deactivation in healthy individuals (Polli *et al*., 2005). Coincident with task-induced deactivation, the CEFs showed increased activation during correct trials, which in the right hemisphere, correlated with a lower antisaccade error rate. These fMRI findings support the hypothesis that a reciprocal pattern of activation between default network regions and the right CEF optimizes the performance of volitional saccades. Similar reciprocal patterns of activation between the dorsal anterior cingulate cortex and default network regions have been reported during a range of cognitive tasks (Drevets and Raichle, 1998; Bush *et al*., 2000).

In the present study, patients differed significantly from controls in that the relations of negative functional connectivity with saccadic latency were absent. They also differed significantly in the asymmetry of negative functional connectivity of the CEF, with controls showing significant rightward asymmetry and patients showing a trend towards leftward asymmetry. These findings suggest that the coordination of activity between the right hemisphere dominant ocular motor control network and the default network is important for efficient task performance and is disrupted in schizophrenia. These findings resonate with existing evidence of abnormalities of default network function during task performance in schizophrenia patients (Garrity *et al*., 2007; Kim *et al*., 2009) and their relatives, including reduced suppression of default network activity during working memory that predicted less accurate performance and reduced negative functional connectivity of the default network with lateral prefrontal cortex (Whitfield-Gabrieli *et al*., 2009).

Several methodological limitations and alternative conceptualizations of our findings merit consideration. First, our schizophrenia sample was limited to patients with chronic exposure to anti-psychotic medications. Dopaminergic medications have been found to modulate fMRI measures of cortico–striato–thalamic functional connectivity, with the anti-psychotic sulpiride increasing functional connectivity (Honey *et al*., 2003). While it would be difficult to account for such lateralized functional findings (and structural findings in the prior report, Manoach *et al*., 2007*a*) on the basis of medications, and statistically controlling for dosage as measured by chloropromazine equivalents did not alter the findings, the effects of anti-psychotic medications on functional connectivity are still largely unknown and we cannot exclude the possibility that medications contributed to our findings.

In addition, we failed to support our prediction, based on diffusion tensor imaging findings (Manoach *et al*., 2007*a*), that like reduced fractional anisotropy in the dorsal anterior cingulate white matter, reduced positive functional connectivity of the right CEF in schizophrenia would also be associated with prolonged saccadic latencies. This may reflect the different measurements used by these two studies. While fractional anisotropy indexes white matter microstructure, including myelination (Beaulieu, 2002; Harsan *et al*., 2006), functional connectivity indexes correlations in the blood oxygen level dependent signal in grey matter structures. Thus, we interpreted the observed correlations between fractional anisotropy and saccadic latency in schizophrenia to reflect the well-established role of white matter myelin thickness and axon diameter in determining conduction velocity. Functional connectivity during task performance instead reflects inter-regional coordination, which may depend, in part, on white matter integrity, but is also influenced by other factors. The present findings suggest that coordination between the default and ocular motor networks plays a bigger role in performance variability than coordination within the ocular motor control network.

Another issue concerns our interpretation of negative functional connectivity. Based on the existing literature (Drevets and Raichle, 1998; Bush *et al*., 2000; Fox *et al*., 2005; Fransson, 2006) and an fMRI study of the same task showing that deactivation in default network regions was coincident with increased activation in dorsal anterior cingulate cortex (Polli *et al*., 2005) the negative correlations raise the possibility of reciprocal patterns of brain activity. However, negative correlations can be an artefact of global signal regression techniques such as those applied here (Chang and Glover, 2009; Murphy *et al*., 2009; Van Dijk *et al*., in press). Based on these prior studies, we expect that if we did not use global signal regression, the relative patterns of connectivity would be preserved, but the negative sign would no longer be present. Regardless of the direction of the correlations, the relations of right CEF functional connectivity with task performance differed significantly by group reflecting that they were significant in controls and absent in patients. This suggests that the coordination of activity in the volitional ocular motor control network and the regions that collectively comprise the default network is important for efficient task performance and is disrupted in schizophrenia. This finding is consistent with a growing literature suggesting that dyscoordination of activity between the default network and

task-active networks compromises cognitive function in schizophrenia (Buckner *et al*., 2008; Whitfield-Gabrieli *et al*., 2009).

Finally, although similar networks are identified by analyses of task-based and resting-state functional connectivity, there is evidence that task alters functional connectivity (Van Dijk *et al*., 2010). Similar to some prior studies in schizophrenia (Garrity *et al*., 2007; Kim *et al*., 2009; Whitfield-Gabrieli *et al*., 2009), we examined functional connectivity while participants performed a specific task. Therefore, we do not know whether similar abnormalities would also be present during rest.

In summary, the present findings demonstrate reduced functional connectivity of the CEF, specifically in the right hemisphere, during the performance of volitional saccades in schizophrenia. Along with our prior observation of reduced microstructural integrity of the white matter underlying the right dorsal anterior cingulate cortex (Manoach *et al*., 2007*a*), the present findings suggest that functional and structural right CEF abnormalities disrupt connectivity and function in a distributed network for spatial attention and volitional ocular motor control. These abnormalities may contribute to the consistently observed deficits on tasks requiring volitional ocular motor control in schizophrenia. More generally, disrupted connectivity in this network may compromise the ability to overcome prepotency in the service of directing eye gaze and attention to the parts of the environment that are the most behaviourally relevant. These findings suggest a neural basis for the deficits in the control of visual spatial attention that characterize schizophrenia (Luck and Gold, 2008).

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Supplementary material

Supplementary material is available at *Brain* online.

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