



## Decreased interhemispheric coordination in schizophrenia: A resting state fMRI study

Matthew J. Hoptman<sup>a,b,\*</sup>, Xi-Nian Zuo<sup>c</sup>, Debra D'Angelo<sup>a</sup>, Cristina J. Mauro<sup>a</sup>, Pamela D. Butler<sup>a,b</sup>, Michael P. Milham<sup>a,d</sup>, Daniel C. Javitt<sup>a,e</sup>

<sup>a</sup> Schizophrenia Research Division, Nathan Kline Institute, Orangeburg, NY, United States

<sup>b</sup> Department of Psychiatry, New York University School of Medicine, New York, NY, United States

<sup>c</sup> Laboratory for Functional Connectome and Development, Key Laboratory of Behavioral Science, Magnetic Resonance Imaging Research Center, Institute of Psychology, Chinese Academy of Sciences, Beijing, China

<sup>d</sup> Child Mind Institute, New York, NY, United States

<sup>e</sup> Department of Psychiatry, College of Physicians and Surgeons, Columbia University, New York, NY, United States

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### ABSTRACT

Schizophrenia has been increasingly conceptualized as a disorder of brain connectivity, in large part due to findings emerging from white matter and functional connectivity (FC) studies. This work has focused primarily on within-hemispheric connectivity, however some evidence has suggested abnormalities in callosal structure and interhemispheric interaction. Here we examined functional connectivity between homotopic points in the brain using a technique called voxel-mirrored homotopic connectivity (VMHC). We performed VMHC analyses on resting state fMRI data from 23 healthy controls and 25 patients with schizophrenia or schizoaffective disorder. We found highly significant reductions in VMHC in patients for a number of regions, particularly the occipital lobe, the thalamus, and the cerebellum. No regions of increased VMHC were detected in patients. VMHC in the postcentral gyrus extending into the precentral gyrus was correlated with PANSS Total scores. These results show substantial impairment of interhemispheric coordination in schizophrenia.

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### 1. Introduction

Interhemispheric interaction is primarily mediated by the brain's commissural system, including the corpus callosum, anterior commissure, posterior commissure, interthalamic adhesions, and cerebellar commissures (Hoptman and Davidson, 1994). Most callosal fibers connect homotopic regions across the two hemispheres (LaMantia and Rakic, 1990). Resting state fMRI (rsfMRI) is a technique that permits assessment of inter- as well as intrahemispheric functional connectivity (FC). The present study uses rsfMRI to assess the integrity of interhemispheric interaction in schizophrenia.

Since the early 1960s, it has been known that humans who have had forebrain commissures sectioned, including the corpus callosum, show disconnection phenomena on divided sensory spatial field tasks (Gazzaniga et al., 1962; Geschwind and Kaplan, 1962; Nebes, 1972). Deficits in sustained attention (Dimond, 1979a,b) and other cognitive processes have also been observed in split brain patients. The bulk of studies on laterally presented cognitive tasks in healthy individuals suggest that there is advantage to bihemispheric processing (Banich and Belger, 1990; Belger and Banich, 1992), provided that each hemisphere

has competence at the given task. Moreover, interhemispheric interaction may be particularly important in the strategic deployment of attentional resources in response to task demands (Levy and Trevarthen, 1976).

Within sensory regions, Sergent and Bindra (1981) proposed that the left visual hemisphere is biased towards processing of high spatial frequencies, whereas the right hemisphere is more specialized for low spatial frequencies. This distinction has been mapped onto a local/global dimension (Ivry and Robertson, 1998; Robertson and Ivry, 2000). The right hemisphere also appears to be specialized for line orientation (Umiltà et al., 1974), line bisection (Bowers and Heilman, 1980; Foxe et al., 2003), and mental rotation (Robertson et al., 1987). Given the advantages for interhemispheric interaction and the dysconnectivity processes implicated in schizophrenia, it would not be surprising if interhemispheric interaction deficits played an important role in the cognitive deficits, psychiatric symptoms, and sensory abnormalities seen in the disorder. Thus, deficits in interhemispheric interaction may contribute to sensory/cognitive impairments in schizophrenia.

The evidence for interhemispheric interaction deficits in schizophrenia predates recent conceptualizations of schizophrenia as a disorder of dysconnectivity (Friston and Frith, 1995; Bullmore et al., 1997; Stephan et al., 2009) and is fairly consistent, despite the fact that it has been underemphasized. Early postmortem studies found increased callosal thickness (Bigelow and Rosenthal, 1972), but more

\* Corresponding author at: Nathan Kline Institute, 140 Old Orangeburg Rd., Bldg. 35, Orangeburg, NY 10962, United States. Tel.: +1 845 398 6569; fax: +1 845 398 6566.  
E-mail address: [hoptman@nki.rfmh.org](mailto:hoptman@nki.rfmh.org) (M.J. Hoptman).

recent postmortem studies (Casanova et al., 1990), and the vast majority of in vivo imaging studies have found reduced callosal thickness or length, and/or altered shape in schizophrenia (Woodruff et al., 1995; Arnone et al., 2008). White matter density abnormalities in the corpus callosum also have been observed (Hulshoff Pol et al., 2004). Moreover, Highley et al. (1999) found reduced fiber density in the anterior commissure in women, but not men, with schizophrenia.

A number of diffusion tensor imaging (DTI) studies have found reduced fractional anisotropy (FA) in the corpus callosum in schizophrenia (Ardekani et al., 2003; Kubicki et al., 2008). It is likely that DTI studies understate the extent of callosal deficits in schizophrenia, in part because they are typically plagued by low image resolution. Many DTI sequences are obtained in the axial plane, which compounds this problem because it maximizes partial volume effects in the callosum. Indeed, in voxelwise studies, Dougherty noted that FA effect sizes are smallest in the corpus callosum (Dougherty et al., 2005), most likely because its thin dorsoventral extent is particularly susceptible to intersubject registration errors and partial volume effects. Nonetheless, recent DTI work has suggested interhemispheric hypoconnectivity in patients with schizophrenia and their relatives (Whitford et al., 2010; Knochel et al., 2012), which in turn predict interhemispheric transfer time (Whitford et al., 2011) and psychotic symptoms (Whitford et al., 2010).

Relatively few behavioral studies have investigated functional interhemispheric interaction in schizophrenia. The Poffenberger (1912) paradigm has long been used to measure interhemispheric dynamics. In this task, simple stimuli are presented either ipsilateral or contralateral to the response hand. The contralateral – ipsilateral difference in reaction time is taken as an estimate of interhemispheric transfer time, and is typically greater than 0. Patients with schizophrenia showed a prolongation of the ipsilateral advantage (Shelton and Knight, 1984), suggesting impaired interhemispheric transfer efficiency. Another early study showed that patients with schizophrenia are impaired on cross-localization tasks on which patients with callosal agenesis are also impaired (Craft et al., 1987). Patients also show deficits consistent with the callosum's role in optimizing processing under computationally complex situations. Under such conditions, healthy individuals show an advantage to processing information presented bilaterally compared to the same amount of information presented initially to one hemisphere alone (Belger and Banich, 1992). This bilateral advantage suggests that it can be more efficient for the two hemispheres to interact than for one hemisphere to perform all of the processing. The bilateral advantage is absent in patients with schizophrenia (Barnett et al., 2007), suggesting a deficit in interhemispheric interaction in schizophrenia.

Psychophysiological measures of interhemispheric functional interaction also have been observed to be abnormal in schizophrenia. For example, in a word task, healthy controls show increased event related potential (ERP) amplitudes to bilateral (and identical) stimulation compared to unilateral stimulation. Patients showed a reduction in this “bilateral redundancy gain” (Mohr et al., 2008). In addition, deficits in electroencephalographic (EEG) measures of interhemispheric alpha band coherence have been found in patients with schizophrenia (Morrison-Stewart et al., 1996) and in individuals at genetic risk for schizophrenia (Winterer et al., 2001). Another longitudinal study found that reduced symptom severity in schizophrenia was associated with higher EEG interhemispheric beta coherence (Higashima et al., 2006), although some studies have found higher interhemispheric coherence in both never-medicated patients with schizophrenia (Wada et al., 1998) and in siblings of patients with schizophrenia (Mann et al., 1997).

Despite the evidence of interhemispheric interaction deficits in schizophrenia, there are no studies examining FC between homotopic brain sites, which are the gray matter regions that are connected by commissural fibers. Here we evaluated interhemispheric resting state FC in patients with schizophrenia. We used a measure, voxel-mirrored

homotopic connectivity (VMHC; (Zuo et al., 2010)), in which the time series for each voxel in one hemisphere was correlated with that of its homotopic voxel (i.e., from the other hemisphere). Similar methodologies have shown deficits in interhemispheric functional connectivity in autism (Anderson et al., 2011), showing that the method is sensitive to abnormal interhemispheric FC in psychopathology. Given the extensive evidence of both structural and functional disconnections in schizophrenia, we expected to observe reductions in homotopic connectivity in schizophrenia.

## 2. Methods

### 2.1. Participants

Participants were 25 healthy controls and 28 patients who met DSM-IV-TR (American Psychiatric Association, 2000) criteria for schizophrenia or schizoaffective disorder ( $n=3$ ) after a Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Patient version (SCID-I/P (First et al., 2002)). Controls had no major Axis I disorders as determined with the SCID-I/NP (First et al., 2001). Additional details are reported in Hoptman et al. (2010a,b). Patients with head injuries with a loss of consciousness of greater than 20 min were excluded, as were patients with neurological disorders. In addition, participants with substance abuse diagnoses in the last month or dependence in the last six months were excluded. Demographic data are given in Table 1. Some subjects were missing data for some of the demographic measures, but the patient characteristics were similar to those in other recent reports from our group (e.g., Martinez et al., 2012). Controls and patients did not differ in age or parental socioeconomic status as measured by the Hollingshead scale. All participants signed informed consent as approved by the local Institutional Review Boards.

### 2.2. MRI acquisition

Scanning took place on the 1.5 T Siemens Vision Scanner (Erlangen, Germany) at the Nathan Kline Institute Center for Advanced Brain Imaging. Participants received a magnetization prepared rapidly acquired gradient echo (MPRAGE) T1-weighted scan (TR=11.6 ms, TE=4.9 ms, TI=1122 ms, flip angle=8°, matrix=256×256, FOV=256 mm, slice thickness=1 mm, 190 slices, no gap, 1 acquisition), and a six minute resting state fMRI scan (TR=2000 ms, TE=50 ms, flip angle=85°, matrix=64×64, FOV=224 mm, 5 mm slice thickness, 22 slices, no gap, 180 acquisitions). For the resting state scan, participants were instructed to close their eyes and remain awake.

**Table 1**  
Demographics of study participants.

Variable	Controls (N=23)	Patients (N=25)	<i>t</i>	<i>p</i>
Age (years)	41.6±11.4	35.5±10.9	−1.89	.07
Education (years)	15.4±2.9	12.4±2.1	−4.08	1.7×10 <sup>−4</sup>
Handedness score (right) <sup>a</sup>	16.7±3.9	15.5±5.7	−0.86	.39
Parental SES <sup>b</sup>	39.8±12.1	39.9±14.8	0.017	.99
Illness duration (years) <sup>c</sup>	–	11.5±6.6	–	–
PANSS Total <sup>d</sup>	–	76.8±17.0	–	–
PANSS Positive <sup>d</sup>	–	18.6±6.3	–	–
PANSS Negative <sup>d</sup>	–	20.8±6.2	–	–
CPZ equivalents (mg)	–	819.9±621.8	–	–
			$\chi^2$	<i>p</i>
Gender <sup>e</sup>	16/7	22/3	2.51	.16

Note: PANSS = Positive and Negative Syndrome Scale, CPZ = chlorpromazine.

<sup>a</sup> From Edinburgh handedness questionnaire (Oldfield, 1971).

<sup>b</sup> From Hollingshead (1957).

<sup>c</sup> Defined as age at first psychiatric hospitalization.

<sup>d</sup> Missing for 1 patient.

<sup>e</sup> By Fisher's exact test.

### 2.3. Data analysis

Resting state data were preprocessed as described elsewhere in detail (Margulies et al., 2007; Hoptman et al., 2010b). Briefly, the first 10 volumes were discarded to eliminate T1 relaxation effects. Thereafter, images were motion-corrected using AFNI (Cox, 1996). Time series were smoothed using a 6 mm FWHM Gaussian kernel using FSL, and grand mean scaled to a value of 10,000 using FSL. Subsequently, the data were bandpass filtered (0.005 Hz–0.1 Hz) and linear and quadratic trends were removed using AFNI. They were then spatially normalized to MNI space ( $2 \times 2 \times 2$  mm<sup>3</sup> resolution) using FSL ([www.fmrib.ox.ac.uk/fsl](http://www.fmrib.ox.ac.uk/fsl)). The MPRAGE image was segmented using FSL's FAST software to obtain the masks for white matter (WM) and cerebrospinal fluid (CSF). The time series for CSF and WM were then averaged across voxels for each tissue type. These time series, as well as the global signal time series and the time series for the six motion parameters were used as covariates of no interest in a general linear model (GLM). These were regressed out from the MNI-space EPI time series. The above steps were carried out using the FCONN scripts (version 1.1), which are part of the 1000 functional Connectomes project and are available at [http://www.nitrc.org/projects/fcon\\_1000/](http://www.nitrc.org/projects/fcon_1000/) (Biswal et al., 2010). The residual time series for each subject was registered to a symmetric MNI template and was used to compute the homotopic functional connectivity.

Methods for computing VMHC are described in Zuo et al. (2010). For each participant, homotopic functional connectivity was computed as the resting state functional connectivity (RSFC) between any pair of symmetric interhemispheric voxels. Specifically, in symmetrical MNI brain space, we calculated the Pearson's correlation coefficient between each voxel's residual time series and that of its symmetrical interhemispheric counterpart. The resultant values were referred to as the VMHC and were used for subsequent group-level analyses. The analyses were masked by a gray matter segmentation of the symmetric MNI template (thresholded at 40%). Global VMHC was extracted as average of voxel-wise VMHC within the gray matter mask for each subject and was used as a covariate in the analyses described below. In some cases, whole brain coverage was not possible, so computations were limited to voxels for which all subjects had data.

Group-level analyses were conducted using FSL's ordinary least squares (OLS) model implemented in FLAME. Two-sample *t*-tests on VMHC maps between patients and controls were performed to examine the differences in VMHC between the two groups. This statistical procedure produced thresholded *z*-statistic maps of clusters defined by a threshold of  $Z = 2.3$  and a corrected cluster threshold of  $p = .05$  using Gaussian Random Field theory (Worsley, 2001). The resultant maps revealed brain regions showing significantly different VMHC between patients and healthy controls. Local maxima were identified using the AFNI program 3dmaxima, using a search radius of 15 voxels.

Because small amounts of movement from volume to volume can influence RSFC results (Power et al., 2012, in press), we computed framewise displacement (FD) for our data, which corresponds to the temporal derivative of the movement parameters. These were used as covariates in the group level analyses. Three patients (one with schizoaffective disorder) and three controls had  $FD > 0.5$  mm on greater than 35 volumes (i.e., less than 4.8 min of useable data) and were eliminated from the final analyses. Mean FD did not differ between patients ( $M \pm SD = 0.22 \pm 0.08$  mm) and controls ( $0.20 \pm 0.09$  mm) included in the final sample ( $t[46] = 0.50, p = .62$ ).

## 3. Results

### 3.1. Group differences

Results are shown in Table 2 and Fig. 1. Patients showed deficits in VMHC in a large spatial extent, primarily between left and right lingual gyri, cuneus, thalamus, and the declive of the cerebellum. No

**Table 2**

Regions showing group differences in voxel-mirrored homotopic connectivity.

Region	Voxels	<i>Z</i> <sup>a</sup>	BA <sup>b</sup>	Talairach coordinates		
				X	Y	Z
Lingual gyrus/culmen	1335	4.97	19	± 14	− 53	− 4
Cuneus	–	–	18	± 18	− 88	24
Thalamus	226	4.07	–	± 8	− 6	4
Declive of cerebellum	459	4.65	–	± 36	− 67	− 20

<sup>a</sup> Maximum *z*-statistic.

<sup>b</sup> BA = Brodmann area.

areas showed increased VMHC in patients. We also examined the results excluding patients with schizoaffective disorder, where results were essentially the same as in the larger analysis (see Supplementary Fig. 1).

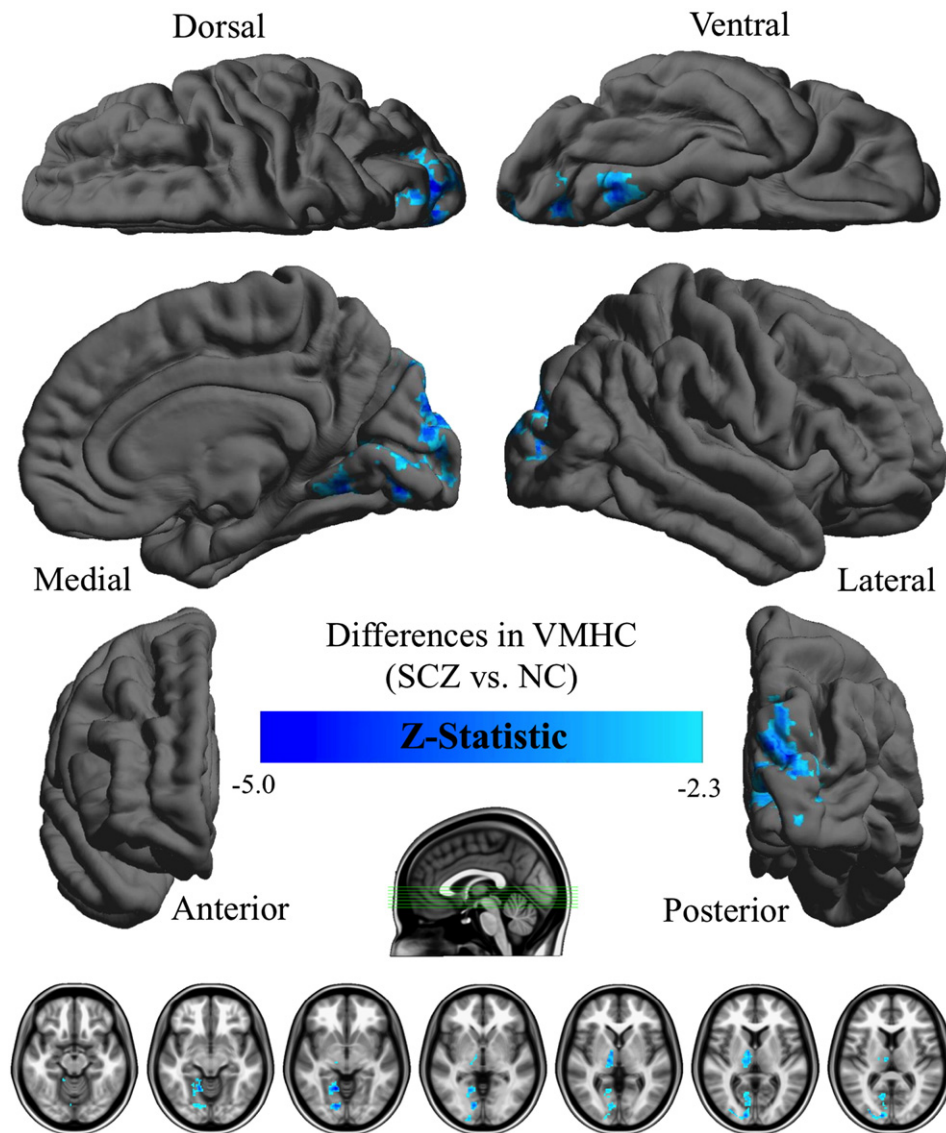
Interhemispheric interaction can vary with strength and consistency of handedness (Hoptman and Davidson, 1994). To examine this issue, we repeated the group analyses limited to only right-handers. Results were essentially identical to those reported above.

The role of medication dosage in interhemispheric interaction deficits in schizophrenia is unknown. We thus examined the correlation between chlorpromazine (CPZ) equivalents and VMHC within the mask containing all voxels found to have reduced connectivity. This correlation was not significant,  $r = .01, p = .95$ , suggesting that it is unlikely that our results can be attributed to a neuroleptic dosage effect. To examine effects of medication effects on VMHC, we computed a multiple regression analysis in patients only with global mean VMHC and FD as covariates of no interest and medication dosage as a covariate of interest. Medication dosage did not correlate with VMHC in that analysis. Moreover, VMHC remained significantly greater than 0 throughout the entire brain after controlling for that variable. Lastly, illness duration correlated negatively with VMHC within the mask containing all voxels found to have reduced connectivity,  $r = -.54, p = .012$ . Interestingly, despite this region-level relationship, voxel-wise multiple regression analyses found a positive relationship between illness duration and VMHC in a medial dorsal nucleus region (Talairach coordinate [6, − 10, 4]; see Supplementary Fig. 2) that slightly overlapped (3%) with the thalamic cluster found to have reduced VMHC in patients. There were voxels with significant negative correlations within the deficit region, as would be expected, though they did not survive statistical correction with Gaussian Random Fields. Nonetheless, VMHC remained significantly greater than 0 throughout the brain despite controlling for illness duration.

We also examined the relationship between PANSS scores and VMHC. To do so, we computed separate multiple regression analyses in the patients group with PANSS Positive, Negative, General, and Total scores as covariates. For the PANSS Total score, we found a negative correlation between VMHC and symptomatology in the postcentral gyrus extending into precentral gyrus (Talairach coordinate [48, − 14, 32]; see Supplementary Fig. 3). The other scales did not show significant positive or negative correlations with VMHC. An examination of correlations at subthreshold levels of significance for the other scales suggested that those with the General subscale were closest to significance.

In order to determine whether deficits in VMHC could be attributed to abnormalities in RSFC in one hemisphere or the other, we performed separate GLMs on the residualized time series data in nonsymmetric MNI space, with global VMHC and FD as covariates. Seeds (spheres with 4 mm radius) for these analyses were generated based on each local maximum and its homotopic homolog. These were thresholded at  $p = .05$  (corrected for Gaussian Random Fields). To visualize these results, for each seed pair, we computed the right-left asymmetry in positive FC in the group difference region (see Fig. 2). These analyses showed that both hemispheres were involved in the observed effects.





**Fig. 1.** Surface renderings of group differences in homotopic voxel-mirrored connectivity (VMHC). Depicted are regions in which VMHC was greater in healthy controls than in patients. Group differences were based on clusters defined by  $Z > 2.3$  and a corrected cluster threshold of  $p = .05$  (Gaussian Random Field Theory corrected). The final Z-statistic maps are visualized as six hemispheric surfaces (cortical regions) and seven symmetric axial slices (subcortical regions).

#### 4. Discussion

The primary finding of this work is that the correlation between homologous brain regions was reduced in patients with schizophrenia and schizoaffective disorder. These reductions encompassed large areas, primarily including occipital regions, and the thalamus, as well as the cerebellum. These findings are consistent with literature reviewed above showing abnormalities in interhemispheric interaction in schizophrenia using a variety of methods including behavioral, psychophysiological, and structural MRI investigations. We also found that higher PANSS Total scores were correlated with lower VMHC in postcentral gyrus extending into the precentral gyrus, suggesting that this measure might have implications for psychopathology.

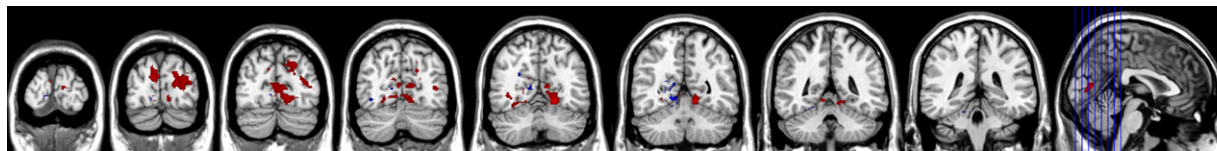
The lack of frontal results is interesting given that anterior white matter abnormalities have been emphasized in the schizophrenia literature (Ellison-Wright et al., 2008). It may be that these will be detected at higher field strength as discussed below. Because the corpus callosum is organized topographically (Hoptman and Davidson, 1994), the findings may have implications for anatomical differences in the callosum, such that more posterior regions might be differentially

affected, although this idea awaits confirmation from concurrent structural imaging studies.

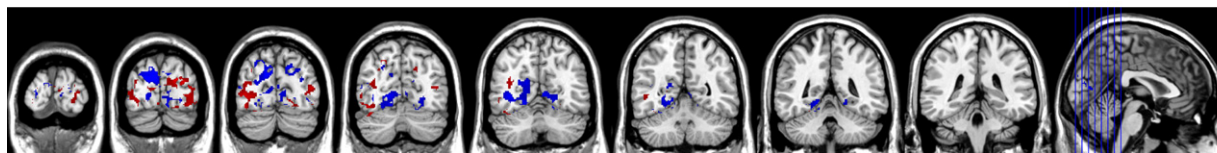
On the other hand, many of the regions in which we showed reduced VMHC were in posterior sensory areas. Patients with schizophrenia also show deficits in relatively low level visual sensory functions, including contrast sensitivity (Butler et al., 2008) and P1 event related potential componentry (Foxe et al., 2001). These low-level deficits appear to upwardly generalize to other cognitive deficits seen in schizophrenia, such as perceptual closure (Doniger et al., 2001; Sehatpour et al., 2010), visual attention (Martinez et al., 2007, 2012), and controlled visual processing (Dias et al., 2011). It may be that deficits in VMHC in higher-level areas are in part due to feed-forward unilateral projections from lower-level sensory areas in addition to direct interhemispherically mediated influences. Thus, although the role of impaired interhemispheric interaction has not been investigated in these paradigms, it could contribute at both sensory and anterior levels. Future studies should address VMHC deficits relative to specific aspects of cognitive dysfunction.

At a more general level, behavioral studies of interhemispheric interaction suggest that it can be more efficient for the two hemispheres

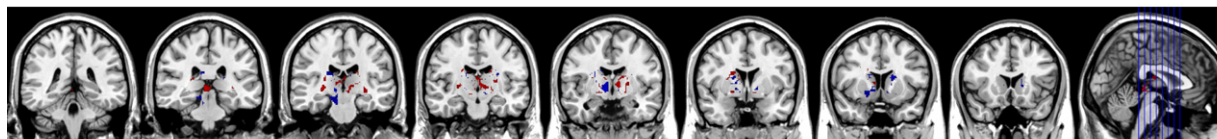
Peak1



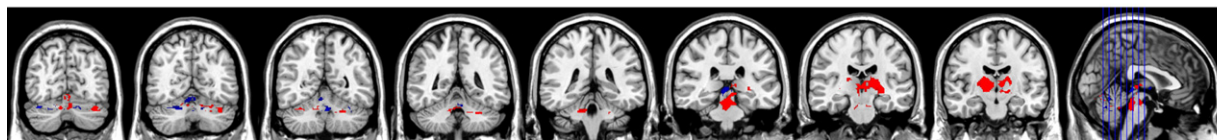
Peak2



Peak3



Peak4



**Fig. 2.** Asymmetries in functional connectivity as seeded for local maxima (left and right) of group differences shown in Fig. 1. Seeds were placed in left and right hemispheres based on maxima shown in Table 1. Asymmetries were computed as the right – left difference in positive FC in the group difference region for each of the peak pairs. Peak 1 = lingual gyrus, Peak 2 = cuneus, Peak 3 = thalamus, Peak 4 = declive of cerebellum. Data are shown in radiological convention, with every 8th slice depicted (red = right > left, blue = left > right).

to interact than for one hemisphere to perform all of the processing (Banich and Karol, 1992; Belger and Banich, 1992). Deficits in interhemispheric interaction in schizophrenia therefore present a cognitive processing bottleneck in the disorder. A related issue is that interhemispheric interaction appears to be particularly important in the strategic deployment of attentional resources in response to task demands (Levy and Trevarthen, 1976) and in sustained attention (Dimond, 1979b). Thus, a deficit in interhemispheric interaction might be related to some of the attentional problems shown in schizophrenia (Nuechterlein et al., 2009).

In the present study, we also found VMHC deficits involving the thalamus, a region that has also been implicated in schizophrenia based upon structural imaging (Andreasen et al., 1994) and postmortem studies (Byne et al., 2002), see Dwork et al. (2008) for a review. However, because deficits in this region partially overlapped with a region that correlated with illness duration, the potential role of chronicity needs to be clarified.

We found a negative correlation between PANSS Total scores and VMHC in the postcentral gyrus extending into the precentral gyrus. Although this correlation was not within the region in which patients showed deficits in VMHC, it may suggest that reductions in this measure have implications for psychiatric symptomatology. The scale with the clearest relationship to VMHC was the General Psychopathology subscale, which has many items, including tension, posturing, motor retardation, and impulse control that relate to motor functions. Top down interactions in post/precentral regions may contribute to symptoms such as hallucinations (Whitford et al., 2012a). Moreover, motor cortex may contribute to “active sensing” of the environment, which contributes to social engagement (Schroeder et al., 2010), which also is problematic in the disorder. Clearly, however, the

relationship between VMHC and symptomatology awaits further explication with larger samples.

The mechanism underlying these deficits in VMHC is unknown. They could be related to widespread white matter integrity abnormalities observed in schizophrenia (White et al., 2011). Deficits in white matter connectivity in the corpus callosum could disrupt the synchrony between homotopically connected regions because neural signals are not transmitted with fidelity. Another, not mutually exclusive, explanation is that dysfunctions in local gray matter structure could account for the deficits. Reductions in cortical thickness (Goghari et al., 2007) and gray matter volume (Shenton et al., 2001) have been observed in many of the regions in which we observed abnormal VMHC. Thus, reduced neuropil or aberrant local oscillatory firing within these regions may disrupt coherent low frequency oscillatory activity and/or its generation in one region, and thereby, impair its functional connectivity with other regions. Finally, when considering the structural underpinnings of VMHC, it is important to note that although the callosum is the largest conduit for information transfer and coordination between the hemispheres, alternative pathways (e.g., subcortical) exist. In support of this notion, a recent examination of RSFC in a split brain patient (Uddin et al., 2008) found correlated spontaneous activity in homotopic regions within the visual system and default mode network, despite the lack of any intact commissural fibers. Which of these, or other, explanations accounts for the present findings awaits combined functional/structural studies.

It is unlikely that the results presented here can be accounted for by differences in hand preference or medication dosage, as VMHC in deficit regions was not correlated with these variables. It also appears that both hemispheres contributed to the observed effects, because when we examined the asymmetry of RSFC for local maxima in our

data (on both sides of the midline), both leftward and rightward asymmetries were observed.

The study has several limitations. All patients were chronic and were taking antipsychotic medication. Indeed, there were correlations between illness duration and VMHC in this sample. It is possible that drug-naïve, first episode patients would show different results. It should be noted in this regard that abnormal callosal thickness in the genu (Walterfang et al., 2008) and white matter integrity in the splenium (Cheung et al., 2008) have been found in first-episode patients, including in never-medicated subjects. Negative findings also have been reported, although as noted in the Introduction, DTI scans have typically not been optimized to study the corpus callosum, and the more recent literature is more consistent (Whitford et al., 2010; Knochel et al., 2012; Whitford et al., 2012b). Abnormalities have also been shown in the genu of ultra high risk individuals who go on to express the disease (Walterfang et al., 2008). Thus, structural abnormalities in the callosum appear to be present at least at disease onset. We only examined linear relationships in this study. It is possible that slope or nonlinear effects are also present in the data. Also, the structural basis of these findings is unclear, as noted above. Studies using resting state fMRI along with higher resolution DTI and ERP methods would provide critical information on structural and temporal aspects of interhemispheric interaction in the same subjects. Another limitation is that there are existing asymmetries in cortical structure. We attempted to mitigate these issues by using a symmetric template. We should note that in previous (unreported) analyses we had used the standard MNI template available from FSL with essentially identical results. We used a 1.5 T scanner for the current study. It is possible that more widespread results might be discovered at higher field, which offers higher signal-to-noise ratios. Finally, whole brain coverage was not always possible in our scans due to technical limitations. It is possible that differences in VMHC might be present in the regions not covered in our scans, which should be studied in further work.

The current results show that interhemispheric resting state fMRI measures of VMHC are reduced in schizophrenia. Moreover, reduced VMHC is associated with higher total PANSS scores in pre/postcentral gyrus. These data are consistent with structural and functional deficits in interhemispheric interaction in schizophrenia. They also suggest an important new avenue to explore in order to better understand the nature of the deficits that are so disabling in patients with schizophrenia.

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#### Contributors

Matthew J. Hoptman designed the study, undertook the statistical analyses, and wrote the manuscript. Xi-Nian Zuo and Michael P. Milham developed the analytic method. Ms. Mauro assisted in the literature review. All authors contributed to and have approved the final manuscript.

#### Conflict of interest

The authors report the following conflicts of interest: Dr. Daniel C. Javitt does consulting for Sanofi, Solvay, Pfizer, Lundbeck, AstraZeneca, NPS Pharmaceuticals, Takeda, Sepracor, Schering Plough, Cypress Bio, and Merck. He has research support from Pfizer, and he has equity in Glytech, and AASI. He also serves on the advisory board of Pfizer. Matthew J. Hoptman, Pamela D. Butler, Debra D'Angelo, Cristina J. Mauro, Xi-Nian Zuo, and Michael P. Milham have declared no conflicts of interest in relation to the subject of this study.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.schres.2012.07.027>.

## References

- American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR). American Psychiatric Association, Washington, D.C.
- Anderson, J.S., Druzgal, T.J., Froehlich, A., Dubray, M.B., Lange, N., Alexander, A.L., Abildskov, T., Nielsen, J.A., Cariello, A.N., Cooperider, J.R., Bigler, E.D., Lainhart, J.E., 2011. Decreased interhemispheric functional connectivity in autism. *Cereb. Cortex* 21, 1134–1146.
- Andreasen, N.C., Arndt, S., Swayze, V., Cizadlo, T., Flaum, M., O'Leary, D., Ehrhardt, J.C., Yuh, W.T., 1994. Thalamic abnormalities in schizophrenia visualized through magnetic resonance image averaging. *Science* 266, 294–298.
- Ardekani, B.A., Nierenberg, J., Hoptman, M.J., Javitt, D.C., Lim, K.O., 2003. MRI study of white matter diffusion anisotropy in schizophrenia. *Neuroreport* 14, 2025–2029.
- Arnone, D., McIntosh, A.M., Tan, G.M., Ebmeier, K.P., 2008. Meta-analysis of magnetic resonance imaging studies of the corpus callosum in schizophrenia. *Schizophr. Res.* 101, 124–132.
- Banich, M.T., Belger, A., 1990. Interhemispheric interaction: how do the hemispheres divide and conquer a task? *Cortex* 26, 77–94.
- Banich, M.T., Karol, D.L., 1992. The sum of the parts does not equal the whole: evidence from bihemispheric processing. *J. Exp. Psychol. Hum. Percept. Perform.* 18, 763–784.
- Barnett, K.J., Kirk, I.J., Corballis, M.C., 2007. Bilateral disadvantage: lack of interhemispheric cooperation in schizophrenia. *Conscious. Cogn.* 16, 436–444.
- Belger, A., Banich, M.T., 1992. Interhemispheric interaction affected by computational complexity. *Neuropsychologia* 30, 923–929.
- Bigelow, L., Rosenthal, R., 1972. Schizophrenia and the corpus callosum. *Lancet* 1, 694.
- Biswal, B., Mennes, M., Zuo, X.N., Gohel, S., Kelly, C., Smith, S., Beckmann, C., Buckner, R., Colcombe, S., Degenowski, A.-M., Ernst, M., Hyde, J.S., Kotter, R., McMahon, K., Maddox, D., Madsen, K., Butler, P.D., Hampson, M., Hoptman, M.J., Kiviniemi, V., Li, S.-J., Lin, C.-P., Lowe, M., Mayberg, H., Peltier, S., Petersen, S., Raichle, M., Rombouts, S., Rypma, B., Schlagger, B., Schmidt, S., Siegle, G.J., Sorg, C., Teng, G.-J., Villringer, A., Walter, M., Wang, L.-H., Whitfield-Gabrieli, S., Windischberger, C., Zhang, H.-Y., Zang, Y.-F., Castellanos, F.X., Milham, M.P., 2010. Towards discovery science of human brain function: the '1000 Connectomes' project. *Proc. Natl. Acad. Sci. U. S. A.* 107, 4734–4739.
- Bowers, D., Heilman, K.M., 1980. Pseudoneglect: effects of hemispace on a tactile line bisection task. *Neuropsychologia* 18, 491–498.
- Bullmore, E.T., Frangou, S., Murray, R.M., 1997. The dysplastic net hypothesis: an integration of developmental and dysconnectivity theories of schizophrenia. *Schizophr. Res.* 28, 143–156.
- Butler, P.D., Silverstein, S.M., Dakin, S.C., 2008. Visual perception and its impairment in schizophrenia. *Biol. Psychiatry* 64, 40–47.
- Byne, W., Buchsbaum, M.S., Mattiace, L.A., Hazlett, E.A., Kemether, E., Elhakem, S.L., Purohit, D.P., Haroutunian, V., Jones, L., 2002. Postmortem assessment of thalamic nuclear volumes in subjects with schizophrenia. *Am. J. Psychiatry* 159, 59–65.
- Casanova, M.F., Sanders, R.D., Goldberg, T.E., Bigelow, L.B., Christison, G., Torrey, E.F., Weinberger, D.R., 1990. Morphometry of the corpus callosum in monozygotic twins discordant for schizophrenia: a magnetic resonance imaging study. *J. Neurol. Neurosurg. Psychiatry* 53, 416–421.
- Cheung, V., Cheung, C., McAlonan, G.M., Deng, Y., Wong, J.G., Yip, L., Tai, K.S., Khong, P.L., Sham, P., Chua, S.E., 2008. A diffusion tensor imaging study of structural dysconnectivity in never-medicated, first-episode schizophrenia. *Psychol. Med.* 38, 877–885.
- Cox, R.W., 1996. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Comput. Biomed. Res.* 29, 162–173.
- Craft, S., Willerman, L., Bigler, E.D., 1987. Callosal dysfunction in schizophrenia and schizo-affective disorder. *J. Abnorm. Psychol.* 96, 205–213.
- Dias, E.C., Butler, P.D., Hoptman, M.J., Javitt, D.C., 2011. Early sensory contributions to contextual encoding deficits in schizophrenia. *Arch. Gen. Psychiatry* 68, 654–664.
- Dimond, S.J., 1979a. Performance by split-brain humans on lateralized vigilance tasks. *Cortex* 15, 43–50.
- Dimond, S.J., 1979b. Tactile and auditory vigilance in split-brain man. *J. Neurol. Neurosurg. Psychiatry* 42, 70–74.
- Doniger, G.M., Silipo, G., Rabinowicz, E.F., Snodgrass, J.G., Javitt, D.C., 2001. Impaired sensory processing as a basis for object-recognition deficits in schizophrenia. *Am. J. Psychiatry* 158, 1818–1826.
- Dougherty, R.F., Ben-Shachar, M., Deutsch, G., Potanina, P., Bammer, R., Wandell, B.A., 2005. Occipital-callosal pathways in children: validation and atlas development. *Ann. N. Y. Acad. Sci.* 1064, 98–112.
- Dwork, A.J., Smiley, J.F., Colibazzi, T., Hoptman, M.J., 2008. Postmortem and in vivo structural pathology in schizophrenia. In: Charney, D.S., Nestler, E.J. (Eds.), *Neurobiology of Mental Illness*. Oxford University Press, New York, pp. 281–302.
- Ellison-Wright, I., Glahn, D.C., Laird, A.R., Thelen, S.M., Bullmore, E., 2008. The anatomy of first-episode and chronic schizophrenia: an anatomical likelihood estimation meta-analysis. *Am. J. Psychiatry* 165, 1015–1023.
- First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 2001. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Non-patient Edition (SCID-I/NP) Biometrics Division. New York State Psychiatric Institute, New York.
- First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 2002. Structured Clinical Interview for DSM-IV-TR Axis I Disorders – Patient Edition (SCID-I/P, 11/2002 revision) Biometrics Research Department. New York State Psychiatric Institute, New York.



- Foxe, J.J., Doniger, G.M., Javitt, D.C., 2001. Early visual processing deficits in schizophrenia: impaired P1 generation revealed by high-density electrical mapping. *Neuroreport* 12, 3815–3820.
- Foxe, J.J., McCourt, M.E., Javitt, D.C., 2003. Right hemisphere control of visuospatial attention: line-bisection judgments evaluated with high-density electrical mapping and source analysis. *NeuroImage* 19, 710–726.
- Friston, K.J., Frith, C.D., 1995. Schizophrenia: a disconnection syndrome? *Clin. Neurosci.* 3, 89–97.
- Gazzaniga, M.S., Bogen, J.E., Sperry, R.W., 1962. Some functional effects of sectioning the cerebral commissures in man. *Proc. Natl. Acad. Sci. U. S. A.* 48, 1765–1769.
- Geschwind, N., Kaplan, E., 1962. A human cerebral disconnection syndrome. A preliminary report. *Neurology* 12, 675–685.
- Goghari, V.M., Rehm, K., Carter, C.S., MacDonald, A.W., 2007. Sulcal thickness as a vulnerability indicator for schizophrenia. *Br. J. Psychiatry* 191, 229–233.
- Higashima, M., Takeda, T., Kikuchi, M., Nagasawa, T., Koshino, Y., 2006. Functional connectivity between hemispheres and schizophrenic symptoms: a longitudinal study of interhemispheric EEG coherence in patients with acute exacerbations of schizophrenia. *Clin. EEG Neurosci.* 37, 10–15.
- Highley, J.R., Esiri, M.M., McDonald, B., Roberts, H.C., Walker, M.A., Crow, T.J., 1999. The size and fiber composition of the anterior commissure with respect to gender and schizophrenia. *Biol. Psychiatry* 45, 1120–1127.
- Hollingshead, A.B., 1957. Two Factor Index of Social Position.
- Hoptman, M.J., Davidson, R.J., 1994. How and why do the two cerebral hemispheres interact? *Psychol. Bull.* 116, 195–219.
- Hoptman, M.J., D'Angelo, D., Catalan, D., Mauro, C.J., Shehzad, Z.E., Kelly, A.M.C., Castellanos, F.X., Javitt, D.C., Milham, M.P., 2010a. Amygdalofrontal functional connectivity and aggression in schizophrenia. *Schizophr. Bull.* 36, 1020–1028.
- Hoptman, M.J., Zuo, X.N., Butler, P.D., Javitt, D.C., D'Angelo, D., Mauro, C.J., Milham, M.P., 2010b. Amplitude of low frequency oscillations in schizophrenia: a resting state fMRI study. *Schizophr. Res.* 117, 13–20.
- Hulshoff Pol, H.E., Schnack, H.G., Mandl, R.C., Cahn, W., Collins, D.L., Evans, A.C., Kahn, R.S., 2004. Focal white matter density changes in schizophrenia: reduced interhemispheric connectivity. *NeuroImage* 21, 27–35.
- Ivry, R.B., Robertson, L.C., 1998. *The Two Sides of Perception*. MIT Press, Cambridge, MA.
- Knochel, C., Oertel-Knochel, V., Schonmeyer, R., Rotarska-Jagiela, A., van de Ven, V., Prvulovic, D., Haenschel, C., Uhlhaas, P., Pantel, J., Hampel, H., Linden, D.E., 2012. Interhemispheric hypoconnectivity in schizophrenia: fiber integrity and volume differences of the corpus callosum in patients and unaffected relatives. *NeuroImage* 59, 926–934.
- Kubicki, M., Styner, M., Bouix, S., Gerig, G., Markant, D., Smith, K., Kikinis, R., McCarley, R.W., Shenton, M.E., 2008. Reduced interhemispheric connectivity in schizophrenia-tractography based segmentation of the corpus callosum. *Schizophr. Res.* 106, 125–131.
- LaMantia, A.S., Rakic, P., 1990. Cytological and quantitative characteristics of four cerebral commissures in the rhesus monkey. *J. Comp. Neurol.* 291, 520–537.
- Levy, J., Trevarthen, C., 1976. Metacognition of hemispheric function in human split-brain patients. *J. Exp. Psychol. Hum. Percept. Perform.* 2, 299–312.
- Mann, K., Maier, W., Franke, P., Roschke, J., Gansicke, M., 1997. Intra- and interhemispheric electroencephalogram coherence in siblings discordant for schizophrenia and healthy volunteers. *Biol. Psychiatry* 42, 655–663.
- Margulies, D.S., Kelly, A.M., Uddin, L.Q., Biswal, B.B., Castellanos, F.X., Milham, M.P., 2007. Mapping the functional connectivity of anterior cingulate cortex. *NeuroImage* 37, 579–588.
- Martinez, A., Ramanathan, D.S., Foxe, J.J., Javitt, D.C., Hillyard, S.A., 2007. The role of spatial attention in the selection of real and illusory objects. *J. Neurosci.* 27, 7963–7973.
- Martinez, A., Hillyard, S.A., Bickel, S., Dias, E.C., Butler, P.D., Javitt, D.C., 2012. Consequences of magnocellular dysfunction on processing attended information in schizophrenia. *Cereb. Cortex* 22, 1282–1293.
- Mohr, B., Pulvermüller, F., Rockstroh, B., Endrass, T., 2008. Hemispheric cooperation – a crucial factor in schizophrenia? Neurophysiological evidence. *NeuroImage* 41, 1102–1110.
- Morrison-Stewart, S.L., Velikonja, D., Corning, W.C., Williamson, P., 1996. Aberrant interhemispheric alpha coherence on electroencephalography in schizophrenic patients during activation tasks. *Psychol. Med.* 26, 605–612.
- Nebes, R.D., 1972. Dominance of the minor hemisphere in commissurotomy man on a test of figural unification. *Brain* 95, 633–638.
- Nuechterlein, K.H., Luck, S.J., Lustig, C., Sarter, M., 2009. CNTRICS final task selection: control of attention. *Schizophr. Bull.* 35, 182–196.
- Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9, 97–113.
- Poffenberger, A.T., 1912. Reaction time to retinal stimulation with special reference to time lost in conduction through nerve centers. *Arch. Psychol.* 21, 1–73.
- Power, J.D., Barnes, K.A., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2012. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *NeuroImage* 59, 2142–2154.
- Power, J.D., Barnes, K.A., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., in press. Steps toward optimizing motion artifact removal in functional connectivity MRI; a reply to Carp. *NeuroImage*.
- Robertson, L.C., Ivry, R., 2000. Hemispheric asymmetries: attention to visual and auditory primitives. *Curr. Dir. Psychol. Sci.* 9, 59–63.
- Robertson, L.C., Palmer, S.E., Gomez, L.M., 1987. Reference frames in mental rotation. *J. Exp. Psychol. Learn. Mem. Cogn.* 13, 368–379.
- Schroeder, C.E., Wilson, D.A., Radman, T., Scharfman, H., Lakatos, P., 2010. Dynamics of active sensing and perceptual selection. *Curr. Opin. Neurobiol.* 20, 172–176.
- 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. *Arch. Gen. Psychiatry* 67, 772–782.
- Sergent, J., Bindra, D., 1981. Differential hemispheric processing of faces: methodological considerations and reinterpretation. *Psychol. Bull.* 89, 541–554.
- Shelton, E.J., Knight, R.G., 1984. Inter-hemispheric transmission times in schizophrenics. *Br. J. Clin. Psychol.* 23 (Pt 3), 227–228.
- Shenton, M.E., Dickey, C.C., Frumin, M., McCarley, R.W., 2001. A review of MRI findings in schizophrenia. *Schizophr. Res.* 49, 1–52.
- Stephan, K.E., Friston, K.J., Frith, C.D., 2009. Dysconnection in schizophrenia: from abnormal synaptic plasticity to failures of self-monitoring. *Schizophr. Bull.* 35, 509–527.
- Uddin, L.Q., Mooshagian, E., Zaidel, E., Scheres, A., Margulies, D.S., Kelly, A.M., Shehzad, Z., Adelstein, J.S., Castellanos, F.X., Biswal, B.B., Milham, M.P., 2008. Residual functional connectivity in the split-brain revealed with resting-state functional MRI. *Neuroreport* 19, 703–709.
- Umiltà, C., Rizzolatti, G., Marzi, C.A., Zamboni, G., Franzini, C., Camarda, R., Berlucchi, G., 1974. Hemispheric differences in the discrimination of line orientation. *Neuropsychologia* 12, 165–174.
- Wada, Y., Nanbu, Y., Jiang, Z.Y., Koshino, Y., Hashimoto, T., 1998. Interhemispheric EEG coherence in never-medicated patients with paranoid schizophrenia: analysis at rest and during photic stimulation. *Clin. Electroencephalogr.* 29, 170–176.
- Walterfang, M., Yung, A., Wood, A.G., Reutens, D.C., Phillips, L., Wood, S.J., Chen, J., Velakoulis, D., McGorry, P.D., Pantelis, C., 2008. Corpus callosum shape alterations in individuals prior to the onset of psychosis. *Schizophr. Res.* 103, 1–10.
- White, T., Magnotta, V.A., Bockholt, H.J., Williams, S., Wallace, S., Ehrlich, S., Mueller, B.A., Ho, B.C., Jung, R.E., Clark, V.P., Lauriello, J., Bustillo, J.R., Schulz, S.C., Gollub, R.L., Andreasen, N.C., Calhoun, V.D., Lim, K.O., 2011. Global white matter abnormalities in schizophrenia: a multisite diffusion tensor imaging study. *Schizophr. Bull.* 37, 222–232.
- Whitford, T.J., Kubicki, M., Schneiderman, J.S., O'Donnell, L.J., King, R., Alvarado, J.L., Khan, U., Markant, D., Nestor, P.G., Niznikiewicz, M., McCarley, R.W., Westin, C.F., Shenton, M.E., 2010. Corpus callosum abnormalities and their association with psychotic symptoms in patients with schizophrenia. *Biol. Psychiatry* 68, 70–77.
- Whitford, T.J., Kubicki, M., Ghorashi, S., Schneiderman, J.S., Hawley, K.J., McCarley, R.W., Shenton, M.E., Spencer, K.M., 2011. Predicting inter-hemispheric transfer time from the diffusion properties of the corpus callosum in healthy individuals and schizophrenia patients: a combined ERP and DTI study. *NeuroImage* 54, 2318–2329.
- Whitford, T.J., Ford, J.M., Mathalon, D.H., Kubicki, M., Shenton, M.E., 2012a. Schizophrenia, myelination, and delayed corollary discharges: a hypothesis. *Schizophr. Bull.* 38, 486–494.
- Whitford, T.J., Wood, S.J., Yung, A., Cocchi, L., Berger, G., Shenton, M.E., Kubicki, M., Phillips, L., Velakoulis, D., Yolken, R.H., Pantelis, C., McGorry, P., Amminger, G.P., 2012b. Structural abnormalities in the cuneus associated with Herpes Simplex Virus (type 1) infection in people at ultra high risk of developing psychosis. *Schizophr. Res.* 135, 175–180.
- Winterer, G., Egan, M.F., Radler, T., Hyde, T., Coppola, R., Weinberger, D.R., 2001. An association between reduced interhemispheric EEG coherence in the temporal lobe and genetic risk for schizophrenia. *Schizophr. Res.* 49, 129–143.
- Woodruff, P.W., McManus, I.C., David, A.S., 1995. Meta-analysis of corpus callosum size in schizophrenia. *J. Neurol. Neurosurg. Psychiatry* 58, 457–461.
- Worsley, K., 2001. Statistical analysis of activation images. In: Jezzard, P., Matthews, P.M., Smith, S.M. (Eds.), *Functional MRI: An Introduction to Methods*. Oxford University Press, Oxford, UK.
- Zuo, X.N., Kelly, C., Di Martino, A., Mennes, M., Margulies, D.S., Bangaru, S., Grzadzinski, R., Evans, A.C., Zhang, Y.-F., Castellanos, F.X., Milham, M.P., 2010. Growing together and growing apart: regional and sex differences in the lifespan developmental trajectories of functional homotopy. *J. Neurosci.* 30, 15034–15043.