Frontotemporoparietal Asymmetry and Lack of Illness Awareness in Schizophrenia

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Abstract: *Introduction:* Lack of illness awareness or anosognosia occurs in both schizophrenia and right hemisphere lesions due to stroke, dementia, and traumatic brain injury. In the latter conditions, anosognosia is thought to arise from unilateral hemispheric dysfunction or interhemispheric disequilibrium, which provides an anatomical model for exploring illness unawareness in other neuropsychiatric disorders, such as schizophrenia. *Methods:* Both voxel-based morphometry using Diffeomorphic Anatomical Registration through Exponentiated Lie Algebra (DARTEL) and a deformation-based morphology analysis of hemispheric asymmetry were performed on 52 treated schizophrenia subjects, exploring the relationship between illness awareness and gray matter volume. Analyses included age, gender, and total intracranial volume as covariates. *Results:* Hemispheric asymmetry analyses revealed illness unawareness was significantly associated with right < left hemisphere volumes in the anteroinferior temporal lobe ($t = 4.83$, $P = 0.051$) using DARTEL, and the dorso-lateral prefrontal cortex ($t = 5.80$, $P = 0.003$) and parietal lobe ($t = 4.3$, $P = 0.050$) using the deformation-based approach. Trend level associations were identified in the right medial prefrontal cortex ($t = 4.49$, $P = 0.127$) using DARTEL. Lack of illness awareness was also strongly associated with reduced total white matter volume ($r = 0.401$, $P < 0.01$) and illness severity ($r = 0.559$, $P < 0.01$). *Conclusion:* These results suggest a relationship between anosognosia and hemispheric asymmetry in schizophrenia, supporting previous volume-based MRI studies in schizophrenia that found a relationship between illness unawareness and reduced right hemisphere gray matter volume. Functional imaging studies are required to examine the neural mechanisms contributing to these structural observations. *Hum Brain Mapp* 34:1035–1043, 2013. © 2012 Wiley Periodicals, Inc.

Key words: schizophrenia; insight; anosognosia; illness awareness; VBM; deformation-based analysis

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INTRODUCTION

Lack of illness awareness or anosognosia is common among individuals with schizophrenia [Buckley 2007; Jablensky et al., 1992; Olfson et al., 2006]. Lack of illness awareness contributes to medication nonadherence, poor treatment outcomes, higher rates of relapse, and rehospitalization [Amadoret et al., 1994; Drake et al., 2007; Kemp and David, 1996; Olfson et al., 2006]. Lack of illness awareness is also unresponsive to commonly used psychological interventions [Olfson et al., 2006].

The neural mechanisms of illness awareness in schizophrenia are not understood [David, 1990]. Anosognosia is also observed in right hemisphere lesions due to stroke, traumatic brain injury, frontotemporal, and Alzheimer's dementia [Orfei et al., 2008]. Anosognosia associated with right hemispheric lesions or interhemispheric dysfunction may provide an anatomical model for exploring the neural correlates in other neuropsychiatric conditions with illness unawareness, such as schizophrenia [Shad et al., 2007].

To date, a number of studies have used volume-based analyses to study the structural correlates of illness awareness and schizophrenia. Investigations that used a region of interest approach demonstrated volumetric reductions within right frontal regions, specifically the orbitofrontal (OFC), dorsolateral prefrontal (DLPFC), anterior cingulate cortices [Flashman et al., 2001; Sapara et al., 2007; Shad et al., 2006, 2004], and also the right parietal lobe [Shad et al., 2007]. The few studies that used voxel-based morphometry (VBM), which allows for the investigation of focal differences in neuroanatomy across the whole brain, however, have produced mixed results [Bassitt et al., 2007; Berge et al., 2010; Cooke et al., 2008; Morgan et al., 2010; Parellada et al., 2011]. One study of schizophrenia outpatients found no association between illness awareness and brain volume [Bassitt et al., 2007]. Another study of subjects with chronic schizophrenia and schizoaffective disorder found contributions from different regions within the temporal and parietal lobes associated with different aspects of illness awareness [Cooke et al., 2008]. Similarly inconsistent, studies of first episode patients have implicated a variety of brain regions in association with poor illness awareness, including decreased cingulate and superior temporal lobe volume bilaterally, and decreased left insula and right cuneus volumes [Morgan et al., 2010]; decreased gray matter volume in the cerebellum, inferior temporal gyrus, and inferior and medial frontal gyri bilaterally [Berge et al., 2010]; and reduced frontal and parietal volumes [Parellada et al., 2011].

The major limitation to compare volume-based studies of illness awareness is the methodological differences between them. Some investigations have included all persons with psychosis (schizophrenia and schizoaffective disorder) versus others that were limited to first episode psychosis. Studies also differed in terms of the MR image preprocessing algorithms and illness awareness measurements that were used. Measures of illness awareness were

devised by combining different aspects of scales, performing factor analyses, or using different scales entirely.

Because of the discrepancies within the literature among volume based studies, the aim of this work was to test the hypothesis of an association between reduced right hemisphere brain volume (relative to the left hemisphere) and illness awareness in schizophrenia. To accomplish this, an analysis of hemisphere asymmetry was performed, which may be more sensitive to these differences than a standard VBM approach. The findings were hypothesized to be lateralized to the right hemisphere with reduced brain volume in the prefrontal cortex, anterior temporal lobe, insula, and parietal regions based on the neurological literature and the studies in schizophrenia that used a region of interest approach.

METHODOLOGY

Subjects

This study is a cross-sectional analysis that included 52 treated voluntary schizophrenia subjects recruited by advertisement/flyers posted across the hospital's campus and/or referral by the psychiatrist of record. The sample analyzed for the current study was collected by our laboratory from various PET studies that were approved by the Research Ethics Board of the Centre for Addictions and Mental Health, Toronto. Written informed consent was obtained after full explanation of the study procedures and risks. An assessment of psychiatric disorders was performed using the MINI-Plus structured interview [Sheehan et al., 1998]. Symptoms of schizophrenia were assessed using the Positive and Negative Symptom Scale (PANSS) by experienced psychiatrists trained in administering the PANSS instrument [Kay et al., 1987]. Subjects were excluded if they had a history of head trauma resulting in loss of consciousness that required medical intervention; positive screen for pregnancy or were breast feeding at the time of the study; serious or unstable medical or neurological condition; met DSM-IV TR [APM, 2000] criteria for current substance abuse (except nicotine and caffeine) or dependence; serious suicidal ideation or had a likelihood of a serious suicide or homicide attempt; schizoaffective disorder, schizophreniform disorder or any affective disorder; or metal implants that would preclude the MRI scan. Urine toxicology screens were done as part of the initial assessment. Standard urine pregnancy tests were performed to exclude pregnancy.

Statistical Analysis

Statistical analyses of clinical and demographic variables were carried out with SPSS software (version 13.0). Anosognosia was measured using the PANSS insight and judgment item (G12), which is the most widely used and validated measure of illness awareness; highly correlated

($r > 0.88$) with more complex illness awareness or insight scales [Sanz et al., 1998]. Means and standard deviations were calculated for the demographic and clinical data, gray, white, CSF, and total intracranial volume. Spearman rho (r) correlations were performed between these variables and illness awareness scores. Mann-Whitney U tests were used to compare illness awareness scores among males and females. The significance level for tests was established at $P < 0.05$.

MR Imaging Parameters

Participants underwent high-resolution MRI fast spin echo T_1 -weighted imaging (fast spoiled gradient echo, TE = 5.3–15 ms, TR = 8.9–12 ms, FOV = 20 cm 3D, 256×256 , voxel $0.8 \times 0.8 \times 1.5 \text{ mm}^3$ isotropic, NEX = 1) acquired on a 1.5-T Sigma-GE scanner (General Electric Medical Systems, Milwaukee, WI).

MRI Data Analysis

MRI data were analyzed using SPM8 software package (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>) running on MATLAB (version R2010a). Each T_1 structural MRI was preprocessed using the Diffeomorphic Anatomical Registration through Exponentiated Lie Algebra (DARTEL) method outlined in the SPM8 manual (see SPM website). The voxel size for all images after normalization was $2 \times 2 \times 2 \text{ mm}^3$. The segmented normalized images were smoothed to a full width half maximum Gaussian kernel of 8 mm [Honea et al., 2005; White et al., 2001; Wilke et al., 2003]. A visual check was performed to ensure the quality, and origin of each image was oriented to the anterior commissure-posterior commissure line using the SPM check registration function.

In order to perform a hemispheric analysis, each native image was flipped along the mid-sagittal plane to create a mirror coronal image volume. Both the native and flipped images were preprocessed using the same DARTEL method described above. Following normalization, the flipped image was subtracted from the native image using the ImCalc function on SPM8 to create a delta image volume, capturing the voxel-by-voxel differences between each hemisphere.

To lend support to the initial analysis of hemispheric asymmetry performed with DARTEL, a second deformation-based morphology strategy that does not involve tissue segmentation was used [Chung et al., 2001]. First, each native MRI volume was corrected for intensity nonuniformities due to MRI gradient inhomogeneities [Sled et al., 1998] and then transformed to MNI space using a linear transformation with 9 degrees of freedom (three scales, rotations, and translations). The transformed volume was then flipped along the mid-sagittal plane to create a mirror coronal image of it. All volumes were transformed such that the mid-sagittal plane was parallel to the Y - Z plane

by applying half the rigid-body transformation (three translations and rotations). Each MRI volume was matched and nonlinearly registered to its respective flipped coronal image volume. The generated transformed image volume was used for the asymmetry analysis. All linear [Collins et al., 1994] and nonlinear [Collins et al., 1995] transformations were estimated using the mni_autoreg package, which is part of the MINC toolbox (<http://www.bic.mni.mcgill.ca/ServicesSoftware/MINC>). Intrasubject nonlinear transformations were estimated using an optimized version of the ANIMAL algorithm [Robbins et al., 2004]. The final transformation is represented by a set of local translations defined on grid nodes with 2 mm spacing. Each nonlinear transformation was then blurred with an 8 mm Gaussian kernel in each dimension and the Jacobian determinant [Chung et al., 2001] (a measure of local expansion and contraction) of each transformation was calculated. In order to perform a group analysis, Jacobian determinants were nonlinearly transformed to MNI using the nonlinear transformation [Collins et al., 1995] that matches each flipped input volume to the ICBM 152 template [Grabner et al., 2006].

Global Gray and White Matter Volume Analyses

In order to obtain volume measurements of the brain lobes of interest, the ANIMAL algorithm [Collins et al., 1995] was used. This technique uses spatial and intensity priors defined on a template to estimate a GM/WM classification. A lobe-wise atlas defined on the template is then nonlinearly transformed using the inverse of the subject-to-atlas nonlinear transformation [Collins et al., 1995]. The regions of interest included were the gray and white matter volumes of the frontal, parietal, and temporal lobes. Partial correlations were performed with illness awareness, controlling for age, gender, and total intracranial volume (given by the sum of all the voxels within the gray matter, white matter, and cerebrospinal fluid compartments of each subject). A Bonferroni correction was calculated to control for multiple comparisons, setting the significance level at $P < 0.01$.

VBM and Brain Hemisphere Asymmetry Analyses

To examine the relationship between regional gray matter volume and illness awareness using VBM, a regression analysis was carried out with SPM8. Similarly, to investigate the relationship between regional gray matter hemispheric asymmetry (delta images) and illness awareness, a separate regression analysis was performed with SPM8. In both the analyses, age, gender, and total intracranial volume (given by the sum of all the voxels within the gray matter, white matter, and cerebrospinal fluid compartments of each subject) were entered as covariates.

TABLE I. Subject demographic and clinical data, and Spearman correlations (*r*) with lack of illness awareness (PANSS G12 item)

	Mean (SD)	<i>r</i>
<i>N</i>	52	
Age, range	41.5 (14.5), 23–77	0.121, <i>P</i> = 0.395
Gender (M:F)	33:19	<i>z</i> = −1.051, <i>P</i> = 0.293 ^a
Age of illness onset	24.5 (5.7)	0.088, <i>P</i> = 0.537
Duration of illness	17.0 (14.1)	0.018, <i>P</i> = 0.898
Total PANSS score ^b	43.0 (11.6)	0.559*
PANSS positive score	10.8 (3.6)	0.397*
PANSS negative score	12.0 (6.4)	0.503*
PANSS general score ^b	20.3 (5.6)	0.498*
Total intracranial volume	1655 cm ³ (215.8)	−0.150, <i>P</i> = 0.288
Antipsychotic agent		$\chi^2 = 1.88$, <i>df</i> = 3, <i>P</i> = 0.597 ^c

^aMann-Whitney *U*-test.^bExcluding insight and judgment item G12.^cKruskal-Wallis *H*-test.**P* < 0.01.

Each within-group analysis of normalized smoothed gray matter images comprised two contrasts, one to test for positive associations between regional gray matter volume and illness awareness scores, and the other to test for negative associations. Correlations were investigated on a voxel-by-voxel basis. As the a priori hypothesis was specific to the right frontal, parietal, and temporal lobes a mask was used to confine the statistical search to these regions. The threshold for these a priori regions was set at *P* < 0.001 level of significance (*t* > 3.25). A cluster was reported as significant if it was ≥ 20 voxels in size and the peak survived a family-wise error (FWE) correction for multiple comparisons of *P* < 0.05 [Friston et al., 1996].

For our second deformation-based morphology strategy, voxel-wise statistics were estimated using the multistat function in the fmristat package [Worsley et al., 2002] (<http://www.math.mcgill.ca/keith/fmristat/>). Correction for multiple comparisons using a FWE of *P* < 0.05 was estimated with the stat_summary function.

RESULTS

Clinical and Demographic Variables

The demographic and clinical data are presented in Table I. The associations between lack of illness awareness scores and demographic and clinical variables are also presented in Table I. Illness severity (total PANSS, positive, negative, and general scores) was strongly associated with lack of illness awareness. No other significant associations were identified.

Global Brain Volume

In the analysis investigating the relationship between lack of illness awareness and total gray and white matter volumes in the frontal, parietal, and temporal lobes, controlling for age, gender, and total intracranial volume, significant correlations were found between lack of illness awareness and reduced global white matter volume and reduced parietal lobe white matter volume (Table II). There were no significant associations found between gray matter volume and illness awareness scores.

VBM: Gray Matter Volume and Illness Awareness

In the analysis exploring the relationship between gray matter volume using DARTEL and illness unawareness, controlling for age, gender, and total intracranial volume, no significant positive or negative relationships were identified.

Brain Hemisphere Asymmetry and Illness Awareness

The analysis of hemisphere asymmetry using DARTEL revealed associations between lack of illness awareness and right < left hemisphere volumes in the anteroinferior temporal lobe, OFC, and medial prefrontal cortex (Table III and Fig. 1). Only the finding in the anteroinferior temporal lobe survived correction for multiple comparisons. Trend level

TABLE II. Partial correlations (*r*) between lack of illness awareness (PANSS G12 item) and regional brain volumes obtained with the ANIMAL algorithm (Collins et al., 1995)

Region	Mean (SD) cm ³	<i>r</i>
Gray matter		
Left frontal	111.8 (25.7)	0.186
Right frontal	112.4 (27.3)	0.193
Left parietal	54.3 (10.9)	0.174
Right parietal	53.8 (10.8)	0.213
Left temporal	76.4 (13.6)	0.177
Right temporal	75.2 (13.4)	0.221
White matter		
Left frontal	83.8 (15.0)	−0.342
Right frontal	85.5 (15.4)	−0.321
Left parietal	48.0 (11.4)	−0.378*
Right parietal	46.6 (11.6)	−0.376*
Left temporal	42.7 (8.6)	−0.318
Right temporal	41.6 (8.7)	−0.280
Left total gray matter	333.8 (63.4)	0.193
Right total gray matter	332.3 (65.0)	0.204
Left total white matter	207.5 (40.7)	−0.401*
Right total white matter	204.8 (41.6)	−0.393*
Total intracranial gray matter	666.1 (128.2)	0.199
Total intracranial white matter	412.2 (82.0)	−0.401*

**P* < 0.01

TABLE III. Relationship between gray matter hemisphere asymmetry and illness awareness, controlling for age, gender, and total intracranial volume

					Cluster Maxima					
Brain Region	BA	Voxels per cluster ^a	<i>P</i> value Uncorrected	<i>P</i> value FWE corrected	<i>x</i>	<i>y</i>	<i>z</i>	<i>T</i> value	<i>P</i> value Uncorrected	<i>P</i> value FWE corrected
VBM										
Right ant. temporal lobe	20	165	0.049	0.130	51	0	−50	4.83	<0.001	0.051
Right medial PFC	10	29	0.389	0.664	1	50	0	4.49	<0.001	0.127
Right lateral OFC	47	172	0.045	0.119	48	48	−12	4.04	<0.001	0.363
Deformation-based										
Right dorsolateral PFC	46	1457	<0.001	0.023	27	49	24	5.80	<0.001	0.003
Right angular gyrus	39	751	<0.001	0.345	44	−65	44	4.30	<0.001	0.050
Right insula	47	341	<0.001	0.300	43	23	2	3.57	<0.001	0.350

PFC, prefrontal cortex; OFC, orbitofrontal cortex; FWE, family wise error.

^aVBM = 1.5 mm³ and deformation-based = 1 mm³.

significance was obtained for the right medial prefrontal cortex (Table III and Fig. 1).

The second analysis of hemisphere asymmetry using the deformation-based morphology strategy that does not involve tissue segmentation showed associations between lack of illness awareness and right < left hemisphere volumes in the DLPFC, angular gyrus/parietal lobe, and insula (Table III and Fig. 1). The associations in the DLPFC and parietal lobe survived correction for multiple comparisons.

DISCUSSION

Anosognosia, was first coined by Babinski [1914], and literally means lacking knowledge (gnosis) of disease (nosos). It is commonly associated with right hemispheric damage secondary to stroke, neurodegeneration, or brain injury [Orfei et al., 2008]. Anosognosia in these contexts provides a neuroanatomical prototype for exploring lack of illness awareness in other neuropsychiatric conditions, such as schizophrenia [Shad et al., 2007]. An intriguing aspect of schizophrenia is that persons with the disorder vary in their degree of anosognosia. They can have equally bizarre delusions or perceptual disturbances but can be quite dissimilar in their ability to recognize that these experiences arise from their mind rather than a part of objective reality.

This study is the first to perform a hemispheric asymmetry analysis exploring the relationship between gray matter volume and illness unawareness in patients with schizophrenia. The results revealed an association between anosognosia in schizophrenia and relatively reduced gray matter volume in right hemisphere frontotemporoparietal regions, namely the right anteroinferior temporal lobe, DLPFC and right parietal lobe (i.e., angular gyrus). These findings support the results of other volume-based imaging studies that used a region of interest approach, which

have collectively identified an association between reduced right hemisphere frontotemporoparietal gray matter volume and anosognosia in schizophrenia [Flashman et al., 2001; Sapara et al., 2007; Shad et al., 2004,2006,2007].

For most healthy individuals, anatomical and functional asymmetry is the norm with respect to language ability and handedness, which are typically lateralized to the left hemisphere in association with greater left planum temporale volume. The right hemisphere (in particular, the right parietal lobe), to a lesser degree, also appears dominant for certain visuospatial abilities [Hugdahl, 2000; Toga and Thompson, 2003]. In contrast to healthy individuals, there is some, although conflicting evidence that persons with schizophrenia have reduced temporal lobe asymmetry, which is proposed to contribute to the experience of auditory hallucinations and other positive symptoms [Oertel-Knochel and Linden, 2011].

To explain the role of the right hemisphere in illness awareness, the cerebral hemispheres may serve distinct functions when confronted with discrepant cognitive or sensory stimuli [Ramachandran et al., 2007]. The left hemisphere may be responsible for various classical psychodynamic defense mechanisms, such as denial, rationalization, confabulation, and repression, to reconcile conflicting or threatening information in order to maintain mental stability and coherence [Ramachandran, 1995]. The right hemisphere, on the other hand, is hypervigilant to sensory inconsistencies serving to orient and reality test in response to divergent or unexpected stimuli [Posner and Petersen, 1990; Ramachandran, 1995; Ramachandran et al., 2007]. Together, the hemispheres provide a system of “checks” (right hemisphere) and “balances” (left hemisphere). The right hemisphere brings to consciousness threats to self (one’s ingrained biopsychosocial patterns of expectations [Basch, 1988]), whereas the left hemisphere attempts to reconcile and integrate conflicting or objectionable stimuli, such as the illness itself. This theory gains

Figure 1.

Regional gray matter hemisphere asymmetry correlations (right < left) with lack of illness awareness.

some support from the neurochemical literature [Toga and Thompson, 2003; Tucker and Williamson, 1984], which shows a leftward asymmetry of dopamine levels in the globus pallidus and basal ganglia [Glick et al., 1982; Wagner et al., 1983], and a rightward lateralization of norepinephrine neurons in the ventrolateral nuclei of the thalamus [Oke et al., 1978]. The above notion of hemispheric specialization remains highly debated and requires further study [Toga and Thompson, 2003].

There are a number of methodological issues with voxel-based MRI data analysis that can contribute to the inconsistency and reliability of findings, including differing tissue segmentation and normalization algorithms, and smoothing filter size [Henley et al., 2010; Honea et al., 2005; Tsang et al., 2008; White et al., 2001]. In the present

study, VBM was performed using DARTEL, which achieves more accurate intersubject registration of brain images, providing better localization and sensitivity than the older unified segmentation method [Ashburner, 2007; Ashburner and Friston, 2005]. To ensure the reliability of the findings from the initial asymmetry analysis, a separate investigator carried out a second deformation-based algorithm that uses the Jacobian of the deformation field to detect volumetric changes and does not involve tissue segmentation [Chung et al., 2001]. Deformation-based procedures are limited by the accuracy of the nonlinear transformation and the heterogeneity of sulcal patterns in both hemispheres (see for example [Van Essen 2005]). In this case, however, the accuracy of the ANIMAL algorithm has been verified in several recent studies [Chakravarty et al.,

2009; Robbins et al., 2004] and compares favorably to other nonlinear registration algorithms [Klein et al., 2009]. Although the results of the hemisphere asymmetry analyses were not precise in terms of the clusters identified (i.e., reduced right anteroinferior temporal and medial prefrontal vs. right dorsolateral PFC and angular gyrus) the main hypothesis of relatively reduced frontotemporoparietal volume was confirmed.

In addition to the main finding, we also found an association between lack of illness awareness and reduced white matter volume (Table II). Diverse regional deficits in white (and gray) matter volume are commonly reported in schizophrenia [Honea et al., 2005]. The effects of these volumetric changes are unclear but may represent a cortical-subcortical or interhemispheric “misconnection syndrome” [Spalletta et al., 2003] that permits left hemisphere dominance over the right. These findings require replication. Similar to a prior VBM study [Bassitt et al., 2007], this study did not identify any significant associations between regional gray matter volume and a lack of illness awareness. Surprisingly, no associations were identified between regional gray matter volumes and anosognosia using a region of interest approach (Table II).

The findings of this study are limited by a few factors. First, we used only one measure of insight. Although lack of insight is measured by a single item on the PANSS, it has been strongly correlated with other more elaborate standardized measures of insight (Pearson's $r > 0.88$) [Sanz et al., 1998]. Moreover, factor analyses of the various components of insight (i.e., general illness awareness, symptom awareness, awareness of the consequences of the disorder, and awareness of need for treatment) have produced single factor solutions, suggesting that these components may represent a single construct [Birchwood, 1994; Cuesta et al., 2000; McEvoy et al., 1989; Mohamed et al., 2009]. Second, the illness unawareness scores were highly correlated with illness severity (Table I). To address the issue of colinearity, subsequent analyses were performed to assess the relationship between illness severity (PANSS total scores, positive symptom, negative symptom and general symptom subscale scores, and delusion item P1 scores) and regional hemisphere asymmetry using VBM. No significant associations were identified in any of these subsequent analyses (Supporting Information Tables A–E), suggesting the study's findings are specific to anosognosia. Third, our sample consisted of treated schizophrenia subjects ($n = 52$) receiving different antipsychotics, which may have differential effects on illness awareness. That being said, we did not see a significant effect of either illness duration or antipsychotic agent on anosognosia (Table I). Moreover, there is little-to-no evidence within the literature to support the possibility of an effect of antipsychotic medication type on illness awareness [Pallanti et al., 1999].

In summary, this is the first study to perform an analysis of hemisphere asymmetry for anosognosia in schizophrenia. The findings of an association between relatively reduced right regional frontotemporoparietal brain volume

and lack of illness awareness are in support of prior volume-based studies that used a region of interest approach, however, require replication.

The study authors are unaware of any functional imaging studies that have directly explored the relationship between illness awareness and schizophrenia. To determine the degree to which the right hemisphere and its associated regions are involved in insight in schizophrenia future functional imaging research is essential. By identifying the brain correlates of anosognosia, common to multiple psychiatric and neurological conditions, the possibility of direct intervention will emerge, including the use of novel pharmacological compounds and transcranial magnetic stimulation to target the neurocircuit of illness awareness.

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