◆ Human Brain Mapping 35:4729–4740 (2014) ◆

The Structural Neuroanatomy of Metacognitive Insight in Schizophrenia and Its Psychopathological and Neuropsychological Correlates

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Abstract: Lack of insight into illness is a multidimensional phenomenon that has relevant implications on clinical course and therapy compliance. Here, we focused on metacognitive insight in schizophrenia, that is, the ability to monitor one's changes in state of mind and sensations, with the aim of investigating its neuroanatomical, psychopathological, and neuropsychological correlates. Fifty-seven consecutive patients with Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision) diagnosis of schizophrenia were administered the Insight Scale, and comprehensive psychopathological and neuropsychological batteries. They underwent a high-resolution T1-weighted magnetic resonance imaging investigation. Gray matter (GM) and white matter (WM) volumes were analyzed on a voxel-by-voxel basis using Statistical Parametric Mapping 8. Reduced metacognitive insight was related to reduced GM volumes in the left ventrolateral prefrontal cortex, right dorsolateral prefrontal cortex and insula, and bilateral premotor area and putamen. Further, it was related to reduced WM volumes of the right superior longitudinal fasciculum, left corona radiata, left forceps minor, and bilateral cingulum. Increased metacognitive insight was related to increased depression severity and attentional control impairment, while the latter was related to increased GM volumes in brain areas linked to metacognitive insight. Results of this study suggest that prefrontal GM and WM bundles, all implied in cognitive control and self-reflection, may be the neuroanatomical correlates of metacognitive insight in schizophrenia. Further, higher metacognitive insight is hypothesized to be a risk factor for depression which may subsequently impair attention. This line of research may provide the basis for the development of cognitive interventions aimed at improving self-monitoring and compliance to treatment. *Hum Brain Mapp 35:4729–4740, 2014.*

Key words: awareness; self-monitoring; prefrontal cortex; white matter; cognition; psychosis

Contract grant sponsor: Italian Ministry of Health; Contract grant numbers: RC08A, RC09A, RC10A, RC11A, and RC12A.

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Received for publication 15 November 2013; Revised 17 February 2014; Accepted 25 February 2014.

DOI 10.1002/hbm.22507
Published online 3 April 2014 in Wiley Online Library (wileyonlinelibrary.com).

INTRODUCTION

Insight into illness in clinical psychiatry is defined as the awareness to be ill and changed plus the ability to evaluate the causes and the severity of illness (Jaspers, 1963). Lack of insight is a key feature in schizophrenia spectrum disorders and gained growing attention in a clinical perspective due to its incidence in the psychiatric population, which is estimated to range between 50 and 80% (Amador and Gorman, 1998). Given its detrimental impact on relapses, number of hospitalizations, compliance to treatment and symptom remission, impaired insight may have important consequences for quality of life and functioning in a work setting (Boyer et al., 2012; Erickson et al., 2011; Kurtz and Tolman, 2011; Mohamed et al., 2009).

Insight is a multidimensional phenomenon which implies several facets at least partially independent from each other (David et al., 2012; Orfei et al., 2008). A classical approach focuses on clinical insight (Amador and Strauss, 1993; David, 1990), that is awareness of illness and the capacity to relabel symptoms as pathological phenomena. At the beginning of 2000, Beck et al. (2004) developed the construct of cognitive insight, which reflects the ability to monitor one's ongoing mental activities. Thus, cognitive insight expresses a general cognitive attitude of information processing, rather than being related specifically to awareness of illness in schizophrenia. In the same years, Marková and Berrios (1992) and Marková et al. (2003) challenged an innovative approach to the issue, focusing on metacognitive processes applied specifically to awareness of illness. Metacognition is a high-order cognitive function which consists in one's knowledge concerning one's cognitive processes and products or anything related to them, such as perception, memory, problem solving and behavior (Flavell, 1979).

The authors stemmed from the assumption that when individuals become mentally unwell, a number of cognitive and experiential changes occur affecting perception of self, of one's environment and of the interaction between these (Marková et al., 2003). In this perspective, insight into illness is considered a form of ongoing self-monitoring of such changes in subjective self-experience and the ability to feel and express the related emotional unease in patients affected by schizophrenia. Given these considerations, in the present article from now on we will refer to this specific dimension of self-awareness as metacognitive insight. The investigation of metacognitive insight gives the advantage to be less susceptible to self deception or simulation than clinical insight. In fact, while clinical insight does not imply necessarily any actual significant change in patients' underlying belief system nor in one's own behavior (Bora et al., 2007; Jaspers, 1963), metacognitive insight best reflects one's actual judgments about the self. The Insight Scale (IS), a self-rated questionnaire, was developed to measure such construct. While several studies have described the neural correlates of clinical insight, reporting an involvement of prefrontal areas (Cooke et al., 2008; Flashman et al., 2001; Laroi et al., 2000; Morgan et al., 2010; Sapara et al., 2007; Shad et al., 2004, 2006), temporal areas (Cooke et al., 2008; Ha et al., 2004; Palaniyappan et al., 2011), or even no structural alterations accompanying poor clinical insight (Bassitt et al., 2007; Buchy et al., 2009; Rossell et al., 2003), only few studies investigated the neural correlates of cognitive insight. Such studies highlighted the involvement of the ventrolateral prefrontal area (Orfei et al., 2013), the hippocampus (Buchy et al., 2010), and the fornix (Buchy et al., 2012).

However, to our knowledge, no investigation on the brain areas involved in metacognitive insight has been carried out so far.

Thus, the main aim of the present study was to investigate the gray matter (GM) and white matter (WM) neuroanatomical correlates of metacognitive insight, using a volumetric neuroimaging approach. In order to do that, the IS was administered to a sample of patients with diagnosis of schizophrenia, and the neuroanatomical correlates of the IS score were explored by performing whole brain GM and WM volumetric analyses. Given the well-established involvement of brain prefrontal areas in self-reflection and self-monitoring tasks (Burianova and Grady, 2007; Liemburg et al., 2012; Orfei et al., 2013), we hypothesized that increased metacognitive insight would be related to: (a) GM volume of ventral and dorsal lateral prefrontal cortices (VLPFC and DLPFC) and (b) WM volume of fascicules connecting prefrontal areas. Secondarily, we explored also the psychopathological and neuropsychological correlates of metacognitive insight.

METHODS

Subjects

We recruited 75 consecutive outpatients diagnosed with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision; DSM-IV-TR; APA, 2000) criteria. All patients were diagnosed by one senior clinical psychiatrist (GS) using the structured clinical interview for DSM-IV-TR (SCID-I/P; First et al., 2002). Other inclusion criteria were (1) age between 18 and 65 years; (2) at least 8 years of education; (3) no dementia or cognitive deterioration according to the DSM-IV-TR criteria, and a Mini-Mental State Examination (MMSE; Folstein et al., 1975) score higher than 24, consistent with normative data in the Italian population (Measso et al., 1993); and (4) suitability for magnetic resonance imaging (MRI) scan. Exclusion criteria were (1) a history of alcohol or drug dependence or abuse in the last two years according to the DSM-IV-TR diagnostic criteria, (2) a history of traumatic head injury, (3) any past or present major medical or neurological illness, (4) any other psychiatric disorder or mental retardation diagnosis, and (5) MRI evidence of focal parenchymal abnormalities or cerebrovascular diseases. In particular, the presence, severity, and

location of vascular lesions were rated according to a protocol designed for the Rotterdam Scan Study. Generally, they are considered present in cases of hyperintense lesions on both proton-density and T2-weighted and were rated semiquantitatively as 0 (none), 1 (pencil-thin lining), 2 (smooth halo), or 3 (large confluent) for three separate regions; adjacent to frontal horns (frontal caps), adjacent to the wall of the lateral ventricles (bands), and adjacent to the occipital horns (occipital caps). The total vascular lesion load was calculated by adding the region-specific scores (range, 0–9). In the present study, only patients rated 0 were included. Of the initial sample of 75 patients, 5 were excluded for cognitive deterioration, 7 for comorbid substance use disorders, 5 for comorbid medical or neurological illnesses, and 1 for previous traumatic brain injury with lack of consciousness. Thus, the final sample consisted of 57 outpatients. All patients were in a phase of stable clinical compensation. Age at onset was defined as age at first hospitalization or, when possible, age at onset of positive or negative symptoms before the first hospitalization. Extrapyramidal side effects due to current treatment were assessed by the Simpson–Angus Rating Scale (SARS; Simpson and Angus, 1970). The Abnormal Involuntary Movement Scale (AIMS) was used to assess tardive dyskinesia; however, no patient suffered from this disturbance. All patients were receiving stable oral doses of one or more atypical antipsychotic drugs such as risperidone, quetiapine, or olanzapine. Antipsychotic dosages were converted to estimated equivalent dosages of olanzapine by using a standard table (Woods, 2003).

Our local Ethics Committee approved the study protocol. Written informed consent was obtained from all patients after they received a full explanation of the study procedures.

Psychopathological and Neuropsychological Assessment

The Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) was administered to rate the severity of psychopathological symptoms. The PANSS rates the patient from 1 to 7 on 30 different symptoms based on the interview as well as reports of family members or primary care hospital workers. The symptoms are grouped in three global scales, i.e., Positive Symptom Scale, Negative Symptom Scale, and the General Psychopathology Scale and five subscales, i.e., Paranoid-Belligerence, Anergia, Depression, Activation, and Thought Disturbance. As 1, rather than 0, is given as the lowest score for each item, a patient cannot score lower than 30 for the total PANSS score. PANSS ratings were obtained on all information available pertaining to the last week of the assessment.

With regard to the neuropsychological assessment, to obtain a global index of cognitive deterioration, the MMSE was administered. This is an amply utilized neurocognitive screening test measuring orientation, language, verbal memory, attention, visuospatial function, and mental control. It is composed of 16 items, with scores ranging from 30 (no impairment) to 0 (maximum impairment). Several tests were selected from the Mental Deterioration Battery (MDB; Carlesimo et al., 1996) to provide information about the functionality of different cognitive domains such as: verbal memory [MDB Rey's 15-word Immediate Recall (RIR) and Delayed Recall (RDR)]; short-term visual memory (MDB Immediate Visual Memory); logical reasoning [MDB Raven's Progressive Matrices' 47 (PM47)]; simple constructional praxis [MDB Copying Drawings (CD) and CD with Landmarks (CDL)]; language (MDB Phonological Verbal Fluency (PVF) and semantic fluency [Category Fluency test (CF); Lucas et al., 1998]; executive functions [Modified Wisconsin Card Sorting test (MWCST); Heaton et al., 1993]; divided attention and attentional control [Double Barrage (DB) test]. The order of administration of all scales was the same for all subjects. The diagnostic and psychopathological battery, included the IS, was administered before the cognitive battery. Assessment of inter-rater reliability for raters in this study was in the excellent to good range for all the psychopathological and neuropsychological scales used, with intraclass correlations ranging from 0.80 to 0.93. At last, the pharmacological side effect assessment was performed.

Metacognitive Insight Assessment

The IS was originally developed in 1992 (Marková and Berrios, 1992) as a 32-item questionnaire and a three-choice answer scale (yes/no/do not know). A subsequent revision (Marková et al., 2003) was realized, by deleting, adding or rephrasing some items. The final refined version resulted in a 30-item questionnaire, each consisting in a sentence with which the subject is asked to agree (Yes) or not (No). When patients agree with items relating to awareness of changes in mental states and in their interaction with the outside world, they are deemed as insightful and characterized by a functional self-monitoring ability, and gain a score of 1. Otherwise, if the subjects fail to detect these inner changes, they are considered as characterized by a defective self-monitoring resulting with a poor insight, and gaining a score of 0. Thus, a sum score of 30 indicates full insight, while a sum score of 0 indicates minimum insight. The IS has proved to be valid and reliable for individuals with schizophrenia (Marková et al., 2003). We administered a validated Italian version of the IS (Orfei et al., 2007).

Image Acquisition and Processing

Participants underwent the same imaging protocol, which included standard clinical sequences (FLAIR, DP-T2-weighted) and a whole-brain 3D high-resolution T1-weighted sequence, performed with a 3T Allegra MR imager (Siemens, Erlangen, Germany). Volumetric whole-brain T1-weighted images were obtained in the sagittal plane using a modified driven equilibrium Fourier

transform (MDEFT) sequence [echo time/repetition time- = 2.4/7.92 ms, flip angle 15°, voxel-size 1 mm × 1 mm × 1 mm]. All planar sequence acquisitions were obtained in the plane of the AC–PC line. Particular care was taken to center subjects' head in the head coil and to restrain their movements with cushions and adhesive medical tape.

T1-weighted images were processed and examined by using the SPM8 software (Wellcome Department of Imaging Neuroscience Group, London, UK; http://www.fil.ion.ucl.ac.uk/spm), specifically the VBM8 toolbox (http://dbm.neuro.unijena.de/vbm.html), running in Matlab 2007b (MathWorks, Natick, MA). The toolbox extends the unified segmentation model (Ashburner and Friston, 2005) consisting of MRI field intensity inhomogeneity correction, spatial normalization and tissue segmentation at several preprocessing steps to further improve the quality of data preprocessing. Initially, to increase the signal-to-noise ratio in the data, an optimized block wise nonlocal-means filter was applied to the MRI scans using the Rician noise adaption (Wiest-Daessle et al., 2008). Then, an adaptive maximum a posteriori segmentation approach extended by partial volume estimation was employed to separate the MRI scans into GM, WM, and cerebrospinal fluid. The segmentation step was finished by applying a spatial constraint to the segmented tissue probability maps based on a hidden Markow Random Field model to remove isolated voxels which were unlikely to be a member of a certain tissue class and to close holes in clusters of connected voxels of a certain class, resulting in a higher signal-to-noise ratio of the final tissue probability maps. Then, the iterative high-dimensional normalization approach provided by the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (Ashburner, 2007; DARTEL) toolbox was applied to the segmented tissue maps in order to register them to the stereotactic space of the Montreal Neurological Institute (MNI). The tissue deformations were used to modulate participants' GM and WM tissue maps. Voxel values of the resulting normalized and modulated GM and WM segments indicated the probability (between 0 and 1) that a specific voxel belonged to the relative tissue. The modulated and normalized GM and WM segments were written with VBM8 standard isotropic voxel resolution of 1.5 mm^3 and smoothed with a 6 mm FWHM Gaussian kernel, thus obeying the "rule of thumb" that the FWHM should be at least twice the voxel dimension in order to ensure a Gaussian distribution of the residuals of the General Linear Model (Moraschi et al., 2010). The segmented, normalized, modulated and smoothed GM and WM images were used for analyses.

Statistical Analyses

Statistical analyses of clinical variables were performed with Statview Software.

Neuropsychological and psychopathological predictors (considered as independent variables) of IS score (considered as the dependent variable) were assessed by using stepwise multiple regression analyses, with a forward procedure and an F to enter of 4.

Preselection of independent variables to include in the stepwise regression models was done by using correlation analyses and Fisher's r to z transformation, in order to determine the significance of correlations. In the stepwise multiple regression analysis only variables with $P < 0.05$ in the preselection correlation analyses were included as independent variables.

To identify the brain regions in which patients showed GM or WM volumetric correlates of the IS, two multiple regression models (one for GM and one for WM) were adopted using the IS as a regressor, and age and years of formal education as covariates of no interest. Statistical analyses were carried out at voxel level using SPM8. To avoid type I errors (i.e., accepting false positives) all these analyses were performed using the Random Fields Theory Family-wise error (FWE) correction ($P < 0.05$), which controls the possibility of any false positives across the entire volume (Ashburner and Friston, 2005). Further, results were considered statistically significant if they were part of a spatially contiguous cluster size of 50 voxels or greater.

To obtain fine anatomical localization of statistical results, two different brain atlases were used: (i) the automated anatomical labeling (Tzourio-Mazoyer et al., 2002), which includes all main gyri and sulci of the cerebral cortex and the subcortical and deep GM structures for a total of 90 anatomical volumes of interest and (ii) the ICBMDTI-81 WM labels atlas (Mori et al., 2005), which includes 50 WM tract labels created by manual segmentation of a standard-space average of diffusion MRI tensor maps from 81 subjects.

Mean GM and WM volumetric values of the global area where significant relationship with IS scale were found, were extracted for each subject as follows: statistical maps of areas where significant relationship between IS scale and GM (or WM) volumetric values emerged were first saved as binary masks (i.e., maps where voxels have the value of 1 where the relationship is significant and 0 otherwise). Then, these masks were multiplied by GM (or WM) maps in order to have, for each subject, a single map with volumetric values only in areas where the relationship was significant. Finally, using an in-house software written in shell-script, we calculated the mean voxel value of these areas, thus resulting, for each subject, in a mean GM (and WM) value of voxels where the relationship between volume and IS score was significant. These two values (one for GM and one for WM) were subsequently related to clinical data by means of univariate correlation analyses.

RESULTS

The sociodemographic, psychopathological and neuropsychological characteristics of the patients are presented in Table I.

TABLE I. Sociodemographic, clinical, and neuropsychological characteristics of 57 patients with diagnosis of schizophrenia

Characteristics	*n* (%)
Gender (male)	42 (74)
	Mean ± SD
Age (years)	37.2 ± 11.4
Educational level (years)	12.8 ± 3.0
Age at illness onset (years)	26.0 ± 8.4
Illness duration (years)	11.3 ± 9.1
Olanzapine equivalents (mg/day)	22.5 ± 40.1
MMSE	28.0 ± 1.7
RIR	33.3 ± 10.2
RDR	5.8 ± 2.7
CD	11.2 ± 1.1
CDL	65.3 ± 5.6
PM47	28.6 ± 6.0
PVF	27.0 ± 8.7
CF	15.2 ± 4.7
DB (correct answers)	10.6 ± 2.6
MWCST achieved categories	5.8 ± 0.7
MWCST perseverative errors	0.8 ± 1.7
MWCST nonperseverative errors	1.4 ± 1.7
PANSS Positive	22.3 ± 6.5
PANSS Negative	19.0 ± 6.0
PANSS GP	44.8 ± 10.6
PANSS Anergy	10.0 ± 3.2
PANSS Thought Disturbance	12.4 ± 4.6
PANSS Activation	7.5 ± 3.1
PANSS Paranoid-Belligerence	8.3 ± 3.0
PANSS Depression	11.5 ± 3.7
SARS	4.5 ± 4.3

MMSE, Mini-Mental State Examination; RIR, Rey's 15-word Immediate Recall; RDR, Rey's 15-word Delayed Recall; CD, Copying Drawings; CDL, Copying Drawings with Landmarks; PM47, Raven's Progressive Matrices' 47; PVF, Phonological Verbal Fluency; CF, Category Fluency Test; DB, Double Barrage; MWCST, Modified Wisconsin Card Sorting Test; SD, Standard Deviation; PANSS, Positive and Negative Syndrome Scale; GP, General psychopathology; SARS, Simpson–Angus Rating Scale.

Several areas of positive significant correlation between GM volumes and IS scores were found, mostly in frontal regions. Specifically, results were located in the pars orbitalis [Brodmann's Area (BA) 11] and triangularis (BA 45) of the left inferior frontal gyrus, in the right middle frontal gyrus (BA 9), in bilateral precentral gyri (BA 6), in right and left putamen, and in the right insula (BA 48).

Statistically significant positive correlations between WM volumes and IS score emerged in bundles subserving bilateral frontal regions, such as the bilateral cingulum, the left anterior and superior corona radiata, the right superior longitudinal fasciculus, and the left portion of the callosal forceps minor (Table II; Figs. 1 and 2).

Univariate correlations between psychopathological and neuropsychological variables and IS score are shown in Table III, upper panel.

Preselection analyses revealed that IS score was significantly and positively correlated with PANSS depression score, and negatively correlated with RIR, CF, and DB scores. The subsequent stepwise multiple regression analysis showed that PANSS depression and DB scores were significant predictors of IS index (Table III, lower panel). The resulting equation was significant ($F = 7.202$; $df = 2, 54$; $P = 0.0017$) and explained 21% of the overall variance of IS score. In particular, higher PANSS depression score and lower DB score predicted higher IS value.

Eventually, mean GM volumetric values of global areas where significant relationships with IS scale were found, negatively correlated with DB scores ($r = -0.30$, $P = 0.021$).

No significant relationships between mean WM volumetric values (in global areas where significant relationships with IS scale were observed) and clinical scores were found.

DISCUSSION

The main aim of the present study was to investigate the neuroanatomical correlates of metacognitive insight in schizophrenia using GM and WM volumetric neuroimaging techniques at the whole brain level. Secondary aims were to investigate the psychopathological and neuropsychological correlates of metacognitive insight, and the clinical correlates of potential structural variations in brain areas linked with metacognitive insight.

Four main results emerged. First, as hypothesized, a reduced metacognitive insight, i.e., the ability to monitor one's own unusual changes in mental experiences as expressed by lower IS scores, was related to reduced GM volumes in the PFC. In particular, we found an association in the left VLPFC and in the right DLPFC. In addition to this, lower levels of metacognitive insight were related to reduced GM volumes in other frontal cortical and deep GM areas, as well as in the right insula. Second, as expected, reduced metacognitive insight was related to reduced WM volumes in several fascicules mainly connecting frontal areas, in particular right superior longitudinal fasciculus, left forcep, minor and left corona radiata, as well as bilateral cingulum. Third, higher ability to detect changes in one's mental activity, or increased metacognitive insight, was related to higher depression severity and reduced attentional control. Fourth, increased GM volumes in those brain areas where a relationship with IS scores emerged, were related to a reduced attention performance.

With regard to our first result, it is interesting to note that all the brain areas highlighted by our study as related to metacognitive insight are described in literature as underpinning high-order cognitive functions, in particular cognitive control and self-appraisal. Cognitive control is a high-order function that encompasses the detection and resolution of conflict among competing response alternatives (Miller and Cohen, 2001), thus suppressing

TABLE II. Topography of the relationship between gray and white matter volumetry signal intensity and Insight Scale score

	Extent (mm^3)	*P* (FWE-corr)	Equiv *Z*	*x*, *y*, *z* (mm)
Gray matter labels for peaks (BA)				
Right putamen	480	<.001	6.25	28, 3, 16
		<.001	5.59	28, −12, 12
Right precentral gyrus (6)	310	<.001	5.83	42, −6, 40
		<.001	5.71	44, 8, 54
Right middle frontal gyrus (9)	415	<.001	5.78	39, 27, 46
Left inferior frontal gyrus, pars orbitalis (11)	282	<.001	5.76	−15, 24, −24
		<.001	5.51	−14, 38, −18
		<.001	5.30	−12, 50, −21
Left putamen	237	<.001	5.67	−27, −1, 13
Left precentral gyrus (6)	84	<.001	5.66	−39, −9, 39
Right insula (48)	212	<.001	5.54	46, 4, 7
Left inferior frontal gyrus, pars triangularis (45)	83	<.001	5.50	−42, 34, 19
White matter labels for peaks				
Right cingulum	158	.001	4.75	12, −6, 42
Right superior longitudinal fasciculus		.001	4.50	28, −12, 12
Left forceps minor	92	.001	4.67	−14, 42, −8
		.001	4.53	−16, 33, −15
Left superior corona radiata	77	.001	4.44	−28, 8, 30
Left anterior corona radiata		.002	4.39	−26, 17, 27
Left cingulum	57	.002	4.30	−8, 10, 31

FEW, family-wise error; BA, Brodman's area.
Coordinates are in Montreal Neurological Institute Space.

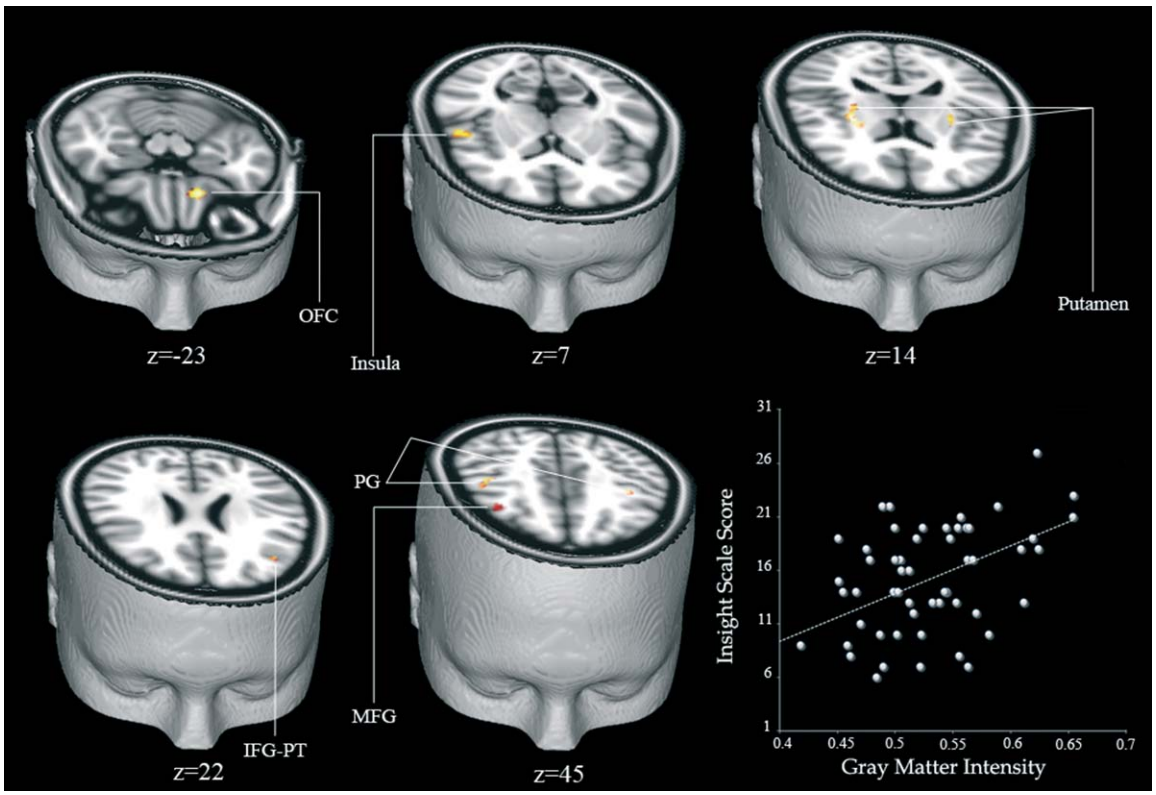

Figure 1.

Brain gray matter volumetric correlates of metacognitive insight in 57 patients with diagnosis of schizophrenia. Areas of significant relationship ($P < 0.05$ FWE corrected) between gray matter signal intensity and IS score. Scatterplot shows mean gray matter volumetric values plotted against individual IS scores. Regression line (dotted white) is also reported. *Z* coordinates are in MNI space. IFG-PT: inferior frontal gyrus, pars triangularis; MFG: middle frontal gyrus; OFC: orbitofrontal cortex; PG: precentral gyrus.

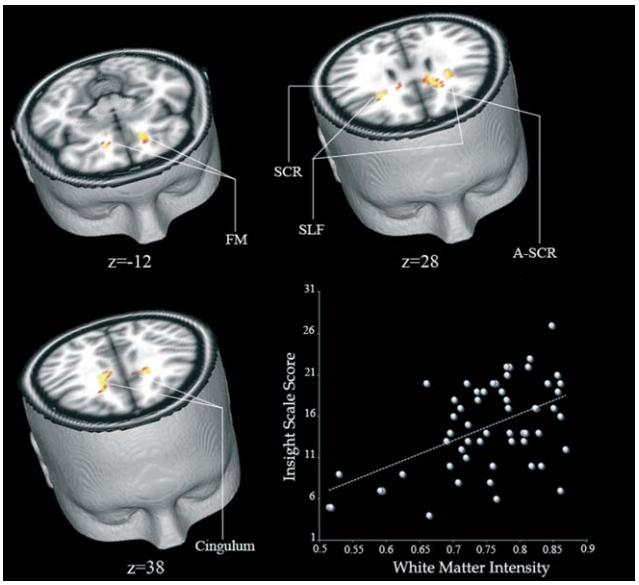

Figure 2.

Brain white matter volumetric correlates of metacognitive insight in 57 patients with diagnosis of schizophrenia. Areas of significant relationship ($P < 0.05$ FWE corrected) between white matter signal intensity and IS score. Scatterplot shows mean white matter volumetric values plotted against individual IS scores. Regression line (dotted white) is also reported. *Z* coordinates are in MNI space. A-SCR: anterior-superior corona radiata; FM: forceps minor; SLF: superior longitudinal fasciculus.

interference or erroneous alternatives, and enhancing task switching in order to guide behavior in accordance with goals and contextual knowledge (Badre et al., 2009; Badre and Wagner, 2006, 2007; Bunge et al., 2001). Left VLPFC (pars orbitalis and triangularis of the left inferior frontal gyrus) and right DLPFC (BA 9), are both significantly involved in cognitive control, cognitive schemata regarding one's abilities, traits and attitudes that guide behaviors and self-appraisal in social decision-making tasks (Johnson et al., 2002; Schmitz and Johnson, 2006; Schmitz et al., 2004). In particular, left pars triangularis, or mid-VLPFC, appears to manage two specific forms of cognitive control, i.e., active retrieval and proactive interference resolution (Badre and Wagner, 2004; Kostopoulos and Petrides, 2008; Petrides, 2005), that are strategic to isolate the target information from other similar events (Kostopoulos et al., 2007; Kostopoulos and Petrides, 2008) and to avoid that past experiences interfere with processing a novel one (Badre and Wagner, 2005, 2006). Further, left pars orbitalis (BA 11) is best involved in self-appraisal (Kjaer et al., 2002) especially in situations characterized by uncertainty in the course of evidence collection (Rushworth et al., 2007; Stern et al., 2010). Differently, in a previous work on cognitive insight (Orfei et al., 2013), right pars orbitalis was related to the ability to question one's judgments and beliefs and to openness to corrective external feedback (Beck et al., 2004). In the light of these findings, left and right pars orbitalis seem to play different roles in cognitive control. In fact, while right pars orbitalis elaborates alternative hypotheses in cognitive tasks in which individuals are required to generate a solution or response to problems, when a variety of answers are possible (Trivedi et al., 2008; Vartanian and Goel, 2005), left pars orbitalis best deals with emotional reactions due to uncertainty in evaluating self personality traits. This observation supports the hypothesis that cognitive insight and metacognitive insight catch two different, although related, aspects of self-reflection that are modulated by either hemisphere. The additional frontal cortical and subcortical areas related to metacognitive insight are all highly structurally and functionally connected to VLPFC and DLPFC such that they seem to constitute a network playing a combined role in emotional self-appraisal (Bergouignan et al., 2009; Ochsner et al., 2005) and multisensory integration leading to self-attribution (Ehrsson et al., 2004). Specifically, the putamen is part and parcel of the frontostriatal neural network managing response inhibition, and thus cognitive control

TABLE III. Clinical and neuropsychological correlates of Insight Scale score in 57 patients with diagnosis of schizophrenia

	IS	
Characteristics	*r*	*P* value
PANSS Positive Symptoms	0.035	0.7974
PANSS Negative Symptoms	0.077	0.5684
PANSS General Psychopathology	0.175	0.1949
PANSS Anergy	0.215	0.1081
PANSS Thought disturbance	0.00	0.9400
PANSS Activation	0.082	0.5482
PANSS Paranoid-Belligerence	−0.047	0.7299
PANSS Depression	**0.296**	**0.0251**
MMSE	−0.024	0.8625
RIR	**−0.292**	**0.0268**
RDR	−0.201	0.1334
CD	−0.038	0.7797
CDL	0.066	0.6265
PM 47	−0.150	0.2677
PVF	−0.045	0.7382
CF	**−0.335**	**0.0104**
DB (correct answers)	**−0.358**	**0.0058**
MWCST achieved categories	−0.131	0.3339
MWCST perseverative errors	0.056	0.6798
MWCST nonperseverative errors	0.137	0.3099

PANSS, Positive and Negative Syndrome Scale; MMSE, Mini-Mental State Examination; RIR, Rey's 15-word Immediate Recall; RDR, Rey's 15-word Delayed Recall; CD, Copy Drawings; CDL, Copy Drawings with Landmarks; PM 47, Raven's Progressive Matrices' 47; PVF, Phonological Verbal Fluency; CF, Category Fluency Test; DB, Double Barrage; MWCST, Modified Wisconsin Card Sorting test.

Significant values at the uncorrected statistical level ($P < 0.05$) are highlighted in bold.

(Ghahremani et al., 2012; van Schouwenburg et al., 2012). Concurrently, functional MRI studies highlighted that increasing activity in right anterior insula correlated with interoceptive monitoring accuracy, and with measures of subjective emotional experience (Critchley et al., 2004), thus providing a substrate for subjective feeling states and one's sense of self (Critchley and Seth, 2012; Modinos et al., 2009). Therefore, the cited prefrontal and frontal areas are all involved in cognitive control and in self-perception. In the light of these considerations, the relationship between prefrontal and frontal areas and metacognitive insight is intriguing, since the latter may be interpreted as the specific ability to monitor changes in the self, requiring both an adequate self-perception and an efficient cognitive control function, to permit the best possible selection among several hypotheses and judgments about unusual mental events.

With regard to our second result, the relationship between reduced WM volumes of a number of frontal fascicules and reduced metacognitive insight can be traced back to the structural and functional involvement in self-perception of the cited bundles. In fact, the cingulum bundles are the most prominent WM fiber tracts within the limbic system, and connect the cingulate cortex with PFC, premotor cortex, cortical association areas in the parietal and occipital lobes, parahippocampal cortex and thalamus (Abdul-Rahman et al., 2011). To note, lesions of cingulum fasciculus showed to be involved in deficits in self-related information processing (Sui et al., 2012). Further, WM microstructural alterations in the superior longitudinal fasciculus, the forceps minor and the corona radiata have been frequently described in schizophrenia as related to deficits in executive control functions (Clark et al., 2011; Perez-Iglesias et al., 2010; Sasson et al., 2012).

Our third result, i.e., the depressive-attentional symptoms linked to higher metacognitive insight, deserves some speculation. In fact, it is comprehensible that the more the subject with schizophrenia diagnosis is able to appreciate the strangeness of his/her own mental products, the more he/she is aware to be mentally ill. This may, in turn, generate a depressive mood, as the stigma of being mentally ill and the need for treatment or hospitalization may heavily affect emotional well-being, quality of life and even increasing risk of suicidality (Barrett et al., 2010; Cooke et al., 2007; Crumlish et al., 2005; Gilbert et al., 2000; Hasson-Ohayon et al., 2006). Further, it is well known that higher depression severity entails cognitive performances, specifically attentional control, memory (Clark et al., 2009; Majer et al., 2004; McClintock et al., 2010) and cognitive flexibility (Austin et al., 2001; Murphy et al., 2012), as described also in schizophrenia (Iosifescu, 2012). We may speculate depression to play the role of mediator between awareness of changes in the self and cognitive performance. Conversely, it is also possible that the observed negative correlation between quantitative measures of cognitive functioning (i.e., number of DB correct responses) and metacognitive insight is accounted for by the relative interdependence between meta-level control processes and basic first-order cognitive processes responsible for quantity performance (Koren et al., 2004; Koriat and Goldsmith, 1996). Intriguingly, while increased metacognitive insight was accompanied by an increase in volume in frontal cortical and subcortical areas, probably resulting from adaptive plasticity to sustain adequate meta-level processes, overgrowth in the same areas impaired attentional control, as revealed by the reported negative correlation between GM volume and correct responses in a divided attention task. Increased cortical volume/density in autism (Hazlett et al., 2011) reflects subtle neuropathological changes involving neurons and neuronal processes, such as a decrease in the normal occurrence of dendritic pruning of superfluous neuronal connections, resulting in increased dendritic arborization (Hazlett et al., 2006). The same abnormalities in the neuropil, expressed as an increase in neuronal density, have been observed in chronic schizophrenic patients and suggested to be more significant than neuronal loss in the pathophysiology of the disorder (Glantz and Lewis, 2000; Selemon et al., 1998). We can therefore speculate that the association between increased prefrontal cortical and subcortical GM volume and attentional control impairment observed in the present sample may be the consequence of subtle abnormalities involving neurones or neuronal processes in the frontal and subcortical cortices which may disrupt the neural circuitry and impair the complex information processing required for attentional control. However, our speculation on the causal chain between these factors deserves further deepening.

Before the conclusions some issues limiting the generalizability of our results have to be acknowledged. First, patients were recruited at various lengths of illness and we may wonder whether the same structure–function relationship is observable in a more homogeneous sample at the onset of the illness, such as in first-episode patients. Thus, further research on this point is needed. Second, as our sample was homogeneous with regard to race and recruitment source, it is not clear whether the same results would emerge from other populations. Thus, future research might replicate the study on different samples. Third, the patients in our sample were in a stable phase of illness and were being treated with stable doses of antipsychotics; therefore, we cannot exclude that medication affected metacognitive insight. Fourth, we included only nondemented patients with a MMSE score equal to or higher than 24 to avoid a confounding effect on the data, because they potentially could not fully understand the IS items. Therefore, it must be determined whether this selection criterion created a bias. Fifth, the cross-sectional structure of the study might also be a limitation. In fact, a longitudinal study on trajectories of metacognitive insight might have been more informative in predicting patients' outcomes, including treatment response and relationships with depressive and cognitive symptoms, as cross-sectional designs are confounded by age cohort effects

(Thompson et al., 2011). Sixth, the IS has been developed to elicitate subject's perception of even subtle change in the self, it appears best suitable in the very early stages of illness, for instance in first-episode patients. Indeed, in our study the sample described is quite heterogeneous with regard to illness duration, thus encompassing also chronic patients. This might represent a confounding factor. However, this issue is rather an interpretation, since the original population of reference for the development of the questionnaire was not specified by Marková and Berrios in terms of illness duration. Thus, future studies investigating metacognitive insight in first episode psychosis are required to clarify this point. Finally, the neural regions found to be significantly correlated with IS scores are predominantly prefrontal and underpin executive functions. However, contrary to what is described with regard to clinical (Aleman et al., 2006) and cognitive insight (Orfei et al., 2010), we have found a correlation between IS and DB, but not MWCST indexes. Indeed, the term "executive functions" is quite wide and encompasses various specific functions. The MWCST is thought to investigate "set-shifting," i.e., the ability to display flexibility in the face of changing schedules of reinforcement. On the other hand, the DB test is aimed at investigating attentional processes. Thus, it is possible that clinical and cognitive insight dimensions are more dependent on strategic planning, organized searching, utilizing environmental feedback to shift cognitive sets, directing behavior toward achieving a goal, and modulating impulsive responding, while the metacognitive dimension of insight is better dependent on attentional processes. These data would support the specific nature of metacognitive insight with respect other self-awareness facets.

In conclusion, this study explored for the first time the neuroanatomy of what we named metacognitive insight, that is a form of self-monitoring of changes in subjective self-experience and the ability to feel and express the related emotional unease in patients affected by schizophrenia (Marková et al., 2003) and its relationships with psychopathological and neuropsychological characteristics. The data emerging from our study confirm our hypotheses that metacognitive insight is mediated by a frontostriatal-limbic circuitry, which would involve some specific cortical and subcortical GM areas and WM bundles. In particular, metacognitive insight appears to be underpinned by top-down cognitive control processes, which would allow the selection among a number of alternative self-representations retrieved from semantic memory and based on a flexible updating of information about the self. This ability in detecting and integrating new elements and cues, would indicate that metacognitive insight reflects patient's actual self-beliefs.

Thus, while clinical insight mostly focuses on patients' verbal statements regarding their mental illness and need for treatment, metacognitive insight is centered on the ability to detect changes in sensations and a related sense of strangeness, which hardly can be described when not actually experienced. Also, while cognitive insight explores general cognitive styles that can deal with various issues, even in healthy subjects, metacognitive insight specifically investigates metacognitive abilities applied to awareness of illness in patients with psychosis. Further, the IS, being focused on awareness of changes in self-perception, may be best informative in first-episode subjects and in the onset stages of illness while the classical scales for clinical insight best investigate more stable pathological pictures.

The study of metacognitive insight may provide a deeper knowledge about the processes underpinning awareness deficits and, more in general, self-monitoring and self-knowledge. Moreover, since metacognitive insight focuses on patient's ability to reflect on oneself and on the mechanisms underlying self-image construction and update, it may provide also relevant indications for the development of specific cognitive therapeutic strategies, aimed at improving self-monitoring and flexibility of thought applied to the detection and evaluation of changes in the self. In turn, this is supposed to encourage compliance to treatment and thus an improvement in quality of life and course of illness (Karow and Pajonk, 2006).

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