ORIGINAL ARTICLE

Case Control Study

Voxel-based magnetic resonance imaging investigation of poor and preserved clinical insight in people with schizophrenia

Adegboyega Sapara, Dominic H Ffytche, Michael A Cooke, Steven CR Williams, Veena Kumari

Adegboyega Sapara, Michael A Cooke, Veena Kumari, Department of Psychology, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London SE5 8AF, United Kingdom

Dominic H Ffytche, Department of Old Age Psychiatry and Neuroimaging Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London SE5 8AF, United Kingdom

Steven CR Williams, Department of Neuroimaging Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London SE5 8AF, United Kingdom

Veena Kumari, NIHR Biomedical Research Centre for Mental Health, South London and Maudsley NHS Foundation Trust, London SE5 8AF, United Kingdom

Institutional review board statement: The study procedures had the approval (reference number 209/02) of the ethics committee of the Institute of Psychiatry and South London and Maudsley Foundation NHS Trust, London.

Informed consent statement: All participants provided written informed consent.

Conflict-of-interest statement: None of the authors declare any conflict of interest in this study.

Data sharing statement: The anonymised dataset is available from the first author and the corresponding author.

Abstract

AIM

To define regional grey-matter abnormalities in schizophrenia patients with poor insight (Insight-), relative to patients with preserved clinical insight (Insight+), and healthy controls.

METHODS
Forty stable schizophrenia outpatients (20 Insight[-] and 20 Insight[+]) and 20 healthy controls underwent whole brain magnetic resonance imaging (MRI). Insight in all patients was assessed using the Birchwood Insight Scale (BIS; a self-report measure). The two patient groups were pre-selected to match on most clinical and demographic parameters but, by design, they had markedly distinct BIS scores. Voxel-based morphometry employed in SPM8 was used to examine group differences in grey matter volumes across the whole brain.

RESULTS
The three participant groups were comparable in age [$F(2,57) = 0.34$, $P = 0.71$] and the patient groups did not differ in age at illness onset [$t(38) = 0.87$, $P = 0.39$]. Insight[-] and Insight[+] patient groups also did not differ in symptoms on the Positive and Negative Syndromes scale (PANSS): Positive symptoms [$t(38) = 0.58$, $P = 0.57$], negative symptoms [$t(38) = 0.61$, $P = 0.55$], general psychopathology [$t(38) = 1.30$, $P = 0.20$] and total PANSS scores [$t(38) = 0.21$, $P = 0.84$]. The two patient groups, as expected, varied significantly in the level of BIS-assessed insight [$t(38) = 12.11$, $P < 0.001$]. MRI results revealed lower fronto-temporal, parahippocampal, occipital and cerebellar grey matter volumes in Insight[-] patients, relative to Insight[+] patients and healthy controls (for all clusters, family-wise error corrected $P < 0.05$). Insight[+] patient and healthy controls did not differ significantly ($P > 0.20$) from each other.

CONCLUSION
Our findings demonstrate a clear association between poor clinical insight and smaller fronto-temporal, occipital and cerebellar grey matter volumes in stable long-term schizophrenia patients.

Core tip: Poor clinical insight is the most prevalent symptom in patients with schizophrenia and is of growing importance due to its direct association with poor clinical outcomes, such as frequent relapses and hospital admissions. This study identified significantly reduced fronto-temporal, parahippocampal, occipital and cerebellar grey matter volumes in Insight[-] patients relative to both Insight[+] patients and healthy controls. The involvement of multiple brain areas and corresponding neural networks supports the theory that clinical insight, as a neurological function, is not confined to specific neuroanatomical regions but probably a function of a complex neurocognitive interplay with contributions from multiple neural networks.

Sapara A, Ffytche DH, Cooke MA, Williams SCR, Kumari V.

INTRODUCTION
Nearly a century ago, Kraepelin (1919) observed that schizophrenia patients often had "no real understanding of the gravity of their disorder" and regularly disputed that they suffer from a mental illness[1]. In the 1930s, Lewis described clinical insight as having "a correct attitude to a morbid change in one's self"[2,3] and low clinical insight is the most prevalent symptom occurring in about 97% of schizophrenia patients[2,4]. Impaired insight in schizophrenia is of growing importance due to its direct correlation with poor clinical outcomes, such as frequent relapses and hospital admissions[5], poor compliance with medication and treatment plans[6-8], severe psychopathology[9], greater suicidal tendencies and self-injurious behaviour[9-12]. Some studies reporting positive correlations between improvement in clinical insight and better global clinical impression and clinical outcome scores[13] have further suggested the adoption of clinical insight as a possible therapeutic target in schizophrenia patients[14].

Similarities between impaired insight in schizophrenia and unawareness of neurological deficits such as ano-sognosia, first described in patients with acute brain lesions with left-sided hemiplegia who were unaware of the impairments in their paralysed limbs[15,16], led to the notion that both phenomena share a common neurological basis[17-19] and prompted investigations of neuroanatomical abnormalities in relation to impaired clinical insight in schizophrenia. Earliest studies, using computerized tomography (CT) scan, reported significant and direct associations between impaired clinical insight and ventricular enlargement[20], total insight scores and total brain volumes[21] and a linear relationship between global cortical atrophy and impaired clinical insight[22]. These studies all concluded that there is a significant association between whole brain volume loss and impaired clinical insight in schizophrenia. Structural magnetic resonance imaging (MRI) studies also reported correlations between impaired clinical insight and smaller regional grey matter volumes, including the frontal lobe, anterior cingulate cortex (ACC), posterior cingulate, temporal and parietal lobes[23-28]. More recently, correlations have been reported between impaired insight and smaller right posterior insula volumes[29], smaller grey matter volumes of the right ventro-lateral prefrontal cortex (PFC)[30], left ventrolateral PFC, right dorsolateral PFC, insula, bilateral premotor area and the putamen; and reduced white matter volumes of the right superior longitudinal fasciculus, left corona radiata, left forceps minor and bilateral cingulum[31].

Although most studies have reported a correlation between brain volume loss and impaired insight, some studies failed to find any correlation between clinical insight and either ventricular or total/regional brain volumes[3,32,33], while others reported associations between impaired clinical insight and increased (rather than decreased) right medial orbitofrontal cortex grey matter volumes[28], and between symptom misattribution and increased grey matter volumes in bilateral caudate regions, right thalamus, left insula, putamen and cerebellum[34]. Bassitt *et al*[35] found no significant inverse correlation between total or regional grey matter volumes and clinical insight but, contrary to their expectations, observed a positive correlation between degree of insight impairment and the left medial PFC and ACC grey matter volumes, which they attributed to higher doses of antipsychotics given to patients with impaired clinical insight in their sample. The marked variation in findings may be due to the use of different brain volumetric assessment techniques, the heterogeneity of clinical insight measures and varying clinical characteristics of schizophrenia patients studied[25,35,36].

The aim of the present study was to characterise grey matter alterations in stable long-term schizophrenia outpatients with impaired clinical insight by directly comparing them, for the first time to our knowledge, with schizophrenia outpatients with preserved clinical insight, matched on average for age, sex and relevant demographic and clinical characteristics. Our approach of utilising the two extremes of the insight distribution should yield the largest structural difference in relation to insight. We also compared how these distinct groups of patients might differ from healthy controls, matched on average on age and sex of the patient groups. Based on the findings (where positive) of existing studies involving solely or predominantly chronic patient samples, we hypothesised that, patients with impaired insight (Insight$^-$) will show smaller frontal and temporal regional grey matter volumes compared to patients with preserved insight (Insight$^+$) and healthy controls. This hypothesis also has support from previous studies showing, on average, poor cognitive function in patients with impaired insight[25,37,38] and a positive association between grey matter volumes of these regions and a range of cognitive functions in schizophrenia[39].

MATERIALS AND METHODS

Participants and study design
This study included 60 right-handed participants. Forty of these were patients with a diagnosis of schizophrenia, confirmed using the Structured Clinical Interview for DSM-IV (SCID)[40]. The patients formed two groups of 20 patients each, pre-selected to have preserved and impaired insight, out of a larger pool of 70 stable community patients. The assessment of insight and differentiating criteria are described in detail under "clinical assessment". All included patients were required to be: (1) on well established antipsychotic medication

doses for $\geqslant$ 3 mo; (2) in the stable (chronic) phase of the illness; and (3) $\geqslant$ 2 years from illness onset. Twenty healthy controls screened to exclude neuropsychiatric conditions and matched, on average, for age and sex of the patients were studied for comparison purposes. Ethics approval was granted by the ethics committee of the Institute of Psychiatry and South London and Maudsley Foundation NHS Trust, London. All participants provided written informed consent.

Clinical assessment
Birchwood Insight Scale (BIS)[41], a self-rated questionnaire, was used to assess insight in all patients. The BIS measures three different aspects of clinical insight[2]: (1) the awareness of the presence of a mental disorder (2nd and 7th statement); (2) the awareness of the need for treatment (3rd, 6th statement); and (3) the ability to label symptoms as abnormal (1st and 8th statement). Each individual BIS statement (8 in total) is rated and given a score of one for unsure, and either 0 or 2 for agree and disagree, depending on whether agreeing with the statement depicts preserved clinical insight (all statements are corrected for response valence). As we did not include any inpatients, Item 4 "My stay in hospital is necessary" was deleted, thus yielding a maximum possible score of 14, compared with a maximum possible score of 16 in the full scale BIS. In operationalising the BIS, Birchwood *et al*[41] classified preserved insight as having a minimum score of 9 (out of 14). In this study, we defined "preserved insight" as a minimum score of 13 (out of 14) and "impaired insight" as a score of 8 or below. This rather conservative method was designed to ensure that the two groups had distinct levels of insight and also to eliminate those with partial clinical insight levels. All patients were supervised during the completion of the BIS. The BIS has acceptable internal consistency (α = 0.75) and one week test-retest reliability (r = 0.90 for the total score[41]), and insight assessed on the BIS correlates positively with scores on other measures of insight[10,26,42]. For sample characterization purposes, symptoms in patients were assessed using the Positive and Negative Syndrome Scales (PANSS[43]). In addition, predicted IQ of all study participants was measured using the National Adult Reading Test (NART[44]).

Image acquisition and processing
Whole brain MRI scans were acquired for all study participants using a 1.5 Tesla GE NV/I Signa system (General Electric, Milwaukee WI, United States) at the Maudsley Hospital, London. A series of sagittal fast gradient echo scout images were obtained to correct for head tilt and to orient subsequent images relative to the anterior-commissure/posterior-commissure line and the interhemispheric fissure. A 3-D inversion recovery prepared fast spoiled GRASS sequence was applied to acquire T1-weighted images in the axial plane with 1.5 mm contiguous sections (TR = 18 ms, T1 = 450 ms, TE = 5.1 ms, flip angle = 20° with one data average and a 256 × 256 × 128 voxel matrix). Acquisition

parameters were selected employing a sophisticated image simulation[45]. All MRI images were converted into ANALYZE format (ANALYZE software, BRU, Mayo Foundation, Rochester, MN) and pre-processed using Statistical Parametric Mapping (SPM8; http://wwwfil.ion.ucl.ac.uk/spm) running in MATLAB 2006a (MathWorks, Natick, MA). Customised T1-weighted templates of the whole brain, grey matter, white matter and cerebrospinal fluid (CSF) were created for patient and healthy participant groups separately, and also for the whole study sample combined.

Statistical analysis
Demographic and clinical measures: Possible group differences in age, education and NART IQ were examined using analyses of variance (ANOVAs), and significant Group effects were followed by independent sample *t*-tests. Possible differences between the two patient groups in clinical variables (age at illness onset, PANSS symptom scores and medication) were examined using independent sample *t*-tests. All statistical analyses were conducted using SPSS 22, with alpha level for significance testing maintained at $P \leqslant 0.05$ (two-tailed), unless stated otherwise.

MRI: Group differences (healthy controls *vs* Insight⁻ patients, health controls *vs* Insight⁺ paitents, and Insight⁺ *vs* Insight⁻ patients) in grey matter volumes, across the whole brain, were examined using ANOVA in SPM8 (height threshold $P < 0.005$; familywise-error (FWE)-corrected at the cluster level $P < 0.05$). To rule out the possibility that any observed group differences were due to trend-level Group differences in education and IQ (see RESULTS, demographic and clinical measures), group differences in grey matter volumes were re-evaluated using analysis of co-variance, with education and IQ entered as co-variates.

RESULTS
Demographic and clinical characteristics
The three participant groups did not differ in age [$F_{(2,57)} = 0.34$, $P = 0.71$]. There were trend level effects of Group in years of education [$F_{(2,57)} = 2.60$, $P = 0.08$] and NART IQ [$F_{(2,57)} = 2.67$, $P = 0.08$]. Healthy controls spent more years in education than Insight⁻ patients [$t_{(38)} = 2.11$, $P = 0.04$] but differed only at a trend level when compared with Insight⁺ patients [$t_{(38)} = 1.77$, $P = 0.08$]. Healthy controls also had higher NART IQ than Insight⁻ patients [$t_{(38)} = 2.47$, $P = 0.02$] but did not differ from Insight⁺ patients [$t_{(38)} = 1.19$, $P = 0.24$]. There were no significant differences the Insight⁻ and Insight⁺ patient groups in education [$t_{(38)} = 0.06$, $P = 0.95$] and NART IQ [$t_{(38)} = 1.04$, $P = 0.31$] (Table 1). The two patient groups were similar in age at illness onset [$t_{(38)} = 0.87$, $P = 0.39$], positive symptoms [$t_{(38)} = 0.58$, $P = 0.57$], negative symptoms [$t_{(38)} = 0.61$, $P = 0.55$], general

psychopathology [$t_{(38)} = 1.30$, $P = 0.20$] and total PANSS symptoms [$t_{(38)} = 0.21$, $P = 0.84$]. Patients in the two groups were on a range of typical and atypical antipsychotics (Table 1) but received, on average, similar doses of antipsychotic medication [$t_{(38)} = 0.86$, $P = 0.40$]. The Insight⁺ patient group, confirming our insight-based pre-selection, had significantly higher BIS score than the Insight⁻ group [$t_{(38)} = 12.11$, $P < 0.001$].

MRI: Group effects in regional grey matter volumes
Group differences in brain MRI grey matter volumes are presented in Table 2, and described below.

Insight⁻ *vs* Insight⁺ patients: Compared to Insight⁻ patients, Insight⁺ patients had larger grey matter volumes in the inferior frontal and precentral gyri, superior and middle temporal gyri, parahippocampus, cuneus and cerebellum of both cerebral hemispheres (Figure 1).

Healthy controls *vs* Insight⁻ patients: Compared to Insight⁻ patients, healthy controls had larger grey matter volumes in the left inferior and middle frontal gyri, left superior, middle and inferior temporal gyri, left parahippocampus, right cerebellum, and bilateral superior, middle and inferior occipital gyri (Figure 1).

Healthy controls *vs* Insight⁺ patients: There were no significant differences between healthy controls and Insight⁺ patients.

Group differences after co-varying for education and predicted IQ
Differences in grey matter volumes (noted earlier) between healthy controls and Insight⁻ patients remained present but with reduced significance when we co-varied for education and IQ (Table 3). Group differences between Insight⁻ and Insight⁺ patients, however, were not affected.

DISCUSSION
In this study, we directly compared two matched groups of schizophrenia patients but with distinct levels of clinical insight (Insight⁻ *vs* Insight⁺) and investigated how they differ from each other and also from healthy controls in regional grey matter volumes examined using voxel-based morphometry (VBM) technique. We tested the hypothesis that Insight⁻ patients will show smaller frontal and temporal grey matter volumes compared to Insight⁺ patients. All three participant groups were comparable in age and the two patient groups were similar in all demographic and clinical parameters, including age at illness onset, years of education, NART IQ, symptoms (PANSS scores) and doses of medication prescribed. Insight⁻ patients, however, had lower IQ and fewer years in education than healthy controls. Although, on average, lower IQ as well as deficits in many specific cognitive

Table 1 Demographics and clinical characteristics of the study groups

	Healthy controls (*n* = 20; 15 male, 5 female)		Patients insight⁺ group (*n* = 20; 16 male, 4 female)		Patients insight⁻ group (*n* = 20; 16 male, 4 female)	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Demographics						
Age (yr)	35.25 (10.93)	20-59	36.15 (10.54)	19-54	37.80 (7.85)	22-49
Education (yr)	15.05 (2.86)	10-20	13.45 (2.86)	9-20	13.40 (2.01)	11-19
Predicted IQ (NART)	113.10 (9.91)	91-128	109.20 (10.80)	86-122	106.10 (7.87)	90-119
Clinical characteristics						
BIS			11.65 (0.57)	13-14	5.88 (2.05)	1-8
Age at illness onset (yr)			25.90 (8.72)	13-48	23.85 (5.84)	10-37
PANSS positive symptoms			16.15 (5.38)	8-25	17.05 (4.43)	8-23
PANSS negative symptoms			17.20 (4.38)	7-27	18.15 (5.46)	8-27
PANSS general psychopathology			34.35 (7.36)	24-56	31.55 (6.27)	21-40
PANSS total symptoms			67.70 (14.90)	43-108	66.75 (14.02)	37-86
Medication (chlorpromazine equivalent in mg)			461.21 (333.95)	100-1600	556.63 (366.49)	200-1367
Medication type						
Atypical antipsychotics			18 (9 olanzapine, 5 risperidone, 3 clozapine, 1 quetiapine)		13 (7 olanzapine, 3 clozapine, 1 aripiprazole, 1 amisulpride, 1 risperidone)	
Typical antipsychotics			2 (1 sulpiride, 1 haloperidol)		5 (2 flupenthixol, 1 fluphenazine, 1 sulpiride, 1 haloperidol)	
Both			--		2 (1 on clozapine + levomepromazine, 1 zuclopenthixol + aripiprazole)	

NART: National Adult Reading Test[44]; BIS: Birchwood insight scale[41]; PANSS: Positive and negative syndrome scale[43].

domains in patients with schizophrenia, relative to the healthy population, are commonly reported[46], our study suggests that this may be particularly true for those with impaired insight[37] and in turn may also explain the finding of significantly fewer years in education in the Insight⁻ (but not Insight⁺) patient group, compared with the healthy controls. The patient groups scored at opposing ends of the BIS scale; this allows for the interpretation of observed neuroanatomical differences in relation to clinical insight levels of the respective patient group.

As hypothesized, we found that Insight⁻ patients had smaller grey matter volumes than Insight⁺ patients, bilaterally in the frontal and temporal lobes (mainly in the inferior frontal and precentral gyri and superior and middle temporal gyri), as well as in the parahippocamal gyrus, occipital lobes (including the cuneus) and the cerebellum. Insight⁻ patients also showed similar grey matter deficits, particularly on the left, when compared to healthy controls (Figure 1).

Our findings of smaller fronto-temporal regional grey matter volumes are in accordance with previous imaging studies, that used the "Region of Interest" (ROI) approach and found a significant and direct correlation between smaller frontal areas, including the dorsolateral PFC, inferior frontal and middle frontal gyri[22,26-28,47,48] and impaired clinical insight. Early reports of poor executive functioning in schizophrenia patients with impaired insight, similar to those with frontal lobe lesions, initiated the interest in the integrity of the frontal lobe in schizophrenia. Since then, several studies[26,30,31,47],

including this one, have reported frontal neuroanatomical abnormalities in relation to impaired clinical insight in schizophrenia. Some functional imaging studies have further associated aberrant frontal functional MRI activity with impaired clinical insight during working memory[49], self-reflection[50], self-monitoring[51] and self-awareness tasks[52] in schizophrenia. In addition, earlier correlational VBM studies have also reported associations between smaller superior and middle temporal lobe grey matter volumes and impaired clinical insight[23,48].

Our other finding of smaller cuneus and occipital grey matter volumes in Insight⁻ patients is also broadly in agreement with the earlier reported association between poor symptom relabelling dimension of clinical insight and smaller grey matter volumes of the precuneus, cuneus and medial occipital gyrus by Morgan *et al*[25]. Unlike Morgan *et al*[25], we did not investigate preferential or predominant contribution of particular insight dimensions because the BIS subscale scores in our sample were highly positively correlated with each other (rho = 0.50-0.882; *P* < 0.001). This might be due to our sampling methods that ensured that our Insight⁻ and Insight⁺ patient groups had markedly different insight levels, possibly in all domains. Other VBM studies have also reported an association between the smaller precuneus grey matter volumes and lower insight in schizophrenia[23]. The role of the precuneus has been described in the facilitation of increased awareness into one's mental states[23,53] and has also been implicated, in conjunction with other midline structures, in the self-appraisal processes[54,55]. Compared to anterior cortical

Table 2 Group differences in grey matter volumes (height threshold *P* < 0.005)

Groups	BA	Size	Side	MNI			*T* value	Cluster *P* FWE-corrected unless in italics	Voxel *P* FWE-corrected
				X	Y	Z			
Insight[+] > Insight[-] patients									
Superior temporal gyrus	22	46555	R	63	-3	5	4.91	0.001	0.020
				45	20	-33	4.74		0.034
				66	-8	4	4.68		0.040
Precentral gyrus	4			66	-5	22	4.55		0.057
Inferior frontal gyrus	47			54	19	0	4.52		0.063
Precentral gyrus	6			64	0	26	4.40		0.088
Postcentral gyrus	43			66	-8	16	4.33		0.106
parahippocampus	28			14	0	-27	4.07		0.406
Inferior frontal gyrus	47	103898	L	-41	15	-6	4.81	< 0.001	0.027
Middle frontal gyrus	9			-37	19	35	4.74		0.034
Inferior frontal gyrus	47			-37	15	-10	4.73		0.035
				-35	20	-10	4.54		0.059
Precentral gyrus	44			-59	8	7	4.39		0.091
Superior temporal gyrus	22			-62	-4	8	4.36		0.097
Precentral gyrus	6			-60	4	6	4.33		0.107
Middle temporal gyrus	21			-35	-3	-23	4.27		0.126
parahippocampal gyrus	20			-34	-5	-28	4.16		0.166
Cuneus	18	35993	L	-5	-83	5	4.43	0.003	0.082
Cerebellum	-		R	35	-90	-17	4.26		0.129
Cuneus	18		R	26	-93	-18	3.90		0.305
Cerebellum	-		R	4	-61	2	3.88		0.317
Cuneus	18		R	5	-98	10	3.50		0.630
			R	5	-96	3	3.44		0.674
Cerebellum	-		L	-36	-82	-15	3.38		0.730
Insight[-] > Insight[+] patients									
Nil significant									
Healthy controls > Insight[-] patients									
Inferior frontal gyrus	47	35300	L	-49	19	-3	4.63	0.004	0.046
Superior temporal gyrus	22			-60	1	3	4.30		0.115
Inferior frontal gyrus	47			-41	18	-5	4.21		0.144
				-38	22	-8	4.19		0.153
				-36	-1	-14	3.86		0.333
Inferior temporal gyrus	20			-28	-14	-41	3.61		0.530
Parahippocamal gyrus	34			-13	4	-23	3.58		0.552
Middle frontal gyrus	11			-42	40	-19	3.39		0.722
Inferior occipital gyrus	18	11168	L	-38	-92	-2	4.51	0.034	0.065
Middle occipital gyrus	19			-52	-76	-10	4.29		0.117
				-48	-80	-14	3.96		0.266
				-49	-81	7	3.90		0.302
Middle temporal gyrus	39/			-53	-72	22	3.37		0.740
	19			-52	-74	18	3.33		0.768
				-49	-76	20	3.29		0.797
Cerebellum	-	25235	R	35	-90	-17	4.46	0.016	0.074
(posterior lobe)				11	-90	-37	4.21		0.146
Occipital lobe	18			23	-94	-18	4.01		0.238
Cerebellum				34	-85	-40	3.93		0.355
(posterior lobe)				38	-82	-41	3.91		0.489
Insight[-] patients > healthy controls									
Nil significant									
Healthy control > Insight[+] patients									
Nil significant									
Insight[+] patients > healthy controls									
Nil significant									

BA: Brodmann area; L: Left; R: Right; MNI: Montreal Neurological Institute.

regions, much less is known about the involvement of posterior medial cortices due to the dearth of research into the contributions of these brain regions to various aspects of psychotic disorders[25]. In our recent study, we found further evidence of functional contributions from the precuneus, as well as the cerebellum, in supporting neural activities sub-serving the preservation of insight in schizophrenia patients[49].

There have been previous reports of cerebellar atrophy, on average, in schizophrenia patients[56]. A previous study[48] also observed a significant association between impaired clinical insight and reduced bilateral

Table 3 Group differences in grey matter volumes after co-varying for education and National Adult Reading Test IQ (height threshold $P < 0.005$)

Groups	BA	Size	Side	MNI X	MNI Y	MNI Z	T value	Cluster P FWE-corrected unless shown in italics	Voxel P FWE-corrected
Insight[+] > Insight[-] patients									
Superior Temporal gyrus	22	37261	R	63	-3	5	4.70	0.002	0.044
				45	20	-33	4.56		0.066
				66	-8	4	4.45		0.088
Precentral gyrus	4			66	-5	22	4.44		0.092
Inferior frontal gyrus	47			54	19	0	4.39		0.103
Precentral gyrus	6			64	0	26	4.28		0.137
Postcentral gyrus	43			66	-8	16	4.15		0.192
Inferior frontal gyrus	47	65047	L	-42	16	-4	4.65	< 0.001	0.050
				-38	14	-8	4.65		0.052
				-36	18	-10	4.52		0.073
Middle frontal gyrus	9			-37	19	35	4.52		0.073
Superior temporal gyrus	22			-61	-2	7	4.28		0.139
Precentral gyrus	44			-59	9	9	4.17		0.184
Parahippocampual gyrus	21			-34	-3	-36	4.10		0.213
Cuneus	18	24291	L	-5	-83	5	4.32	0.014	0.125
Cerebellum	-		R	35	-90	-17	4.17		0.181
Cuneus	18		R	26	-93	-18	3.73		0.466
Cerebellum	-		R	4	-61	2	3.80		0.409
Cuneus	18		R	5	-98	10	3.35		0.787
Medial frontal gyrus	10	16854	L	0	60	3	3.98	0.050	0.285
Superior frontal gyrus	9			0	51	26	3.64		0.544
Insight[-] > Insight[+] patients									
Nil significant									
Healthy controls > Insight[-] patients									
Inferior frontal gyrus	47	9770	L	-51	19	-2	3.68	0.036	0.511
Superior temporal gyrus	38			-21	5	-24	3.35		0.786
Inferior frontal gyrus	47			-26	18	-7	3.34		0.796
Parahippocampal gyrus	34			-16	4	-23	3.29		0.827
Inferior occipital gyrus	18	4935	L	-38	-92	-2	3.92	0.122	0.323
Middle occipital gyrus	19			-52	-76	-10	3.70		0.494
				-44	-83	8	3.37		0.775
Middle temporal gyrus	18			-43	-81	13	3.22		0.873
Cerebellum (posterior lobe)	-	6085	R	35	-90	-17	3.68	0.089	0.304
				11	-90	-37	3.60		0.378
Occipital lobe	18			28	-94	-16	3.32		0.656
				23	-94	-18	3.26		0.713
Insight[-] patients > healthy controls									
Nil significant									
Healthy controls > Insight[+] patients									
Nil significant									
Insight[+] patients > healthy controls									
Nil significant									

BA: Brodmann area; L: Left; R: Right; MNI: Montreal Neurological Institute.

cerebellar grey matter volumes in schizophrenia, and that this relationship was not associated with any specific dimension of clinical insight. Other studies have described the involvement of the cerebellum in higher cognitive functioning, with its extensive connectivity with limbic structures, including the parahippocampal gyrus, and associated cortical areas involved in cognition and executive function[57,58], and this has been implicated in the neuropathology of schizophrenia and poor clinical insight[48,59]. Our recent finding of increased cerebellar activity, detected using fMRI, in Insight[+] patients compared to Insight[-] patients, during a working memory task, also indicated cerebellar involvement in the preservation of clinical insight in schizophrenia[49].

In accordance with the observations made by other studies, we also found grey matter reductions in many areas in Insight[-] patients, compared to healthy controls[48]. These differences remained, but became less significant, after we co-varied for education and NART IQ. Co-varying for education and NART IQ had no effects on grey matter volume differences between preserved and Insight[-] patient groups, most likely because these two groups were comparable on these parameters.

Strengths and limitations
We employed a direct comparison method between distinct groups of schizophrenia patients (Insight[-] and Insight[+]) with closely matched demographic and clinical
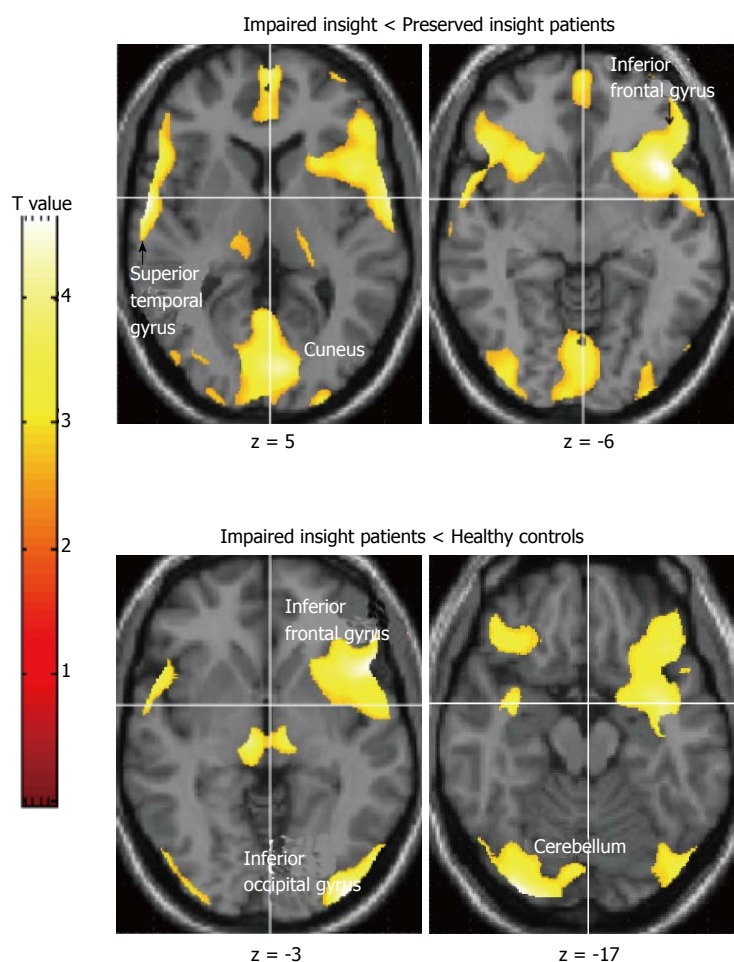
Impaired insight < Preserved insight patients

Figure 1 Images showing regions of decreased grey matter volume in the impaired insight patient group, relative to the preserved insight patient and healthy controls (maps thresholded at *P* = 0.005; left = right).

qualities, thereby facilitating valid comparisons and inferences. The study also had 60 participants (n = 20 per group) and thus was adequately powered for the observations made. We were, however, limited in our ability to explore the effects of sex on brain volumes and in the observed group differences, as our sample was predominantly male. Nonetheless, male:female ratios were similar and any possible effect is expected to be uniform in all groups. Also, although the patient groups were comparable in all relevant areas, our healthy controls had more education than our patient groups, and had higher IQ scores than Insight⁻ patient group, although co-varying for these differences did not change the pattern of observed group differences. By adopting a direct comparison method between matched patient groups at the extremes of insight measures, we minimised confounding effects of partial insight levels and were able to exclude overall effects of schizophrenia on brain volumes. However, in as much as we endeavoured that our two patient groups are highly comparable but for their insight levels, there are possibilities of other differential properties, such as brain functional properties, which could possibly contribute to our findings. Lastly, patients in both the Insight⁺ and Insight⁻ groups were on a range of atypical and typical antipsychotics (Table 1) which vary in their pharmacological profiles[60,61] as well as in their effects on brain volumes[62]. This may have

influenced the results we observed in this study.

In conclusion, schizophrenia patients with impaired insight patients have smaller fronto-temporal, parahippocampal, occipital and cerebellar grey matter volumes, compared with preserved insight schizophrenia patients and healthy controls. The involvement of multiple brain areas and corresponding neural networks supports the theory that clinical insight, as a neurological function, is not confined to specific neuroanatomical regions in the brain but probably a function of a complex neurocognitive interplay with contributions from neural networks, including working memory and executive functioning, self-monitoring and awareness and others[19,23,49,63,64].

COMMENTS

Background

Impaired insight in schizophrenia is found to have a direct correlation with poor clinical outcomes, such as frequent relapses and hospital admissions, poor compliance with medication, greater suicidal tendencies and self-injurious behaviour. Some studies reporting positive correlations between improvement in clinical insight and better clinical outcomes have further suggested the adoption of clinical insight as a possible therapeutic target in schizophrenia

patients.

Research frontiers

The ability to target insight therapeutically is highly complex and remains elusive to most methods trialled so far. The identification of the underpinning neural correlates of clinical insight will aid the development of specific treatment strategies aimed at improving insight in schizophrenia.

Innovations and breakthroughs

The study reported in this manuscript is distinct from all previous studies in this area (mostly correlational) in that it identifies regional grey matter abnormalities in stable schizophrenia outpatients with impaired clinical insight, relative to those with preserved clinical insight (impaired and preserved insight groups scoring at extreme ends of a multidimensional insight scale but matched on age, sex and other symptoms) as well healthy controls, using a categorical approach. The authors found a clear association between impaired clinical insight and smaller fronto-temporal, occipital and cerebellar grey matter volumes in stable long-term schizophrenia patients.

Applications

Clinical insight, as a neurological function, is likely to be dependent on complex neurocognitive interplay with contributions from multiple neural networks.

Terminology

Voxel-based-morphometry is a neuroimaging analysis technique in which structural brain properties are examined on a voxel-by-voxel basis and reported in standardized coordinates. Clinical insight refers to a patient's complex state of awareness of his or her own mental disorder.

Peer-review

The study is well designed and the manuscript is clearly written and easy to read all throughout.

REFERENCES

1   **Amador XF**, Seckinger RA. The assessment of insight: A methodological review. *Psychiatr Ann* 1997; **27**: 798-805 [DOI: 10.3928/0048-5713-19971201-09]
2   **David AS**. Insight and psychosis. *Br J Psychiatry* 1990; **156**: 798-808 [PMID: 2207510 DOI: 10.1192/bjp.156.6.798]
3   **Ouzir M**, Azorin JM, Adida M, Boussaoud D, Battas O. Insight in schizophrenia: from conceptualization to neuroscience. *Psychiatry Clin Neurosci* 2012; **66**: 167-179 [PMID: 22443240 DOI: 10.1111/j.1440-1819.2012.02325.x]
4   **Sartorius N**, Shapiro R, Kimura M, Barrett K. WHO international pilot study of schizophrenia. *Psychol Med* 1972; **2**: 422-425 [PMID: 4656537 DOI: 10.1017/S0033291700045244]
5   **Kelly BD**, Clarke M, Browne S, McTigue O, Kamali M, Gervin M, Kinsella A, Lane A, Larkin C, O'Callaghan E. Clinical predictors of admission status in first episode schizophrenia. *Eur Psychiatry* 2004; **19**: 67-71 [PMID: 15051104 DOI: 10.1016/j.eurpsy.2003.07.009]
6   **McEvoy JP**, Freter S, Everett G, Geller JL, Appelbaum P, Apperson LJ, Roth L. Insight and the clinical outcome of schizophrenic patients. *J Nerv Ment Dis* 1989; **177**: 48-51 [PMID: 2535871]
7   **David AS**, Amador XF, Morgan KD. Neuropsychological studies of insight in psychosis, in Insight and Psychosis: Awareness of Illness in Schizophrenia and Related Disorders. Oxford: Oxford University Press, 2004: 177-193
8   **Lysaker PH**, Vohs J, Hillis JD, Kukla M, Popolo R, Salvatore G, Dimaggio G. Poor insight into schizophrenia: contributing factors, consequences and emerging treatment approaches. *Expert Rev Neurother* 2013; **13**: 785-793 [PMID: 23898850 DOI: 10.1586/14737175.2013.811150]
9   **Mintz AR**, Addington J, Addington D. Insight in early psychosis: a 1-year follow-up. *Schizophr Res* 2004; **67**: 213-217 [PMID: 14984880 DOI: 10.1016/S0920-9964(03)00047-1]
10   **Amador XF**, Strauss DH, Yale SA, Flaum MM, Endicott J, Gorman JM. Assessment of insight in psychosis. *Am J Psychiatry* 1993; **150**: 873-879 [PMID: 8494061 DOI: 10.1176/ajp.150.6.873]
11   **López-Moríñigo JD**, Ramos-Ríos R, David AS, Dutta R. Insight in schizophrenia and risk of suicide: a systematic update. *Compr Psychiatry* 2012; **53**: 313-322 [PMID: 21821236 DOI: 10.1016/j.comppsych.2011.05.015]
12   **Sharaf AY**, Ossman LH, Lachine OA. A cross-sectional study of the relationships between illness insight, internalized stigma, and suicide risk in individuals with schizophrenia. *Int J Nurs Stud* 2012; **49**: 1512-1520 [PMID: 22939218 DOI: 10.1016/j.ijnurstu.2012.08.006]
13   **Gharabawi GM**, Lasser RA, Bossie CA, Zhu Y, Amador X. Insight and its relationship to clinical outcomes in patients with schizophrenia or schizoaffective disorder receiving long-acting risperidone. *Int Clin Psychopharmacol* 2006; **21**: 233-240 [PMID: 16687995 DOI: 10.1097/00004850-200607000-00006]
14   **McGorry PD**, McConville SB. Insight in psychosis: an elusive target. *Compr Psychiatry* 1999; **40**: 131-142 [PMID: 10080260 DOI: 10.1016/S0010-440X(99)90117-7]
15   **Bisiach E**, Vallar G, Perani D, Papagno C, Berti A. Unawareness of disease following lesions of the right hemisphere: anosognosia for hemiplegia and anosognosia for hemianopia. *Neuropsychologia* 1986; **24**: 471-482 [PMID: 3774133 DOI: 10.1016/0028-3932(86)90092-8]
16   **Pia L**, Neppi-Modona M, Ricci R, Berti A. The anatomy of anosognosia for hemiplegia: a meta-analysis. *Cortex* 2004; **40**: 367-377 [PMID: 15156794 DOI: 10.1016/S0010-9452(08)70131-X]
17   **Amador XF**, Strauss DH, Yale SA, Gorman JM. Awareness of illness in schizophrenia. *Schizophr Bull* 1991; **17**: 113-132 [PMID: 2047782 DOI: 10.1093/schbul/17.1.113]
18   **McGlynn SM**, Schacter DL. The neuropsychology of insight: Impaired awareness of deficits in a psychiatric context. *Psychiatr Ann* 1997; **27**: 806-811 [DOI: 10.3928/0048-5713-19971201-10]
19   **Shad MU**, Keshavan MS, Tamminga CA, Cullum CM, David A. Neurobiological underpinnings of insight deficits in schizophrenia. *Int Rev Psychiatry* 2007; **19**: 437-446 [PMID: 17671876 DOI: 10.1080/09540260701486324]
20   **Takai A**, Uematsu M, Ueki H, Sone K. Insight and its related factors in chronic schizophrenic patients: A preliminary study. *Eur J Psychiatry* 1992; **6**: 159-170 [DOI: 10.1016/0920-9964(91)90197-Y]
21   **Flashman LA**, McAllister TW, Andreasen NC, Saykin AJ. Smaller brain size associated with unawareness of illness in patients with schizophrenia. *Am J Psychiatry* 2000; **157**: 1167-1169 [PMID: 10873930 DOI: 10.1176/appi.ajp.157.7.1167]
22   **Larøi F**, Fannemel M, Rønneberg U, Flekkøy K, Opjordsmoen S, Dullerud R, Haakonsen M. Unawareness of illness in chronic schizophrenia and its relationship to structural brain measures and neuropsychological tests. *Psychiatry Res* 2000; **100**: 49-58 [PMID: 11090725 DOI: 10.1016/S0925-4927(00)00063-9]
23   **Cooke MA**, Fannon D, Kuipers E, Peters E, Williams SC, Kumari V. Neurological basis of poor insight in psychosis: a voxel-based MRI study. *Schizophr Res* 2008; **103**: 40-51 [PMID: 18539438 DOI: 10.1016/j.schres.2008.04.022]
24   **Ha TH**, Youn T, Ha KS, Rho KS, Lee JM, Kim IY, Kim SI, Kwon JS. Gray matter abnormalities in paranoid schizophrenia and their clinical correlations. *Psychiatry Res* 2004; **132**: 251-260 [PMID: 15664796 DOI: 10.1016/j.pscychresns.2004.05.001]
25   **Morgan KD**, Dazzan P, Morgan C, Lappin J, Hutchinson G, Suckling J, Fearon P, Jones PB, Leff J, Murray RM, David AS. Insight, grey matter and cognitive function in first-onset psychosis. *Br J Psychiatry* 2010; **197**: 141-148 [PMID: 20679268 DOI: 10.1192/bjp.bp.109.070888]
26   **Sapara A**, Cooke M, Fannon D, Francis A, Buchanan RW, Anilkumar AP, Barkataki I, Aasen I, Kuipers E, Kumari V. Prefrontal cortex and insight in schizophrenia: a volumetric MRI study. *Schizophr Res* 2007; **89**: 22-34 [PMID: 17097853 DOI: 10.1016/j.schres.2006.09.016]
27   **Shad MU**, Muddasani S, Prasad K, Sweeney JA, Keshavan MS. Insight and prefrontal cortex in first-episode Schizophrenia.

Neuroimage 2004; **22**: 1315-1320 [PMID: 15219603 DOI: 10.1016/j.neuroimage.2004.03.016]

28   **Shad MU**, Muddasani S, Keshavan MS. Prefrontal subregions and dimensions of insight in first-episode schizophrenia--a pilot study. *Psychiatry Res* 2006; **146**: 35-42 [PMID: 16361089 DOI: 10.1016/j.pscychresns.2005.11.001]

29   **Palaniyappan L**, Mallikarjun P, Joseph V, White TP, Liddle PF. Reality distortion is related to the structure of the salience network in schizophrenia. *Psychol Med* 2011; **41**: 1701-1708 [PMID: 21144116 DOI: 10.1017/S0033291710002205]

30   **Orfei MD**, Piras F, Macci E, Caltagirone C, Spalletta G. The neuroanatomical correlates of cognitive insight in schizophrenia. *Soc Cogn Affect Neurosci* 2013; **8**: 418-423 [PMID: 22287264 DOI: 10.1093/scannss016]

31   **Spalletta G**, Piras F, Piras F, Caltagirone C, Orfei MD. The structural neuroanatomy of metacognitive insight in schizophrenia and its psychopathological and neuropsychological correlates. *Hum Brain Mapp* 2014; **35**: 4729-4740 [PMID: 24700789 DOI: 10.1002/hbm.22507]

32   **David A**, van Os J, Jones P, Harvey I, Foerster A, Fahy T. Insight and psychotic illness. Cross-sectional and longitudinal associations. *Br J Psychiatry* 1995; **167**: 621-628 [PMID: 8564318 DOI: 10.1192/bjp.167.5.621]

33   **Rossell SL**, Coakes J, Shapleske J, Woodruff PW, David AS. Insight: its relationship with cognitive function, brain volume and symptoms in schizophrenia. *Psychol Med* 2003; **33**: 111-119 [PMID: 12537042 DOI: 10.1017/S0033291702006803]

34   **McFarland J**, Cannon DM, Schmidt H, Ahmed M, Hehir S, Emsell L, Barker G, McCarthy P, Elliott MA, McDonald C. Association of grey matter volume deviation with insight impairment in first-episode affective and non-affective psychosis. *Eur Arch Psychiatry Clin Neurosci* 2013; **263**: 133-141 [PMID: 22673767 DOI: 10.1007/s00406-012-0333-8]

35   **Bassitt DP**, Neto MR, de Castro CC, Busatto GF. Insight and regional brain volumes in schizophrenia. *Eur Arch Psychiatry Clin Neurosci* 2007; **257**: 58-62 [PMID: 16960651 DOI: 10.1007/s00406-006-0685-z]

36   **Shad MU**, Tamminga CA, Cullum M, Haas GL, Keshavan MS. Insight and frontal cortical function in schizophrenia: a review. *Schizophr Res* 2006; **86**: 54-70 [PMID: 16837168 DOI: 10.1016/j.schres.2006.06.006]

37   **Aleman A**, Agrawal N, Morgan KD, David AS. Insight in psychosis and neuropsychological function: meta-analysis. *Br J Psychiatry* 2006; **189**: 204-212 [PMID: 16946354 DOI: 10.1192/bjp.189.3.204]

38   **Dazzan P**, Lloyd T, Morgan KD, Zanelli J, Morgan C, Orr K, Hutchinson G, Fearon P, Allin M, Rifkin L, McGuire PK, Doody GA, Holloway J, Leff J, Harrison G, Jones PB, Murray RM. Neurological abnormalities and cognitive ability in first-episode psychosis. *Br J Psychiatry* 2008; **193**: 197-202 [PMID: 18757976 DOI: 10.1192/bjp.bp.107.045450]

39   **Antonova E**, Sharma T, Morris R, Kumari V. The relationship between brain structure and neurocognition in schizophrenia: a selective review. *Schizophr Res* 2004; **70**: 117-145 [PMID: 15329292 DOI: 10.1016/j.schres.2003.12.002]

40   **First M**, Gibbon M, Spitzer RL, William J, Benjamin L. Users guide for the Structured Clinical Interview for DSM IV Axis II Personality Disorders. Psychiatric Institute, Biometrics Research: New York, 1997

41   **Birchwood M**, Smith J, Drury V, Healy J, Macmillan F, Slade M. A self-report Insight Scale for psychosis: reliability, validity and sensitivity to change. *Acta Psychiatr Scand* 1994; **89**: 62-67 [PMID: 7908156 DOI: 10.1111/j.1600-0447.1994.tb01487.x]

42   **David A**, Kemp R. Five perspectives on the phenomenon of insight in psychosis. *Psychiatr Ann* 1997; **27**: 791-797 [DOI: 10.3928/0048-5713-19971201-08]

43   **Kay SR**, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987; **13**: 261-276 [PMID: 3616518]

44   **Nelson H**, Willison J. National Adult Reading Test. Windsor: Manual Nfer-Nelson, 1991

45   **Simmons A**, Arridge SR, Barker GJ, Williams SC. Simulation of MRI cluster plots and application to neurological segmentation. *Magn Reson Imaging* 1996; **14**: 73-92 [PMID: 8656992 DOI: 10.1016/0730-725X(95)02040-Z]

46   **Reichenberg A**, Harvey PD. Neuropsychological impairments in schizophrenia: Integration of performance-based and brain imaging findings. *Psychol Bull* 2007; **133**: 833-858 [PMID: 17723032 DOI: 10.1037/0033-2909.133.5.833]

47   **Flashman LA**, McAllister TW, Johnson SC, Rick JH, Green RL, Saykin AJ. Specific frontal lobe subregions correlated with unawareness of illness in schizophrenia: a preliminary study. *J Neuropsychiatry Clin Neurosci* 2001; **13**: 255-257 [PMID: 11449033 DOI: 10.1176/jnp.13.2.255]

48   **Bergé D**, Carmona S, Rovira M, Bulbena A, Salgado P, Vilarroya O. Gray matter volume deficits and correlation with insight and negative symptoms in first-psychotic-episode subjects. *Acta Psychiatr Scand* 2011; **123**: 431-439 [PMID: 21054282 DOI: 10.1111/j.1600-0447.2010.01635.x]

49   **Sapara A**, Ffytche DH, Birchwood M, Cooke MA, Fannon D, Williams SC, Kuipers E, Kumari V. Preservation and compensation: the functional neuroanatomy of insight and working memory in schizophrenia. *Schizophr Res* 2014; **152**: 201-209 [PMID: 24332795 DOI: 10.1016/j.schres.2013.11.026]

50   **van der Meer L**, de Vos AE, Stiekema AP, Pijnenborg GH, van Tol MJ, Nolen WA, David AS, Aleman A. Insight in schizophrenia: involvement of self-reflection networks? *Schizophr Bull* 2013; **39**: 1288-1295 [PMID: 23104865 DOI: 10.1093/schbul/sbs122]

51   **Sapara A**, Ffytche DH, Cooke MA, Williams SC, Kumari V. Is it me? Verbal self-monitoring neural network and clinical insight in schizophrenia. *Psychiatry Res* 2015; **234**: 328-335 [PMID: 26549744 DOI: 10.1016/j.pscychresns.2015.10.007]

52   **Shad MU**, Keshavan MS. Neurobiology of insight deficits in schizophrenia: An fMRI study. *Schizophr Res* 2015; **165**: 220-226 [PMID: 25957484 DOI: 10.1016/j.schres.2015.04.021]

53   **Vogeley K**, Fink GR. Neural correlates of the first-person-perspective. *Trends Cogn Sci* 2003; **7**: 38-42 [PMID: 12517357 DOI: 10.1016/S1364-6613(02)00003-7]

54   **Andreasen NC**, O'Leary DS, Cizadlo T, Arndt S, Rezai K, Watkins GL, Ponto LL, Hichwa RD. Remembering the past: two facets of episodic memory explored with positron emission tomography. *Am J Psychiatry* 1995; **152**: 1576-1585 [PMID: 7485619 DOI: 10.1176/ajp.152.11.1576]

55   **Northoff G**, Heinzel A, de Greck M, Bermpohl F, Dobrowolny H, Panksepp J. Self-referential processing in our brain--a meta-analysis of imaging studies on the self. *Neuroimage* 2006; **31**: 440-457 [PMID: 16466680 DOI: 10.1016/j.neuroimage.2005.12.002]

56   **Shenton ME**, Dickey CC, Frumin M, McCarley RW. A review of MRI findings in schizophrenia. *Schizophr Res* 2001; **49**: 1-52 [PMID: 11343862 DOI: 10.1016/S0920-9964(01)00163-3]

57   **Andreasen NC**, O'Leary DS, Cizadlo T, Arndt S, Rezai K, Ponto LL, Watkins GL, Hichwa RD. Schizophrenia and cognitive dysmetria: a positron-emission tomography study of dysfunctional prefrontal-thalamic-cerebellar circuitry. *Proc Natl Acad Sci USA* 1996; **93**: 9985-9990 [PMID: 8790444 DOI: 10.1073/pnas.93.18.9985]

58   **Schmahmann JD**. From movement to thought: anatomic substrates of the cerebellar contribution to cognitive processing. *Hum Brain Mapp* 1996; **4**: 174-198 [PMID: 20408197 DOI: 10.1002/(SICI)1097-0193(1996)4: 3< 174: : AID-HBM3> 3.0.CO; 2-0]

59   **Picard H**, Amado I, Mouchet-Mages S, Olié JP, Krebs MO. The role of the cerebellum in schizophrenia: an update of clinical, cognitive, and functional evidences. *Schizophr Bull* 2008; **34**: 155-172 [PMID: 17562694 DOI: 10.1093/schbul/sbm049]

60   **Raveendran V**, Kumari V. Clinical, cognitive and neural correlates of self-monitoring deficits in schizophrenia: an update. *Acta Neuropsychiatr* 2007; **19**: 27-37 [PMID: 26952795 DOI: 10.1111/j.1601-5215.2007.00151.x]

61   **Kumari V**, Fannon D, Ffytche DH, Raveendran V, Antonova E,

Premkumar P, Cooke MA, Anilkumar AP, Williams SC, Andrew C, Johns LC, Fu CH, McGuire PK, Kuipers E. Functional MRI of verbal self-monitoring in schizophrenia: performance and illness-specific effects. *Schizophr Bull* 2010; **36**: 740-755 [PMID: 18997158 DOI: 10.1093/schbul/sbn148]

62 **Arnt J**, Skarsfeldt T. Do novel antipsychotics have similar pharmacological characteristics? A review of the evidence. *Neuropsychopharmacology* 1998; **18**: 63-101 [PMID: 9430133 DOI: 10.1016/S0893-133X(97)00112-7]

63 **Miyamoto S**, Merrill DB, Lieberman JA, Fleischhacker WW, Marder SR. Antipsychotic drugs, in Psychiatry. In: Tasman A, Kay J, Lieberman JA, First MB, Mario M, editors. USA: John Wiley & Sons, Chichester, 2008: 2161-2201 [DOI: 10.1002/9780470515167.ch102]

64 **Haijma SV**, Van Haren N, Cahn W, Koolschijn PC, Hulshoff Pol HE, Kahn RS. Brain volumes in schizophrenia: a meta-analysis in over 18 000 subjects. *Schizophr Bull* 2013; **39**: 1129-1138 [PMID: 23042112 DOI: 10.1093/schbul/sbs118]