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Case Control Study

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

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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.

Key words: Psychosis; Insight; Grey matter volumes; Fronto-temporal; Neural networks; Birchwood insight scale

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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.

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[4-6]. Impaired insight in schizophrenia is of growing importance due to its direct correlation with poor clinical outcomes, such as frequent relapses and hospital admissions[9], poor compliance with medication and treatment plans[10-18], severe psychopathology[9], greater suicidal tendencies and self-injurious behaviour[19-22]. 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 anosognosia, 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 fasciculum, left corona radiata, lent 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[32]. 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 ≥ 3 mo; (2) in the stable (chronic) phase of the illness; and (3) ≥ 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\(^{(40)}\). All MRI images were converted into ANALYZE format (ANALYZE software, BRU, Mayo Foundation, Rochester, MN) and pre-processed using Statistical Parametric Mapping (SPM8; http://www.fil.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 \(P \leq 0.05\) (two-tailed), unless stated otherwise.

**MRI:** Group differences (healthy controls vs Insight\(^+\) patients, health controls vs Insight\(^-\) patients, 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...
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 parahippocampal 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 gyrus[23,26,28,47,48] 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 clinical insight levels, possibly in all domains. Other VBM studies have also reported an association between the precuneus grey matter volumes and impaired clinical insight[23,48].

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) |
|----------------|---------------------------------------------|--------------------------------------------------|--------------------------------------------------|
| Demographics   | Mean (SD) Range                             | Mean (SD) Range                                  | Mean (SD) Range                                  |
| 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                          | 16.15 (3.38) 8-25                                | 12.70 (13.90) 43-108                            |
| Age at illness onset (yr)                                   | 25.90 (8.72) 13-48                            | 17.00 (5.38) 8-25                                | 15.05 (2.86) 13-14                              |
| PANSS positive symptoms                                     | 16.15 (3.38) 8-25                            | 17.00 (5.38) 8-25                                | 15.05 (2.86) 13-14                              |
| PANSS negative symptoms                                     | 17.20 (4.38) 7-27                            | 18.15 (5.46) 8-27                                | 17.20 (4.38) 7-27                               |
| PANSS general psychopathology                               | 34.35 (7.36) 24-56                           | 35.25 (10.93) 20-59                              | 35.25 (10.93) 20-59                             |
| PANSS total symptoms                                        | 43.90 (10.93) 20-59                          | 113.10 (9.91) 91-128                             | 113.10 (9.91) 91-128                            |
| Medication (chlorpromazine equivalent in mg)                | 461.21 (333.95) 100-160                       | 596.63 (366.49) 200-1367                         | 596.63 (366.49) 200-1367                         |
| Medication type                                            | Atypical antipsychotics                       | --                                               | --                                               |
| Typical antipsychotics                                      | 18 (9 olanzapine, 5 risperidone, 3 clozapine,  | 13 (7 olanzapine, 3 clozapine, 1 aripiprazole, 1  |
|                                                           | 1 quetiapine)                                | amisulpride, 1 risperidone)                      |
|                                                           | 2 (1 sulpiride, 1 haloperidol)               | fluphenazone, 1 sulpiride, 1 haloperidol)        |
|                                                           | Both                                         | 2 (1 on clozapine + levomepromazine, 1 zuclopenthixol + aripiprazole) |

NART: National Adult Reading Test[46]; BIS: Birchwood insight scale[46]; PANSS: Positive and negative syndrome scale[46].
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. 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. There have been previous reports of cerebellar atrophy, on average, in schizophrenia patients. A previous study also observed a significant association between impaired clinical insight and reduced bilateral

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 |
|---|---|---|---|---|---|---|---|
| Insight $>$ Insight patients | Superior temporal gyrus | 22 | 46555 | R | 63 | -3 | 5 | 4.91 | 0.001 | 0.020 |
| Inferior frontal gyrus | 6 | 54 | 0 | 4.74 | 0.034 |
| Inferior frontal gyrus | 6 | 64 | 0 | 4.68 | 0.040 |
| Precentral gyrus | 4 | 66 | -5 | 22 | 4.55 | 0.057 |
| Postcentral gyrus | 43 | 66 | -8 | 16 | 4.33 | 0.106 |
| Inferior frontal gyrus | 47 | 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 |
| 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 |
| Cuneus | 18 | -35 | 99 | 3 | 4.43 | 0.003 | 0.082 |
| Cerebellum | - | R | 35 | -90 | 5 | 4.26 | 0.129 |
| Cuneus | 18 | 26 | -93 | 3 | 4.30 | 0.097 |
| Cerebellum | - | R | 4 | -61 | 2 | 3.88 | 0.317 |
| Cuneus | 18 | 5 | -98 | 10 | 3.50 | 0.630 |
| Cerebellum | - | 5 | -96 | 3 | 3.44 | 0.674 |
| Cerebellum | - | -36 | -82 | -15 | 3.38 | 0.730 |
| Insight $>$ Insight patients | Healthy controls $>$ Insight patients | Nil significant |
| 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 |
| Inferior temporal gyrus | 20 | -28 | -14 | 41 | 3.61 | 0.333 |
| Parahippocampal gyrus | 34 | -13 | 4 | 23 | 3.58 | 0.552 |
| Middle frontal gyrus | 11 | -42 | 40 | -19 | 3.39 | 0.722 |
| Inferior occipital gyrus | 18 | 3511 | L | -38 | 92 | -2 | 4.51 | 0.034 | 0.065 |
| Middle occipital gyrus | 19 | -52 | -76 | 10 | 4.29 | 0.117 |
| Middle temporal gyrus | 39 | -53 | -72 | 22 | 3.37 | 0.740 |
| 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 | 0.335 |
| (posterior lobe) | 38 | -82 | -41 | 3.91 | 0.489 |
| Insight $>$ healthy controls | Healthy controls $>$ Insight patients | Nil significant |
| Insight $>$ healthy controls | Nil significant |

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

There have been previous reports of cerebellar atrophy, on average, in schizophrenia patients. A previous study also observed a significant association between impaired clinical insight and reduced bilateral
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...
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 profiles60,61 as well as in their effects on brain volumes62. 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 others19,23,49,63,64.

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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.

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).
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.

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