

## Insight and prefrontal cortex in first-episode Schizophrenia

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Few studies have investigated the neurobiological basis of impaired insight in antipsychotic-naïve schizophrenia. However, the relationship between insight and specific prefrontally mediated cognitive functions suggests that insight deficits may be an expression of prefrontal cortical dysfunction. This study was designed to examine the relationship among insight, neurocognition, and dorsolateral prefrontal cortex (DLPFC) volumes in first-episode antipsychotic-naïve schizophrenia subjects. DLPFC volumes were compared between 35 first-episode schizophrenia subjects with good ( $n = 17$ ) and poor insight ( $n = 18$ ). Morphometric measurements were based on MRI scans by trained raters blind to clinical information. First-episode schizophrenia subjects with poor insight showed decreased right DLPFC volumes relative to those with good insight. In addition, those with poor insight had higher levels of perseverative errors (PEs) on the Wisconsin Card Sort Test (WCST). No differences in other neuropsychological measures were found between the good and poor insight groups. Similarly, no differences were found between schizophrenia subjects with good versus poor insight on any of the psychopathological measures employed in this study. These findings suggest that poor insight in schizophrenia may be a function of specific prefrontally mediated neurocognitive deficits rather than a global impairment in neuropsychological functioning or different profiles of psychopathology.

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### Introduction

Insight has been identified as an important clinical outcome measure in schizophrenia (Amador and Gorman, 1998). Poor insight

has been associated with treatment nonadherence (Amador and Gorman, 1998; Amador et al., 1994; Carpenter et al., 1996; Lin et al., 1979; McEvoy et al., 1989; Pini et al., 2001), poor prognosis (Amador et al., 1993), higher frequency of involuntary hospitalizations (David, 1992; McEvoy et al., 1989), and poor psychosocial functioning (Amador et al., 1994). Insight into illness has been increasingly described as a multidimensional phenomenon encompassing awareness of various aspects of the disease such as being aware of the illness itself, the social consequences of the illness, the need for treatment, awareness of symptoms, and correct attribution of symptoms to that illness (Amador et al., 1994).

In the past, poor insight in schizophrenia has been variously attributed to defensive denial, willful preference for psychosis, and personality style (Amador and David, 1998). However, a growing body of literature suggests that poor insight may be a function of specific neurocognitive deficits (Amador and David, 1998). Among different neurocognitive functions assessed in insight studies, only prefrontally mediated cognitive measures, such as perseverative errors (PEs) and categories completed (CC) on Wisconsin Card Sorting Test (WCST), were observed to have an association with insight deficits. For example, 12 out of 19 studies reported a positive relationship between various insight deficits and impaired performance on the WCST (Laroi et al., 2000; Lysaker and Bell 1994; Lysaker et al., 1998, 2002; Marks et al., 2000; McEvoy et al., 1996; Mohamed et al., 1999; Rossell et al., 2003; Smith et al., 2000; Voruganti et al., 1997; Young et al., 1993, 1998). However, the studies that failed to show a relationship between WCST performance and insight had methodological problems, such as being conducted in acutely ill hospitalized patients who can have difficulties completing the WCST because of acute confusion rather than persistent cognitive deficits (Chen et al., 2001; Cuesta et al., 1995; Sanz et al., 1998) or in patients with few positive symptoms (Collins et al., 1997; Dickerson et al., 1997). Some of these studies used a single-item insight measure (Goldberg et al., 2001; Kim et al., 2003) and a heterogeneous sample (Goldberg et al., 2001). The evidence linking poor insight to impaired executive function suggests that poor insight may be related specifically to abnormalities of prefrontal cortex (Goldstein et al., 1999; Gur et al., 2000; Hirayasu et al., 2001) rather than abnormalities in other brain areas such as in hippocampus (Martin et al., 2000).

Few studies, however, have examined the relation between brain structure and impaired insight in schizophrenia. The findings from

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these studies have been inconsistent. For example, two studies have failed to find any relationship between ventricle–brain ratio (VBR; David et al., 1995) or whole brain volume (Russell et al., 2003) and poor insight, while one study has observed an increase in VBR (Takai et al., 1992) and one has reported cortical atrophy (Lorai et al., 2002) in schizophrenia subjects with poor insight. However, these studies were performed on chronic schizophrenia patients making it difficult to tease out the effects of illness chronicity and exposure to antipsychotic medications. The only study that examined the association between impaired insight and specific brain regions was conducted in chronic schizophrenia; this study observed an association between unawareness of illness and bilateral volume reductions in the middle frontal gyrus, gyrus rectus, and left anterior cingulate gyrus (Flashman et al. 2001). However, a small sample size and effects of long-term use of antipsychotic medications and illness chronicity on the prefrontal regional volumes may limit interpretation of results from this study.

We examined the relationship between dorsolateral prefrontal cortex (DLPFC) volume and insight in first-episode antipsychotic-naive schizophrenia subjects. We hypothesized that (1) reductions in DLPFC volume would be greater in subjects with poor insight compared to those with good insight, and (2) subjects with poor insight would have poorer performance on tests of prefrontally mediated cognitive functions compared to those with good insight. We used hippocampal volume, known to be reduced in schizophrenia (Shenton et al., 2001) as a comparison brain region.

## Methods

### Subjects

A series of first-episode antipsychotic-naive subjects ( $n = 35$ ,  $M/F = 24/11$ , age =  $26.3 \pm 7.0$ ) with DSM IV diagnosis of schizophrenia ( $n = 30$ ) or schizoaffective disorder ( $n = 5$ ) were recruited through the Western Psychiatric Institute and Clinic, Pittsburgh, and through the Center for Nervous and Mental Disorder—a large ongoing study of first-break psychosis (Table 1). The subjects were recruited and studied during their first hospitalization, before they were started on their antipsychotic medications. Diagnoses were based on the Structured Clinical Interview for DSM IV disorders (SCID; Spitzer et al., 1992). All diagnoses were confirmed in a consensus diagnostic conference of

senior diagnosticians where all the professionals who had a contact with the patient participated. All patients were followed up for at least 6 months to confirm diagnostic stability and obtain additional history. We obtained written informed consents from the subjects after fully explaining the study. The study was approved by the University of Pittsburgh School of Medicine Institutional Review Board (IRB). All subjects were physically healthy and did not have a systemic or neurological illness, mental retardation, or head injury temporally related to the psychosis onset. None of the subjects was diagnosed with substance abuse in the previous 4 weeks or dependence within the past 6 months. Antipsychotic-naive status was confirmed based on detailed history taking, collateral information, and diagnostic interviews.

### Clinical ratings

Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962), Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1989, 1990), and Scale for the Assessment of Negative Symptoms (SANS; 1989) were used to rate psychopathology. Global functioning was assessed with Global Assessment of Function Scale (GAF; Luborsky, 1962).

### Neuropsychological assessments

The neuropsychological battery comprised of computerized version of Wisconsin Card Sorting Test (WCST; Heaton, 1981) to assess executive functioning, California Verbal Learning Test (CVLT; Delis et al., 1983) to assess verbal learning and memory, and Benton Judgment of Line of Orientation Test (BJLOT; Benton, 1975) to assess visuospatial perception and learning. While Grooved Pegboard Test (Reitan and Wolfson, 1985) and Ammons Quick IQ Test (Ammons and Ammons, 1962) were used to control for psychomotor speed and intelligence, respectively, Annett Scale was administered to control for handedness (Annett, 1967). These test data provide the opportunity to determine whether reduced insight is specifically related to specific cognitive functions mediated by DLPFC.

### Insight assessment

A single question, derived from the insight item of the Hamilton Depression Rating Scale (HDRS; Hamilton, 1960)

Table 1  
Demographic characteristics and WCST scores of subjects with and without insight deficits

	Good insight ( $n = 17$ , $M/F = 9/8$ )	Poor insight ( $n = 18$ , $M/F = 15/3$ )	Statistic	<i>df</i>	<i>P</i>
Age ( $\pm$ SD)	25.36 $\pm$ 7.83	26.13 $\pm$ 6.70	$t = -0.31$	33	0.75
IQ ( $\pm$ SD)	97.63 $\pm$ 14.64	90.0 $\pm$ 15.44	$t = 1.42$	28	0.16
GAF ( $\pm$ SD)	33.11 $\pm$ 12.54	29 $\pm$ 8.20	$t = 0.88$	33	0.39
SAPS ( $\pm$ SD)	2.83 $\pm$ 0.92	2.71 $\pm$ 1.10	$t = 0.37$	33	0.71
SANS ( $\pm$ SD)	2.60 $\pm$ 0.65	2.44 $\pm$ 0.92	$t = 0.58$	33	0.56
BPRS ( $\pm$ SD)	54.33 $\pm$ 8.18	49.82 $\pm$ 8.76	$t = 1.57$	33	0.12
Illness duration ( $\pm$ SD) <sup>a</sup>	143 $\pm$ 287	147 $\pm$ 159	$U = 134$		0.54 <sup>b</sup>
Handedness ( $\pm$ SD)	0.39 $\pm$ 0.78	0.12 $\pm$ 0.33	$U = 139$		0.66 <sup>b</sup>
WCST PE ( $\pm$ SD)	12.33 $\pm$ 5.24	37.600 $\pm$ 26.48	$t = 3.53$	33	0.001
WCST CC ( $\pm$ SD)	5.10 $\pm$ 0.80	4.80 $\pm$ 0.48	$t = 2.32$	28	0.103

<sup>a</sup> In weeks; DLPFC = dorsolateral prefrontal cortex; Rt. = right; Lt. = left; GAF = global assessment scale; IQ = intelligent quotient; SD = standard deviation; *df* = degree of freedom; WCST = Wisconsin Card Sorting Test; PE = perseverative errors; CC = categories completed; *U* = Mann Whitney *U* test.

<sup>b</sup> Two times one-sided exact *P*.

was used to assess insight similar to the approach previously described by Fennig et al. (1996). The insight question was completed to address the level of awareness into psychiatric illness in general rather than into depression. In this single insight item, 0 referred to good insight (patient acknowledges being ill), 1 referred to partial insight (patient acknowledges illness but attributes it to external causes), and 2 referred to poor insight (patient denies being ill at all). Eighteen subjects received a score of 0 (good insight); 6 received a score of 1 (partial insight), and 11 received 2 (poor insight). Similar to the method described by Fennig et al. (1996), the group with partial insight (score = 1) was added to the group with poor insight (score = 2), thus resulting in two insight groups, one with good insight (score = 0) and the other with poor insight (score = 1 or 2). The relatively older sample of first-episode schizophrenia in our study may not be explained on the basis of delay in seeking treatment due to lack of insight as there were more subjects with good insight as compared to those with partial or poor insight.

To test the validity of insight evaluation in this study, scores on 3-point insight-item of HDRS were adjusted for and correlated with scores on 5-point awareness of illness subitem of Scale to Assess Unawareness of Mental Disorder (SUMD; Amador et al., 1994). In 14 of 35 subjects who were administered both HDRS and SUMD, we observed a significant correlation between scores on HDRS insight-item and SUMD awareness of illness subitem (Spearman  $R = 0.685$ ,  $P = 0.006$ ). All insight assessments were conducted by a single well-trained clinician (KE) who had no knowledge of other clinical or MRI data.

#### MR scans

MRI studies were conducted using the UPMC 1.5 T GE Signa whole-body system. One hundred and twenty-four contiguous 1.5-mm-thick coronal images were obtained using a spoiled gradient (SPGR) pulse sequence (TE = 5 ms, TR = 25 ms,  $256 \times 192$  acquisition matrix, FOV = 24 cm, flip angle =  $40^\circ$ ). Images were obtained perpendicular to the anterior commissure–posterior commissure (AC–PC) line. Morphometric measurements for the DLPFC, hippocampus, and intracranial volume (ICV) were conducted based on MRI scans using NIH IMAGE (Rasband and Bright, 1995) by reliable and trained raters blind to clinical information. Raters had intraclass correlation of 0.87 and 0.86 for right and left DLPFC volumes, respectively, as measured on 10 scans, when they manually outlined the DLPFC in the coronal plane based on a method published earlier (Gilbert et al., 2001). Briefly, the DLPFC was defined using 10 successive slices anterior to the genu of corpus callosum. The superior boundary was the superior frontal sulcus and the inferior boundary was the lateral fissure posteriorly and the horizontal ramus of the lateral fissure anteriorly. The lateral border was formed by the outer edge of the cerebral cortex and the medial border was created by connecting the deepest points on the anterior frontal sulcus and the lateral fissure.

Hippocampal volume was measured using a previously published method (Keshavan et al., 2002). Hippocampus was defined anteriorly at the beginning of the mammillary bodies and posteriorly where inferior colliculi were first visualized (the point of separation of the crux of fornix from the fimbria of the hippocampus). The lateral border was formed in the anterior slices by the temporal horn of lateral ventricle, and more posteriorly, by the gray–white junction along the lateral edge of the hippocampus.

The inferomedial border was formed by a line joining the mammillary body superiorly with the collateral sulcus inferiorly that forms the lateral border of the entorhinal cortex. The superolateral border was formed by the third ventricle. Inter-rater reliability (intraclass correlation coefficient, ICC) for the measurements of hippocampus was 0.81 for the right and 0.83 for the left hippocampus.

Intracranial volume (ICV) was measured using the technique described in Gilbert et al. (2001). ICV included the total brain, ventricular and extra-ventricular CSF, brain stem, and cerebellum. All brain volume measurements were controlled for intracranial volume. Raters had an intraclass correlation of 0.098 for ICV as measured on 10 scans.

#### Statistical analysis

We examined the data for normality of distribution. We applied appropriate statistical corrections for the non-normally distributed data and when the data still remained non-normally distributed, nonparametric tests were performed. A linear correlational analysis was conducted between dichotomous HDRS insight item and ICV-adjusted DLPFC and hippocampal volumes. ICV-adjusted volumes were derived from dividing DLPFC or hippocampus by ICV and multiplying with 100 (DLPFC or hippocampus/ICV  $\times 100$ ) (Table 2). A linear correlation was also conducted between right DLPFC volume and scores on a 3-point HDRS insight-item before it was converted into a dichotomous item. Analysis of covariance (ANCOVA) was used to compare the scores on neuropsychological measures across the groups of schizophrenia subjects with and without good insight using age, gender, and scores on IQ and GAF as covariates.

Table 2  
Raw and intracranial volume (ICV)-adjusted total DLPFC and hippocampal volumes of subjects with and without insight deficits

	Good insight ( $n = 17$ , $M/F = 9/8$ )	Poor insight ( $n = 18$ , $M/F = 15/3$ )
Average Lt. DLPFC ( $\pm$ SD)	18.31 $\pm$ 2.11	17.99 $\pm$ 2.64
Average Rt. DLPFC ( $\pm$ SD)	19.06 $\pm$ 2.10	17.06 $\pm$ 1.69
ICV-adjusted Lt. DLPFC ( $\pm$ SD)	1.29 $\pm$ 0.15	1.28 $\pm$ 0.17
ICV-adjusted Rt. DLPFC ( $\pm$ SD)	1.34 $\pm$ 0.15	1.22 $\pm$ 1.2
Average Lt. hippocampal ( $\pm$ SD)	3.35 $\pm$ 0.80	3.20 $\pm$ 0.97
Average Rt. hippocampal ( $\pm$ SD)	3.40 $\pm$ 1.1	3.17 $\pm$ 0.87
ICV-adjusted Lt. Hippocampal ( $\pm$ SD)	0.24 $\pm$ 0.08	0.23 $\pm$ 0.07
ICV-adjusted Rt. hippocampal ( $\pm$ SD)	0.24 $\pm$ 0.05	0.23 $\pm$ 0.06

## Results

Based on independent *t* tests, no significant differences were observed in scores on SANS, SAPS, or BPRS between subjects with and without poor insight: SAPS ( $t = 0.58, P = 0.56$ ), SANS ( $t = 0.37, P = 0.71$ ), or BPRS ( $t = 1.57, P = 0.12$ ). Similarly, no significant differences were observed in age ( $t = -0.31, P = 0.75$ ) IQ ( $t = 1.42, P = 0.16$ ) or GAF ( $t = 0.88, P = 0.39$ ) between subjects with and without poor insight (Table 1). In addition, based on Mann Whitney *U* Test, no significant differences were observed in the duration of illness ( $U = 0.94, P = 0.54$ ) and handedness ( $U = 0.09, P = 0.66$ ) between the two insight groups. While the number of perseverative errors on the WCST were significantly different between the two insight groups ( $t = 3.53, P = 0.001$ ), the number of categories completed on the test were not ( $t = 2.32, P = 0.103$ ) (Table 1).

Based on correlational analysis, an inverse correlation was found between insight scores and right DLPFC (Spearman  $R = -0.61, P = 0.008$ ) but not left DLPFC volume (Spearman  $R = -0.20, P = 0.71$ ) or right (Spearman  $R = 0.31, P = 0.10$ ) or left hippocampal volumes (Spearman  $R = 0.16, P = 0.82$ ). Similarly, poor insight had a significant relationship with perseverative errors ( $df = 23, F = 13.05, P = 0.001$ ) but not categories completed ( $df = 23, F = 0.52, P = 0.103$ ). Similarly, a linear correlation was observed between 3-point HDRS insight item and ICV-adjusted right DLPFC volume (Spearman  $R = -0.38, P = 0.02$ ).

No differences were observed in schizophrenia subjects with poor versus good insight on CVLT ( $df = 28, F = 0.91, P = 0.35$ ), BJOLT ( $df = 33, F = 0.34, P = 0.57$ ), or Grooved Pegboard scores ( $df = 32, F = 0.94, P = 0.34$ ) after covarying for age, gender, IQ, and GAF.

## Discussion

First-episode schizophrenia patients with poor insight showed significantly smaller right DLPFC volumes as compared to those with preserved insight. The correlation between right DLPFC volume reduction and insight deficits is independent of global cognitive functioning and illness severity as suggested by lack of significant differences in IQ and GAF scores between the two insight groups. Similarly, lack of significant differences in psychopathological measures between the two insight groups suggests that impaired insight may be mediated by different somewhat distinct neurobiological mechanisms than those driving global positive and negative symptom severity. Although this lack of correlation between psychopathology and insight has been reported earlier (McEvoy et al., 1989), this finding is inconsistent with those of several studies that have found a modest but significant relationship between psychopathology and insight (Mintz et al., 2003). This may at least partially be explained by a relatively small sample size, relatively less severity of psychotic symptoms, and the use of a single-item insight measure.

In addition, the association between DLPFC volume and insight observed in first-episode schizophrenia and the absence of differences in illness duration between patients with and without insight suggest that insight deficits may be linked with abnormal maturation of prefrontal brain systems rather than progressive brain deficits. The correlation between IQ and bilateral DLPFC volumes but not IQ and poor insight suggests that there may be a different neuroanatomical basis for insight and IQ deficits within the

DLPFC. The lack of correlation between general intelligence and insight is also reported by earlier studies as well (Goldberg et al., 2001; Kim et al., 2003; Lysaker et al., 1998; Marks et al., 2000). IQ is a reflection of general associative brain function, and absence of correlation of insight with IQ suggests that poor insight may not be due to a generalized cognitive deficit.

The observed deficits in frontal lobe structure were associated with greater deficits in executive functions, such as self-monitoring and conceptual organization, which may be critical for awareness of illness. This suggests that insight deficits may be related to impairments in executive functioning and working memory, which are mediated by the prefrontal cortex (Lysaker et al., 1998; Young et al., 1998). The finding that reduction in the right, but not left DLPFC volume, was significantly associated with insight deficits is consistent with the view that lack of insight in schizophrenia may be similar to anosognosia reported in the right parietal and/or frontal cortical lesions in right-handed subjects (Amador and David, 1998; Stuss and Benson, 1986). The correlation between insight deficits and WCST PE scores, but not verbal fluency (Young et al., 1993), which is primarily mediated by the left frontal cortex, may explain the lack of correlation between insight and left DLPFC volume in our study. It is also noteworthy that if general deficits could explain lack of insight, then one would expect to see a correlation between poor insight and global cognitive impairment or nonspecific deficits in brain structure.

Although schizophrenia subjects have been found to have deficits in multiple domains of cognitive functioning (Hill et al., 2001), no differences were observed in schizophrenia subjects with poor as compared to good insight on cognitive measures mediated by hippocampus, such as verbal memory and learning (CVLT). However, in the context of this profile of generalized neurocognitive deficit within the schizophrenia subjects, only the increased rate of perseverative errors on the WCST differentiated those with poor insight compared to those with good insight. Thus, neurocognitive data are consistent with our observations of structural differences in DLPFC but not hippocampus between subgroups with versus without insight deficits. This suggests that insight deficits may be at least in part independent of generalized intellectual deficits but be more tightly related to disease-related abnormalities in prefrontal cortical anatomy and function.

The clinical significance of this study is underscored by the fact that this was the first study that examined insight deficits in first-episode antipsychotic-naïve schizophrenia subjects. This subject population provides a clinically homogeneous group of patients without the confounding effects of illness chronicity and antipsychotic medications on the formation of insight. However, the study is limited by the fact that insight was assessed by a single categorical item in a relatively small sample size. Insight is a multidimensional phenomenon and involves an awareness and attributional component; thus, further studies are needed to separately examine the neurobiological correlates of the specific dimensions of insight deficits in schizophrenia.

In spite of aforementioned limitations, these structural and neuropsychological data point to the need for future studies to investigate the structural, functional, and neurochemical correlates of insight deficits in early schizophrenia. An understanding of the neurobiological correlates of insight during early schizophrenia may help predict who might need early therapeutic interventions, such as cognitive remediation, to address lack of insight. This is of considerable clinical significance in this population as an improvement in

insight may potentially enhance treatment adherence and thus clinical and functional outcome.

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