White matter integrity and lack of insight in schizophrenia and schizoaffective disorder

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ABSTRACT

Objective: Poor insight into illness is commonly associated with schizophrenia and has implications for the clinical outcome of the disease. A better understanding of the neurobiology of these insight deficits may help the development of new treatments targeting insight. Despite the importance of this issue, the neural correlates of insight deficits in schizophrenia remain poorly understood.
Method: Thirty-six individuals diagnosed with schizophrenia or schizoaffective disorder underwent diffusion tensor imaging (DTI). The subjects were assessed on two dimensions of insight (symptom awareness and attribution of symptoms) using the Scale to Assess Unawareness of Mental Disorder (SUMD). Level of psychosis was assessed with the Positive and Negative Syndrome Scale (PANSS).
Results: White matter abnormalities in the right superior frontal gyrus, left middle frontal gyrus, bilateral parahippocampal gyrus, adjacent to the right caudate head, right thalamus, left insula, left lentiform nucleus, left fusiform gyrus, bilateral posterior cingulate, left anterior cingulate, right cingulate gyrus, left lingual gyrus, and bilateral claustrum were associated with symptom unawareness. Misattribution of symptoms was related to deficits in the white matter adjacent to the right lentiform nucleus, left middle temporal gyrus, and the right precuneus.
Conclusions: Impaired insight in schizophrenia implicates a complex neural circuitry: white matter deficits in fronto-temporo brain regions are linked to symptom unawareness; compromised temporal and parietal white matter regions are involved in the misattribution of symptoms. These findings suggest the multidimensional construct of insight has multiple neural determinants.

1. Introduction

Insight into illness is widely considered to be an important factor in coping with and treating schizophrenia (Amador and David, 2004). For this reason, there is considerable interest in understanding the underlying neural mechanisms of insight, which may have important implications for the development of future insight-oriented neuro-psychiatric treatment. However, although extant research indicates a neurological etiology of insight deficits in schizophrenia (Pia and Tamietto, 2006; Shad et al., 2006b), the specific neural circuitry involved remains poorly understood.

Within clinical psychiatry, insight is commonly considered a multidimensional construct that refers to an individual's awareness of having a mental illness, understanding the need for treatment, awareness of the social consequences of mental disorder, and insight into specific psychopathological symptoms and ability to attribute these symptoms to a mental disorder (Amador et al., 1991, 1993). Diminished insight is associated with severity of psychopathology (Kemp and Lambert, 1995) and is more prevalent in schizophrenia compared to other psychotic disorders (Amador et al., 1994). Moreover, impaired insight poses a problem for adherence to treatment (Buckley et al., 2007; Lacro et al., 2002), prolongs duration of psychosis (Drake et al., 2000), and increases the risk for relapse, re-hospitalization (Drake et al., 2007) and involuntary status in the hospital (Kelly et al., 2004). Conversely, better insight into illness is related to better psychological coping mechanisms (Donohoe et al., 2004; Lysaker et al., 2003), as well as compliance with treatment and improved prognosis (Schwartz et al., 1997).

Early theories on the neurological etiology of insight deficits were partially based on the shared behavioral similarities between insight deficits in schizophrenia and the neurological disorder anosognosia

(unawareness of deficits caused by brain injury). These theories focus on frontal, prefrontal (Amador et al., 1991), and right parietal lobe (David, 1990) deficits. More recent theoretical conceptualizations of insight in schizophrenia argue that the deficits are more complex, with various distinct brain areas implicated (David, 1999).

Neuropsychological studies largely support a relationship between poor insight and brain impairment in the frontal (Lysaker et al., 1998; Ritsner and Blumenkrantz, 2007; Young et al., 1993), and prefrontal and parietal lobes (Laroi et al., 2000; McEvoy et al., 1996), although the findings are inconsistent (Arduini et al., 2003; Cuesta and Peralta, 1994; Drake and Lewis, 2003; Freudenreich et al., 2004; Goodman et al., 2005; Kemp and David, 1996). In fact, reviews of neuropsychological studies suggest that the pathogenesis of insight deficits in schizophrenia is associated with impaired functioning in the frontal and parietal lobes, and these insight deficits are similar to impaired insight found in individuals suffering from anosognosia (Pia and Tamietto, 2006; Shad et al., 2006b).

Neuroimaging research provides further evidence for underlying brain impairment in insight deficits in schizophrenia. Brain studies on insight deficits implicate larger ventricular volume, in particular in the third ventricle (Takai et al., 1992), smaller total brain and intracranial size (Flashman et al., 2000), and frontal lobe atrophy (Laroi et al., 2000). Additionally, insight deficits have been associated with smaller right dorsolateral prefrontal cortex (Shad et al., 2004, 2006a), and smaller bilateral middle frontal gyrus, right gyrus rectus, and left anterior cingulate gyrus volumes (Flashman et al., 2001). Imaging research also links insight deficits to reduced gray matter concentration in the left posterior cingulate, right anterior cingulate, bilateral inferior temporal regions including the lateral fusiform gyri (Ha et al., 2004), the right superior frontal gyrus, total inferior frontal gyrus, right orbitofrontal gyrus, and total prefrontal region (Sapara et al., 2007).

Three imaging studies found no significant correlations between lack of insight and total ventricular volume (David et al., 1995), gray and white matter volumes (Bassitt et al., 2007; Rossell et al., 2003), and cerebrospinal fluid and total brain matter volumes (Rossell et al., 2003). In a longitudinal study on insight improvement, one study found that patients with better insight showed increased activation in the left medial prefrontal cortex and right lingual gyrus (Lee et al., 2006). Two imaging studies report on the attribution of the psychiatric symptoms to a mental disorder; misattribution of symptoms were linked to larger right medial orbitofrontal cortex (Shad et al., 2006a) and smaller superior frontal gyrus volumes (Flashman et al., 2001).

Using a voxel-based morphometry approach to specifically examine insight sub-factors and gray matter volumes in patients with schizophrenia or schizoaffective disorder, Cooke et al. (2008) found correlations between: higher awareness of problems and increased regional gray matter volume in the left precuneus; higher symptom re-labeling and greater absolute gray matter in the right superior temporal gyrus; and, better awareness of and attribution to illness and greater regional gray matter in the left superior-middle temporal gyrus, the right inferior temporal gyrus, and the lateral parietal gyri. A fourth sub-factor, the awareness of need for medication, was not found to correlate with gray matter volumes. More recently, Palaniyappan et al. (2010) used high resolution MRI to examine the white matter volume of the posterior insula, specifically, and found that lower surface area and white matter volume of the right posterior insula, but not the left, was related to reduced insight.

Taken together, the neuroimaging and neuropsychological findings support a neurological etiology of insight deficits in schizophrenia (with some similarities to anosognosia). The distribution of impaired brain regions suggests that the insight deficits may be due to a disruption in neural circuitry, as compared to distinct brain region impairment. Thus far, neuroimaging studies on insight in schizophrenia have utilized either computed tomography (David et al., 1995; Laroi et al., 2000), structural magnetic resonance imaging (sMRI; Cooke et al., 2008; Flashman et al., 2000, 2001; Ha et al., 2004;

Palaniyappan et al., 2010; Rossell et al., 2003; Sapara et al., 2007; Shad et al., 2006a; Takai et al., 1992) or functional MRI (Lee et al., 2006) techniques. To further advance our understanding of the neural circuitry involved in impaired insight in schizophrenia, we employed diffusion tensor imaging (DTI) to study white matter integrity, which provides information on the organization and integrity of white matter.

2. Method

2.1. Participants

Participants were selected from a larger, ongoing neuroimaging study of white matter abnormalities in schizophrenia, which was approved by the Nathan S. Kline Institute for Psychiatric Research/ Rockland Psychiatric Center Institutional Review Board and the Rockland County Department of Mental Health Institutional Review Board. All participants provided written informed consent prior to participation.

Thirty-six patients were included in the analysis. Demographic information is presented in Table 1. All patients met DSM-IV diagnostic criteria for schizophrenia ($n = 32$) or schizoaffective disorder ($n = 4$) as confirmed by the Structured Clinical Interview for DSM-IV Axis I Disorders − Patient Edition (First et al., 1998). Patients were excluded if they met SCID-I/P criteria for substance dependence (lifetime), or substance abuse within the 6 months prior to study enrollment. Patients with neurological disorders or history of head trauma with loss of consciousness greater than 15 min were also excluded.

2.2. Procedure

2.2.1. Clinical ratings

Insight into illness was measured using the Scale to Assess Unawareness of Mental Disorders (SUMD; Amador and Strauss, 1990). The SUMD is a twenty-item scale used to assess a patient's insight based on three dimensions: 1) general awareness of mental illness (including awareness of his or her current and past mental disorder, achieved effects of medication, and social consequences of mental disorder); 2) awareness of psychiatric symptoms, and; 3) attribution of symptoms, which refers to the degree to which he or she attributes the psychiatric symptoms to mental illness. Each item is rated on a Likert-type scale from 0 to 5. General and symptom

Table 1
Demographic and clinical information.

N	36
Age (mean age in years)	37.4 (SD: 10.5)
Sex	Female: 9
	Male: 27
Ethnicity	Black/African-American: 18
	White: 16
	Other: 2
	Hispanic: 5
Diagnostic subtypes	Schizophrenia
	Paranoid: 16
	Disorganized: 2
	Undifferentiated: 12
	Residual: 2
	Schizoaffective
	Bipolar: 2
	Depressed: 2
PANSS total mean score	78.5 (SD: 17.1)
PANSS positive subscale mean score	19.3 (SD: 6.0)
PANSS negative subscale mean score	20.5 (SD: 6.2)
PANSS general subscale mean score	38.7 (SD: 8.4)
PANSS judgment and insight (G12)	4.4 (SD: 1.3)
SUMD symptom awareness (items 4–20 mean score)	3.5 (SD: 1.1)
SUMD attribution awareness (items 4b–20b mean score)	4.1 (SD: 1.1)