Thalamic morphology in schizophrenia and schizoaffective disorder

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ABSTRACT

Background: Biomarkers are needed that can distinguish between schizophrenia and schizoaffective disorder to inform the ongoing debate over the diagnostic boundary between these two disorders. Neuromorphometric abnormalities of the thalamus have been reported in individuals with schizophrenia and linked to core features of the disorder, but have not been similarly investigated in individuals with schizoaffective disorder. In this study, we examine whether individuals with schizoaffective disorder have a pattern of thalamic deformation that is similar or different to the pattern found in individuals with schizophrenia.

Method: T1-weighted magnetic resonance images were collected from individuals with schizophrenia (n = 47), individuals with schizoaffective disorder (n = 15), and controls (n = 42). Large-deformation, high-dimensional brain mapping was used to obtain three-dimensional surfaces of the thalamus. Multiple analyses of variance were used to test for group differences in volume and measures of surface shape.

Results: Individuals with schizophrenia or schizoaffective disorder have similar thalamic volumes. Thalamic surface shape deformation associated with schizophrenia suggests selective involvement of the anterior and posterior thalamus, while deformations in mediodorsal and ventrolateral regions were observed in both groups. Schizoaffective disorder had distinct deformations in medial and lateral thalamic regions.

Conclusions: Abnormalities distinct to schizoaffective disorder suggest involvement of the central and ventroposterior medial thalamus which may be involved in mood circuitry, dorsolateral nucleus which is involved in recall processing, and the lateral geniculate nucleus which is involved in visual processing.

Keywords: Schizophrenia; Schizoaffective disorder; MRI; Neuroimaging; Thalamus

1. Introduction

There is ongoing debate as to whether the DSM-V should replace the distinction between schizophrenia and psychotic mood disorders with a dimensional approach that considers a continuum of psychotic illnesses, including schizophrenia, schizoaffective disorder and psychotic bipolar disorder (Laursen et al., 2009). This approach draws support from recent findings in the genetic, cognitive, and clinical literature that have challenged distinctions between schizophrenia and psychotic mood disorders.

The genetic literature suggests that schizophrenia and schizoaffective disorder share a common genetic risk where the risk of schizoaffective disorder is higher in relatives of schizophrenia patients and vice versa (Gershon et al., 1988; Kendler and Diehl, 1993). Also, some research suggests that schizophrenia and schizoaffective disorder share a number of equally severe cognitive deficits (Barch, 2009), while others have found the severity to be of a lesser magnitude in schizoaffective disorder (Heinrichs et al., 2008). Perhaps the most controversial distinction between schizophrenia and schizoaffective disorder is in the domain of psychopathology. Recent findings are disparate as some show that the severity of positive, negative and disorganized symptoms are similar between individuals with schizophrenia and schizoaffective disorder (Evans et al., 1999; Smith et al., 2009), while others show severity in positive and negative symptoms that rank individuals with schizoaffective disorder as intermediate between individuals with schizophrenia and controls (Peralta and Cuesta, 2008).
Research examining the relationship of cognitive impairment to the psychopathology of individuals with schizophrenia or schizoaffective disorder suggests that both groups show moderate correlations between negative symptoms and cognitive deficits, with the magnitude of correlations in the individuals with schizoaffective disorder being somewhat smaller (Smith et al., 2009).

The debate as to whether schizophrenia and schizoaffective disorder are separable disorders would be greatly informed by determining whether or not schizophrenia and schizoaffective disorder shared similar neurobiological features. In this regard, studies of brain structures, known to play central roles in supporting key cognitive constructs, such as the thalamus, may be particularly helpful (Byne et al., 2009; Csernansky et al., 2004a; Harms et al., 2007).

The results of several studies suggest that the thalamus, a brain region that plays an integral role in cognitive processing and acts as a relay station between the basal ganglia and the cerebral cortex, has a significantly reduced volume in individuals with schizophrenia (Konick and Friedman, 2001; Sim et al., 2006). Multiple studies also examined whether the shape of the thalamus among individuals with schizophrenia has patterns of deformation that are characteristic of the disorder. Shape analysis can be used to identify subtle regional deformations within a structure, and thus can be complimentary to volumetry. Using computational anatomy to examine two independent samples of individuals with schizophrenia, our group has previously found significant inward deformations of the anterior, medial, and posterior regions of the thalamus; thus, implicating the anterior and mediodorsal nucleus and the pulvinar in the pathophysiology of schizophrenia (Csernansky et al., 2004a; Harms et al., 2007).

Although several studies have documented structural abnormalities of the thalamus in individuals with schizophrenia (for review see (Byne et al., 2009)), similar studies have not compared thalamic morphometry between individuals with schizophrenia and individuals with schizoaffective disorder. However, structural abnormalities of the thalamus were found in individuals who are at increased genetic risk for developing schizophrenia or schizoaffective disorder (Ettinger et al., 2007; Harms et al., 2007; Lawrie et al., 1999).

Based on prior research suggesting that schizophrenia and schizoaffective disorder share similar clinical and cognitive profiles (with a lesser magnitude in schizoaffective disorder), and that first-degree relatives are at increased genetic risk and share attenuated thalamic abnormalities, we hypothesized that individuals with schizoaffective disorder would have similar, but perhaps less marked, patterns of thalamic volume loss and shape deformation as compared to individuals with schizophrenia. Given that mood dysregulation is characteristic of schizoaffective disorder (Malhi et al., 2008) and that the thalamus is involved with the neurobiological circuitry associated with mood disorders (Price and Drevets, 2010), we also hypothesized that schizoaffective disorder would have abnormal neurobiological features of the thalamus that are distinct from the patterns associated with schizophrenia. We previously compared the clinical and cognitive profiles of individuals with schizophrenia or schizoaffective disorder using a sample that overlaps with the current one (Smith et al., 2009). Thus, we will report on the clinical and cognitive profiles of the groups in the current study to confirm our prior results, and explore whether there are neurormorphometric abnormalities that correlate to cognition and psychopathology.

2. Methods

2.1. Sample

Participants included 47 individuals with schizophrenia (SCZ), 42 controls (CON), and 15 individuals with schizoaffective disorder (SA). Recruitment methods by our group have been described previously (Smith et al., 2009). The SCZ and CON subjects in this study were selected from a larger sample of available participants from our previous work (Csernansky et al., 2004a; Harms et al., 2007; Smith et al., 2009), in order to match the SA subjects with respect to age, gender, parental SES, and race. Socioeconomic status was measured with the Hollingshead Four Factor Index of Social Status (Hollingshead, 1975).

Given that a longer duration of illness, mood stabilizing psychotropic–anti-psychotic medication treatment, and a history of substance use disorders have been shown to affect thalamic morphometry (Dazzan et al., 2005; Frodl et al., 2008; Gur et al., 1998; Sassi et al., 2002; Wang et al., 2008) and that nicotine reduces gray matter density (McClernon, 2009), we examined whether between-group differences were present for these potential confounds. Between-group differences on demographic and clinical variables are summarized in Table 1. SCZ and SA did not have statistically different durations of illness and lifetime history of substance use disorders. Thus, these variables were not examined as potential confounds. SCZ and SA differed with respect to treatment with antidepressant medication (see Table 1). We also found that SCZ and SA had greater nicotine use than CON. Although the quantity of nicotine use and whether or not patients received treatment with first- and second generation anti-psychotic (FGA, SGA) and antidepressant medications differed between groups, using them as covariates did not contribute a significant amount of variance to the model nor did they change the pattern of the results in volume and shape. Hence, nicotine use, and whether or not patients received FGA, SGA, and antidepressant treatment (for SCZ vs. SA comparisons only) were not used as covariates in the final analysis. However, based on recent evidence by Andresen et al., 2010, we explored whether quantitative FGA...
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