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A meta-analysis of diffusion tensor imaging studies of the corpus callosum in schizophrenia

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ABSTRACT

Background: The corpus callosum has been hypothesized to play an important role in neurobiological models of schizophrenia. Diffusion tensor imaging studies have provided evidence for a disruption in corpus callosum morphology in schizophrenia, but the regional distribution of abnormalities is not well known.
Methods: We conducted 2 meta-analyses investigating the genu and splenium of the corpus callosum in schizophrenia, respectively, based on published diffusion tensor imaging studies that employed a region-of-interest approach. Seven studies investigating the genu and splenium involving a total of 202 patients with schizophrenia and 213 healthy volunteers were included.
Results: The meta-analysis of the genu yielded an effect size of 0.223 and was not statistically significant. The second meta-analysis investigating the splenium yielded a modest effect size of 0.527 ($p = 0.001$), indicating that patients had lower fractional anisotropy in this region compared to healthy volunteers. Studies that included fewer men had a larger effect size for the splenium.
Discussion: These findings implicate an abnormality involving the splenium of the corpus callosum in the neurobiology of schizophrenia as inferred by diffusion tensor imaging. A defect in the splenium could contribute to abnormalities in posterior interhemispheric connectivity in patients, including regions of the heteromodal association cortex.

1. Introduction

The corpus callosum is the largest white matter tract in the brain and is responsible for the majority of communication between homologous cortical regions in the right and left cerebral hemispheres (Gazzaniga, 2000). This tract has been hypothesized to play a critical role in the neurobiology of schizophrenia and to contribute to findings of abnormal interhemispheric connectivity (Hulshoff Pol et al., 2004; Mohr et al., 2000, 2008; Gruzelier, 1999; Crow et al., 2007; Stephan et al., 2006). There is considerable evidence from post-mortem studies implicating a corpus callosum defect in schizophrenia. For example, a reduction in callosal fiber density in female (but not male) patients with schizophrenia relative to same-sex controls has been reported (Highley et al., 1999). These disturbances may contribute to the development of the disorder and sex differences known to mediate factors such as age-of-onset and illness course (e.g. Crow et al., 2007).

The use of *in-vivo* structural magnetic resonance (MR) imaging has further implicated abnormalities in corpus callosum size (Downhill et al., 2000; Narr et al., 2000; Nasrallah et al., 1986; Venkatasubramanian et al., 2010) and shape (Narr et al., 2000; Frumin et al., 2002; DeQuardo, et al., 1999; Casanova et al., 1990) in patients with schizophrenia, which have been hypothesized to contribute to disruptions in interhemispheric connectivity (Keshavan et al., 2002b; Mohr et al., 2008; David, 1993). Volumetric studies have identified abnormalities in the corpus callosum that are most robust in the anterior portion of this tract in patients (Di et al., 2009; Walterfang et al., 2006). Furthermore, neuropsychological deficits in patients observed on tasks involving visual and tactile information transfer (Mohr et al., 2008; Barnett et al., 2005; Hatta et al., 1984) and dichotic listening (Bruder et al., 1999; Hugdahl et al., 2003) may also be mediated by a disruption in corpus callosum morphology.

More recently, investigators have used diffusion tensor imaging (DTI) to examine the integrity of the corpus callosum and its subregions in schizophrenia. DTI allows for the assessment of white matter tissue through the computation of diffusion indices such as fractional anisotropy (FA). Briefly, FA refers to the degree to which water within a voxel diffuses preferentially along one axis (anisotropic diffusion) rather than diffusing equally along all axes (isotropic diffusion) and may be correlated with

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white matter integrity (e.g. Basser, 1995). The genu and the splenium of the corpus callosum have been the focus of investigation for many DTI studies examining white matter integrity in schizophrenia given its importance to neurobiological models of the disorder and ease of identification. Across voxelwise, region-of-interest, and tractography-based analyses of DTI data, evidence has accumulated indicating that this region is abnormal in schizophrenia. The splenium, in particular, has been identified as an area of abnormally low FA in patients with schizophrenia relative to controls (Agartz et al., 2001; Foong et al., 2000; Ardekani et al., 2003; Cheung et al., 2008; Friedman et al., 2008; Gasparotti et al., 2009; Koch et al., 2010; Rotarska-Jagiela et al., 2008), although negative findings have been reported (Price et al., 2005; Foong et al., 2002; Caan et al., 2006; Miyata et al., 2007; Buchsbaum et al., 2006), particularly in patients experiencing their first psychotic episode (Price et al., 2005; Friedman et al., 2008; Peters et al., 2008). The genu has also emerged as a region in which patients may have lower FA compared to controls (Buchsbaum et al., 2006; Caan et al., 2006; Davenport et al., 2010; Kubicki et al., 2008; Camchong et al. (2011); Rotarska-Jagiela et al., 2008; Whitford et al., 2010; Pérez-Iglesias et al., 2010; Shergill et al., 2007), although many negative reports have appeared for this region as well (Foong et al., 2000, 2002; Price et al., 2005; Miyata et al., 2007; Cheung et al., 2008; Friedman et al., 2008; Peters et al., 2008; Mandl et al., 2010; Gasparotti et al., 2009). Such conflicting results suggest that potential case–control differences in callosal FA may be subtle and thus clarified through meta-analytic approaches.

A recent qualitative review of DTI findings in schizophrenia identified FA abnormalities in the corpus callosum that were evident in the genu, splenium and in distributed regions along the body of the corpus callosum (Kyriakopoulos et al., 2008). More recently, however, a quantitative analysis of voxelwise studies involving 407 patients with schizophrenia and 383 comparison subjects identified significantly lower FA in two regions including the left frontal and temporal lobe white matter (Ellison-Wright and Bullmore, 2009). Inconsistencies among DTI studies investigating the corpus callosum in schizophrenia may be related, in part, to differences in data acquisition and definitions of brain structures. Furthermore, the choice of analysis methodology is critically important to the study of white matter particularly with respect to the examination of well-defined white matter structures such as the corpus callosum. The use of voxelwise analyses to investigate corpus callosum morphology as assessed via DTI in schizophrenia could include potential disadvantages such as image misregistration, smoothing, and partial volume effects compared to region-of-interest approaches.

In this study we conducted a meta-analysis of diffusion tensor imaging studies in schizophrenia that used a region-of-interest approach to examine the genu and splenium of the corpus callosum. We hypothesized that lower fractional anisotropy would be evident in both the genu and splenium of the corpus callosum in patients with schizophrenia compared to healthy controls. Moreover, we investigated the potential effects of moderator variables that may have influenced the observed FA findings.

2. Materials and methods

2.1. Literature search and study selection

An extensive search was conducted from electronic databases including PsychINFO and Pub MED from January, 1985 to May, 2010. The key words used to extract studies included: schizophrenia, diffusion, corpus, callosum, diffusion, DTI, diffusion and schiz*, diffusion and callos*, diffusion and schiz* and callos*. In addition, a manual search through the references of published studies was conducted to identify relevant articles. Studies were evaluated and included based on the following criteria: the study included a comparison of patients with schizophrenia to healthy controls, employed a region of interest approach that specifically included the genu and/or splenium, reported fractional anisotropy (FA), and reported sufficient statistics for an effect size to be derived. We limited our analysis to studies that included a region-of-interest approach to limit potential methodologic and data analytic issues associated with voxelwise analysis. Data extracted from studies included dependent variables (FA means and standard deviations, effect sizes, *t*-values), DTI method related values (slice thickness, number of slices, number of directions) and potential moderator variables (age, sex, handedness, antipsychotic medication status and illness duration).

2.2. Quantitative meta-analysis procedures

Two separate meta-analyses were conducted for the genu and splenium of the corpus callosum. Hedge's g was used as the effect size measure and was computed for each study, representing standardized mean differences between patients and controls in the region of interest. Individual Hedge's g statistics were combined to produce an overall mean effect size using a random effect model, which takes heterogeneity among studies into account. For a statistically significant overall effect size, heterogeneity was examined by the Q-test and I^2 test. In addition, Egger's regression test (Egger et al., 1997), the classic fail-safe N (Rosenthal, 1979), Duval and Tweedie's "Trim and Fill" method (Duval and Tweedie, 2000), and a funnel plot were used to assess potential publication bias. Finally, moderator variables were examined as continuous or dichotomous variables for their influence on the effect sizes. All meta-analyses were conducted in the Comprehensive Meta-Analysis (Version 2) program (Borenstein et al., 2005).

2.3. Moderator variables

We considered the potential impact of moderator variables such as age, duration of illness, and sex on the observed findings given evidence for their influence on corpus callosum morphology in schizophrenia (Keshavan et al., 2002b; Panizzon et al., 2003; Hoff et al., 1994; Arnone et al., 2008; Venkatasubramanian et al., 2010). Because all studies included a majority of dextral subjects, however, this variable could not be examined as a potential moderator. In order to examine the potential effect of antipsychotics we computed Hedge's g for the two studies that included antipsychotic-naive samples as well as for the six medicated samples.

3. Results

3.1. Studies included in the meta-analysis

Seven studies with eight samples were identified and included in the meta-analyses. Separate meta-analyses were conducted for the genu and the splenium and included both chronic and first-episode patients (see Tables 1–2). Four of the seven studies included patient samples comprised of adults treated with antipsychotics (Foong et al., 2000; Price et al., 2005; Rotarska-Jagiela et al., 2008; Friedman et al., 2008), one study included a sample of adolescents with early-onset schizophrenia (Kumra et al., 2004), one study included a sample of young adults in their first episode of schizophrenia (Friedman et al., 2008), and two studies included samples of patients in their first episode of the illness who had never been treated with antipsychotic medication (Cheung et al., 2008; Gasparotti et al., 2009). The study conducted by Friedman et al. (2008) included a chronic patient group, a first-episode patient group, and two separate age-matched control groups. Therefore, two studies were conducted based on the same published report. This meta-analysis included the effect sizes derived from the study comparing the first episode patients to an age-matched healthy control group and the effect sizes derived from the same study comparing the chronic patients to a separate age-matched healthy control group. In both meta-analyses, a total of 202 patients and 213 healthy controls were included.