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White matter volume abnormalities and associations with symptomatology in schizophrenia

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ABSTRACT

The cerebral white matter (WM) is critically involved in many bio-behavioral functions impaired in schizophrenia. However, the specific neural systems underlying symptomatology in schizophrenia are not well known. By comparing the volume of all brain fiber systems between chronic patients with DSM-III-R schizophrenia ($n=88$) and matched healthy community controls ($n=40$), we found that a set of a priori WM regions of local and distal associative fiber systems was significantly different in patients with schizophrenia. There were significant positive correlations between volumes (larger) in anterior callosal, cingulate and temporal deep WM regions (related to distal connections) with positive symptoms, such as hallucinations, delusions and bizarre behavior, and significant negative correlation between volumes (smaller) in occipital and paralimbic superficial WM (related to local connections) and posterior callosal fiber systems with higher negative symptoms, such as alogia. Furthermore, the temporal sagittal system showed significant rightward asymmetry between patients and controls. These observations suggest a pattern of volume WM alterations associated with symptomatology in schizophrenia that may be related in part to predisposition to schizophrenia.

1. Introduction

Numerous neuropathological, neurogenetic and neuroimaging studies suggest a relation between schizophrenia and white matter (WM) abnormalities e.g., see Walterfang et al., 2006. WM alterations are important because they directly represent one form of connectivity in the brain, thought to be abnormal in schizophrenia (Seidman, 1983; Friston and Frith, 1995; Friston, 1998; Andreasen et al., 1999; Friston, 1999, 2002, 2005; Kubicki et al., 2005a,b). Given the extensive array of symptoms in schizophrenia and widespread gray and WM brain alterations, it is likely that multiple networks underlying these functional systems are impaired (Seidman, 1983; Andreasen et al., 1999). Furthermore, the volume of total WM has been shown to be smaller in schizophrenia than controls e.g., see Kubicki et al., 2005a; Tanskanen et al., 2009. To date, several structural studies have shown WM volumetric differences in schizophrenia e.g., see Kubicki et al., 2005a, both smaller and larger depending on region, in either the whole brain (e.g., see Andreasen et al., 1994; Cannon et al., 1998; Meisenzahl et al., 1999; Sigmundsson et al., 2001; Okugawa et al., 2002; Bartzokis et al., 2003; Christensen et al., 2004; Hulshoff Pol et al., 2004; Kubicki et al., 2005b; Mitelman et al., 2007a) or particular regions such as the frontal and/or prefrontal lobes (Breier et al., 1992; Cannon et al., 1998; Paillere-Martinot et al., 2001; Sigmundsson et al., 2001; Bartzokis et al., 2003; Mitelman et al., 2007a), the temporal lobes (Marsh et al., 1997; Okugawa et al., 2002; Bartzokis et al., 2003) or the WM within the parahippocampal gyrus (Colter et al., 1987). In addition, specific fiber tracts have been investigated such as the perforant pathway in the hippocampal formation and cingulum bundle (Benes, 1989), uncinate fasciculus, inferior longitudinal fasciculus, anterior limb of the internal capsule (Sigmundsson et al., 2001; Suzuki

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et al., 2002), occipitofrontal fasciculus (Suzuki et al., 2002) and corpus callosum (Downhill et al., 2000; Hulshoff Pol et al., 2004; Sun et al., 2009).

In schizophrenia, studies using diffusion tensor-magnetic resonance imaging (DT-MRI) (e.g., Kubicki et al., 2007) have also shown a significant decrease in fractional anisotropy (FA) in frontal and temporal WM, specifically anterior limbs of the internal and external capsules (Buchsbaum et al., 1998; Suzuki et al., 2002), corpus callosum (Foong et al., 2000; Argartz et al., 2001), arcuate fascicle (Hubl et al., 2004), cingulum bundle (Kubicki et al., 2003; Hubl et al., 2004), WM throughout the whole brain ("widespread") (Mitelman et al., 2006) and prefrontal (Lim et al., 1999) and temporoparietal (Mitelman et al., 2006) regions specifically. Importantly, recently WM alterations have started to be associated with symptoms of schizophrenia (Downhill et al., 2000; Hubl et al., 2004; Hulshoff Pol et al., 2004; Mitelman et al., 2006; Mitelman et al., 2007b; Rotarska-Jagiela et al., 2008).

Herein we addressed this issue using T1-weighted MRI of 88 patients with schizophrenia and 40 controls to study the variation in volume of WM fiber systems within a framework of a WM morphometric system (Makris et al., 1999; Meyer et al., 1999). This comprehensive system of quantitative WM analysis subdivides WM regionally by lobes and also radially into a comprehensive set of fine-grained regions of interest or parcellation units (PUs) (Makris et al., 1999; Meyer et al., 1999). This allowed the investigation of specific WM fiber systems from an anatomic volumetric point of view and their affiliation with different neural systems (Filipek et al., 1994; Caviness et al., 1996a,b, 1999; Makris et al., 1999). Furthermore, the comprehensive and detailed nature of the approach adopted in this study allowed the identification of altered patterns in WM regions and, uniquely, volumetric comparisons between local connections located within superficial WM sectors and distal connections located in deep WM sectors. Volume is an evolutionary and developmentally regulated property of tissue, which is sensitive to the regularities of normal histogenetic sequence and normal systems operations (Caviness et al., 1999). Thus alterations in WM volume may be important in understanding the illness in tandem with its association with well-defined symptoms. Furthermore, findings of an alteration in normative volumetric asymmetry (Geschwind and Behan, 1984; Geschwind and Galaburda, 1985a,b,c) would argue for a potential genetic etiology a fact well studied in vertebrates (e.g., (Supp et al., 1997; Hyatt and Yost, 1998; Piedra et al., 1998)). In this study, in addition to performing morphometric measurements of white matter brain structures, we conducted clinical evaluations, including negative and positive symptoms. We placed special emphasis on the associative limbic and paralimbic WM, in particular WM within the cingulate gyrus, with the expectation that it would be altered volumetrically, given that limbic prefrontal connections and limbic system abnormalities, which underlie disconnection of affect and cognition, are central in schizophrenia. Furthermore, we explored the associations of WM volume alterations with positive and negative symptoms, such as hallucinations, delusions and bizarre behavior, and negative symptoms such as alogia.

2. Materials and methods

2.1. Subjects

Simplex patients: Cases were recruited from three public Boston area psychiatric hospitals serving primarily psychotic patients (Goldstein et al., 1999). The sample included subjects reported in a previous work (Goldstein et al., 2002; Seidman et al., 2002). Recruitment criteria consisted of subjects with ages at MRI scanning of 23–68 years, ≥8th grade education, English as first language, and an estimated IQ≥70. Criteria required absence of: substance abuse for the past six months; history of head injury with documented cognitive sequelae or loss of consciousness >5 min; neurologic disease or damage; medical illnesses significantly impairing neurocognitive function. Cases were DSM-III-R schizophrenia probands ($n=40$), based on interview by experienced diagnostic interviewers and systematic review of medical records. Senior investigators (JMG, LJS) reviewed all material to determine diagnosis (see previous work listed above for details and excellent reliability).

Multiplex probands were reascertained from the Harvard cohort of the NIMH Genetics Schizophrenia Initiative. Families with ≥ two persons affected with DSM-III-R schizophrenia or schizoaffective disorder, depressed type, were identified by systematic screening in psychiatric hospitals and clinics. Test–retest reliabilities were excellent (Nurnberger et al., 1994). Procedures for diagnosing multiplex probands were similar to the simplex probands described above. Re-recruitment of the Harvard cohort (NIMH MH56956, JMG, P.I.) involved recruitment letters to probands, case managers, guardians, and home visits for those without phones or listed numbers. Fifty probands were scanned, out of whom data from two were excluded due to motion artifacts.

Normal comparison subjects ($n=40$) were recruited through advertisements in the catchment areas and notices posted on hospital bulletin boards from which the patients were ascertained (Goldstein et al., 2002; Seidman et al., 2002). They were selected to be comparable to patients on age, sex, ethnicity, parental socioeconomic status (SES), and handedness and screened for current psychopathology (Vincent et al., 1984) and family history of psychoses or psychiatric hospitalizations. Potential controls were excluded if they had current psychopathology or lifetime history of any psychosis, family history of psychosis or psychiatric hospitalization, or if any MMPI clinical or validity scale, except Masculinity–Femininity, was above 70.

Blindness of assessments was maintained among MRI data and psychiatric status and subjects' sex. Written informed consent was obtained from all subjects after providing a complete description of the study, and they were compensated for their time and participation. This study was approved by Harvard Medical School and hospital (Massachusetts Mental Health Center and Massachusetts General Hospital) Human Studies committees.

Multiplex and simplex cases and normal comparisons were comparable on gender, middle- to lower-middle parental SES and right-handedness, thus Table 1 shows the combined proband characteristics. Level of education in the probands was typically high school completion and some college. Probands primarily had undifferentiated or paranoid subtypes (see Table 1) and were clinically stable, living in the community with mild to moderate negative and positive symptomatology. Patients were a chronically disabled group with average chlorpromazine-equivalent neuroleptic daily dose not significantly different between family types. Patients and controls did not differ significantly on parental education, handedness, or past alcohol use (see Table 1). There were significant differences by education, estimated IQ, and past drug use, most likely reflecting illness effects.

2.2. Neuropsychological and clinical measures

The Vocabulary and Block Design subtests of the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981) estimated current general intelligence (Brooker and Cyr, 1986); and the Reading subtest of the Wide Range Achievement Test-Revised (Jastak and Jastak, 1984) was used as an estimate of intellectual potential (Kremen et al., 1995). The Annett Scale (Annett, 1970) was used as a measure of handedness. Quantitative symptomatology was assessed using the Scales for the Assessment of Negative (SANS) and Positive (SAPS) Symptoms (Andreasen and Olsen, 1982). Positive symptom domains included delusions, hallucinations, positive formal thought disorder, and bizarre behavior. Negative symptom domains included flat affect, alogia, anhedonia/associability and avolition/apathy.

2.3. MRI parameters and segmentation procedures

T1-weighted MRI scans were acquired at the Athinoula Martinos Biomedical Imaging Center at Massachusetts General Hospital (MGH) with a 1.5 T General Electric Signa scanner. Contiguous 3.1 mm coronal