Psychiatry Research: Neuroimaging ∎ (∎∎∎∎) ∎∎∎–∎∎∎

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Corpus callosum size and diffusion tensor anisotropy in adolescents and adults with schizophrenia

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ARTICLE INFO

Article history:
Received 14 August 2014
Received in revised form
7 November 2014
Accepted 11 December 2014

Keywords:
Diffusion tensor imaging
White matter
Schizophrenia spectrum
Magnetic resonance imaging (MRI)

ABSTRACT

The corpus callosum has been implicated as a region of dysfunctional connectivity in schizophrenia, but the association between age and callosal pathology is unclear. Magnetic resonance imaging (MRI) and diffusion-tensor imaging (DTI) were performed on adults ($n=34$) and adolescents ($n=17$) with schizophrenia and adult ($n=33$) and adolescent ($n=15$) age- and sex-matched healthy controls. The corpus callosum was manually traced on each participant's MRI, and the DTI scan was co-registered to the MRI. The corpus callosum was divided into five anteroposterior segments. Area and anisotropy were calculated for each segment. Both patient groups demonstrated reduced callosal anisotropy; however, the adolescents exhibited reductions mostly in anterior regions while the reductions were more prominent in posterior regions of the adults. The adolescent patients showed greater decreases in absolute area as compared with the adult patients, particularly in the anterior segments. However, the adults showed greater reductions when area was considered relative to whole brain white matter volume. Our results suggest that the initial stages of the illness are characterized by deficiencies in frontal connections, and the chronic phase is characterized by deficits in the posterior corpus callosum; or, alternatively, adolescent-onset schizophrenia may represent a different or more severe form of the illness.

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1. Introduction

Schizophrenia has been described as a 'disconnection syndrome,' characterized by dysfunctional cortical integration and abnormal functional connectivity. Defective interhemispheric communication of language, somatosensory and attentional information (Endrass et al., 2002; Mohr et al., 2000; Phillips et al., 1996; Rushe et al., 2007), and decreased language lateralization (Spironelli et al., 2008) have been demonstrated in this disorder. As the largest white matter tract in the human brain, the corpus callosum has been implicated as an important region of interest in the neuropathology of schizophrenia (Crow, 1998).

Indeed, structural abnormalities in the corpus callosum have been widely reported in schizophrenia patients. Post-mortem studies initially revealed increased callosal thickness in the brains of schizophrenia patients (Rosenthal and Bigelow, 1972), particularly chronic patients with an early-onset of illness (Bigelow et al., 1983). More recently, magnetic resonance imaging (MRI) studies of schizophrenia patients have largely reported reduced size of the corpus callosum, both in chronic (Downhill et al., 2000; Mitelman et al., 2009; Rotarska-Jagiela et al., 2008) and first-episode patient groups (Arnone et al., 2008; Walterfang et al., 2008a). More recently, diffusion tensor imaging (DTI) methods for examining white matter tracts have revealed reduced anisotropy, which may be indicative of poor alignment of axon bundles and unhealthy or unmyelinated axons (Kantarci et al., 2001), in the corpus callosum in both first-episode (Cheung et al., 2008; Federspiel et al., 2006; Gasparotti et al., 2009; Kyriakopoulos and Frangou, 2009; Perez-Iglesias et al., 2010; Price et al., 2007) and chronic adult patients (Friedman et al., 2008; Kong et al., 2011; Mitelman et al., 2009), as well as first-episode

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http://dx.doi.org/10.1016/j.pscychresns.2014.12.005
0925-4927/Published by Elsevier Ireland Ltd.

adolescent patients (Davenport et al., 2010; Douaud et al., 2007; Henze et al., 2012; Kyriakopoulos et al., 2008; White et al., 2009). Furthermore, lower values of anisotropy in chronic patients are associated with greater symptom severity (Mitelman et al., 2009). The genu and splenium have been examined and cited most often as sub-regions of the corpus callosum with reduced area (Downhill et al., 2000; Rotarska-Jagiela et al., 2008; Walterfang et al., 2008a) and anisotropy (e.g., Ellison-Wright et al., 2014; Federspiel et al., 2006; Friedman et al., 2008; Perez-Iglesias et al., 2010), perhaps due to their relationship to the frontal and temporal lobes, two areas strongly implicated in the neuropathology of schizophrenia. Dense small diameter myelinated fibers in the anterior corpus callosum reciprocally interconnect the prefrontal cortex in each of the hemispheres while those in the posterior corpus callosum interconnect the parietal, temporal and occipital lobes (Hofer and Frahm, 2006).

Although corpus callosum pathology has consistently been shown to be a feature of schizophrenia, investigations into the association between corpus callosum pathology and illness duration have yielded inconsistent results. Disturbances in the size and structural integrity of white matter tracts of the corpus callosum appear to be present at, and even before, illness onset (Henze et al., 2012; Walterfang et al., 2008a, 2008b). Cross-sectional studies report more severe corpus callosum size and anisotropy reductions in chronic vs. first-episode patients (Collinson et al., 2014; Downhill et al., 2000; Friedman et al., 2008; Kong et al., 2011), suggesting a degenerative pattern. However, a longitudinal approach revealed anisotropy abnormalities become less marked over time in chronic patients (Mitelman et al., 2009), and a meta-analysis reported that first-episode patients, compared with chronic patients, exhibit a greater effect of reduced absolute area (Arnone et al., 2008).

The aim of the current study was to examine both area and anisotropy of the corpus callosum in adult and antipsychotic drug-naïve adolescent schizophrenia patients and age- and sex-matched healthy controls to evaluate (1) whether differences in these measures are present in adolescent patients prior to the use of medication and (2) how alterations in the corpus callosum, albeit in a cross-sectional sample, may vary with age. Studying antipsychotic drug-naïve adolescent patients affords the opportunity to examine potential neurological abnormalities in this patient population without the influence of prolonged exposure to antipsychotic medication and/or hospitalization. To date, only one study has examined corpus callosum abnormalities in antipsychotic drug-naïve adolescent patients using stereotaxically-located regions of interest and reported no differences in anisotropy (Schneiderman et al., 2009). The current study improves on this research by using manually-traced regions-of-interest (the gold standard) and examining the corpus callosum in its near entirety. The following hypotheses were tested: (1) the patient groups will demonstrate reductions in anisotropy and area of the corpus callosum, particularly in the genu and splenium, as these areas have been most commonly cited as areas of abnormality and are related to the frontal and temporal lobes—areas strongly implicated in the pathology of schizophrenia (Buchsbaum et al., 1990; Hazlett et al., 2000); (2) the adult patients would demonstrate more severe reductions in anisotropy and area as we propose that age is associated with more severe reductions, assuming degenerative processes are at work. We also tested two exploratory hypotheses; (3) lateral-medial effects were explored as much of the research to date has only examined more medial portions of the corpus callosum; and (4) correlations were conducted to explore the hypothesis that *lower* anisotropy and size of the corpus callosum would be associated with *greater* clinical symptom severity.

The current study reports novel data from manually-traced corpus callosum regions-of-interest in the adolescent samples and examines diagnostic group by age group effects and symptom correlates that have not been previously published. White matter anisotropy data from the participants were described in earlier reports which utilized investigatory methods of stereotaxically-located regions of interest to examine normal aging effects (Schneiderman et al., 2007) and aging effects in the patient groups (Schneiderman et al., 2009). Volume of cortical and subcortical structures and cortical and corpus callosum anisotropy in the adult patients and adult healthy controls have also been previously published by our group (Mitelman et al., 2005a, 2005b, 2005c, 2005d, 2006, 2009). Neurocognitive functioning of the adolescent patients has been described by Brickman et al. (2004). All participants received the PANSS on the day of their scan to assess clinical symptom severity.

2. Methods

2.1. Participants

Adolescent ($n=17$) and adult schizophrenia patients ($n=34$) and age- and sex-matched healthy controls ($n=15$ and $n=33$, respectively) were recruited as described elsewhere (Schneiderman et al., 2009; see Table 1 for demographic information). Only those adolescents who ultimately received a diagnosis of schizophrenia were included in the current study. All adolescents were 21 years old or younger, and the adults over 21 years of age. The adolescent patients were experiencing their first psychotic episode. The adult patients had a mean illness duration of 21.2 years. One participant's scan was unable to be traced and was excluded from the analysis.

2.2. Image acquisition and processing

T1-weighted MR images were acquired using a 1.5 T Signa 5× scanner (GE Medical Systems) with a 3D-SPGR sequence (TR=24 ms, TE=5 ms, flip angle=40°, matrix size=256 × 256, field of view=23 cm, NEX=1, slice thickness=1.2 mm, and total slices=128). The diffusion tensor sequence acquired 14 7.5-mm thick slices TR=10 s, TE=99 ms, TI=2.2 s, $b=750$ s/mm^2, $\delta=31$ ms, $\Delta=73$ ms, NEX=5, voxel size 1.8 × 1.8 × 7.5 mm^3, and FOV=230, no gaps). In order to solve the components

Table 1
Sample characteristics.

Variable	Adults				Adolescents			
	Patients ($n=34$)	Healthy controls ($n=33$)	Statistic	p	Patients ($n=17$)	Healthy controls ($n=15$)	Statistic	p
Age, *M* (S.D.)	43.7 (10.2)	42.2 (11.5)	$t(65)=0.58$	0.57	15.9 (1.7)	17.1 (2.1)	$t(30)=1.73$	0.44
Sex, *n* (%)			$\chi^2(1)=1.89$	0.17			$\chi^2(1)=0.098$	0.75
Male	25 (74%)	19 (58%)			10 (59%)	8 (53%)		
Female	9 (26%)	14 (42%)			7 (41%)	7 (47%)		
Handedness, *n* (%)			$\chi^2(1)=3.24$	0.08			$\chi^2(1)=0.098$	0.68
Right	34 (100%)[a]	30 (91%)			14 (82%)	13 (87%)		
Left	0 (0%)	3 (9%)			3 (18%)	2 (13%)		
PANSS scores, *M* (S.D.)								
Positive	18.7 (6.9)	–			21.2 (5.0)[b]	–	$t(47)=1.25$	0.22
Negative	17.1 (6.4)	–			25.3 (8.2)[b]	–	$t(47)=3.81$	<0.001
Total	71.9 (17.4)	–			90.8 (14.7)	–	$t(49)=3.84$	<0.001

[a] Includes one mixed-handed participant.
[b] Scores unavailable for two participants.

Please cite this article as: Balevich, E.C., et al., Corpus callosum size and diffusion tensor anisotropy in adolescents and adults with schizophrenia. Psychiatry Research: Neuroimaging (2015), http://dx.doi.org/10.1016/j.pscychresns.2014.12.005