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Original article

Comparative neuropsychiatry: White matter abnormalities in children and adolescents with schizophrenia, bipolar affective disorder, and obsessive-compulsive disorder

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ABSTRACT

Background: There is considerable evidence that white matter abnormalities play a key role in the pathogenesis of a number of major psychiatric disorders, including schizophrenia, bipolar affective disorder, and obsessive-compulsive disorder. Few studies, however, have compared white matter abnormalities early in the course of the illness.
Methods: A total of 102 children and adolescents participated in the study, including 43 with early-onset schizophrenia, 13 with early-onset bipolar affective disorder, 17 with obsessive-compulsive disorder, and 29 healthy controls. Diffusion tensor imaging scans were obtained on all children and the images were assessed for the presence of non-spatially overlapping regions of white matter differences, a novel algorithm known as the pothole approach.
Results: Patients with early-onset schizophrenia and early-onset bipolar affective disorder had a significantly greater number of white matter potholes compared to controls, but the total number of potholes did not differ between the two groups. The volumes of the potholes were significantly larger in patients with early-onset bipolar affective disorder compared to the early-onset schizophrenia group. Children and adolescents with obsessive-compulsive disorder showed no differences in the total number of white matter potholes compared to controls.
Conclusions: White matter abnormalities in early-onset schizophrenia and bipolar affective disorder are more global in nature, whereas children and adolescents with obsessive-compulsive disorder do not show widespread differences in FA.

1. Introduction

The constellation of symptoms associated with both schizophrenia and bipolar affective disorder (BPAD) support processes that involve global brain disruptions. While the classic symptoms of these two disorders show different patterns, there is considerable overlap in specific symptoms, genes associated with the disorders [23,52,16], underlying neurobiology [8], and patterns of cognitive deficits [47]. In addition, both patients with schizophrenia and BPAD benefit from similar treatment strategies, primarily the use of neuroleptics [14,78,15]. The findings that both schizophrenia and BPAD show an array of clinical symptoms (i.e., thought disorder, psychosis), non-focal findings on brain MRI, and global cognitive deficits support mechanisms that involve multiple brain regions. This led to the concept of schizophrenia being considered a 'disconnection syndrome' involving brain networks [6,20], which later spread to include BPAD as well [11,68,55].

While patients with both schizophrenia and BPAD can show obsessive and compulsive symptoms, individuals with classic obsessive-compulsive disorder (OCD) have symptoms that tend to fit more focal patterns of brain involvement. Functional imaging studies suggest network abnormalities between the caudate nucleus and the orbitofrontal cortex (OFC). Patients with OCD generally do not show severe global cognitive deficits [53,59], have similar symptom profiles, and some individuals with severe OCD have partial relief of symptoms from neurosurgery involving connectivity with the anterior cingulate [80,27]. This raises question whether processes involving global brain processes, such as myelination, would be abnormal in schizophrenia and BPAD

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compared to OCD. Based on the symptoms, cognitive patterns, and studies of the underlying neurobiology of schizophrenia, BPAD, and OCD, we would expect much more similarities between schizophrenia and BPAD compared to OCD.

One approach to evaluate global versus local abnormalities in structural brain connectivity is to evaluate the white matter (WM) in the brain. Myelinated neurons in the brain allows for the high-speed transfer of neuronal signals. While the vast majority of myelination takes place prior to four years of age, there is evidence for continued myelination in specific brain regions throughout adolescence and into early adult life, most notably in the association cortices [76]. Since the individual neurons within the major WM tracts tend to travel in parallel bundles, they are well suited to be studied using diffusion tensor imaging (DTI). Once commonly used metric of white matter coherence derived from DTI is fractional anisotropy (FA), which is a rotationally invariant scalar value reflecting the underlying WM microstructure [13,51]. The protracted development of WM into adolescence and young adulthood, coupled with its role to enhance the overall efficiency of brain function, has made it a key target for exploring the underlying neurobiology of major neuropsychiatric disorders, especially since the period of adolescence is also associated with a higher incidence of major mood and psychotic disorders. Multiple studies have found abnormalities in the WM microstructure in patients with schizophrenia [73,57,38], bipolar affective disorder (BPAD) [44], and obsessive-compulsive disorder (OCD) [60,33,18]. While these studies have shown WM abnormalities within disorders, few have directly compared the WM abnormalities across disorders.

Early-onset schizophrenia (EOS) reflects the presence of schizophrenia prior to 18 years of age. EOS has been shown to be on a continuum with the adult form of the illness [54], although those with EOS tend to have greater genetic loading [9] and more pronounced negative symptoms [19,34] compared to adult-onset schizophrenia. There have been a number of studies exploring WM abnormalities in EOS and in early-onset BPAD (EOB) [37,36,72,74,58,24,65,39,25,12,1,28,32]. Similar to studies in adults [73], there is considerable heterogeneity of the WM findings in both EOS and EOB [73]. There are also differences in the WM microstructure based on the age of onset of the illness [40]. One possibility is that different WM tracts or different sections of WM tracts are affected in different individuals. If this is the case, then both ROI and voxel-based approaches will be less able to detect regions that show spatial heterogeneity. In order to circumvent this problem, we have developed an algorithm to assess non-spatially specific WM abnormalities. This approach, known as the 'pothole approach', does not rely on the assumption that WM abnormalities are spatially overlapping [74,75]. The underlying tenet of the pothole approach is that disruptions in WM integrity may occur at different "points of weakness" in different individuals, similar to what is seen in tuberous sclerosis [22,43]. Thus, voxel-based or region of interest techniques may miss WM abnormalities that are spatially different between individuals.

Thus, the goal of this study was to utilize the pothole approach to examine the specificity of WM abnormalities between EOS, EOB, and children and adolescents with OCD. Our hypothesis was that EOS and EOB would show considerable overlap and have global differences in WM, whereas children and adolescents with OCD would show more focal WM differences.

2. Methods

2.1. Participants

The study sample included a total of 102 children and adolescents, 43 with EOS (6 of these with schizophreniform disorder), 13 with EOB with psychotic symptoms, 17 with OCD, and 29 healthy controls (see Table 1 for demographic information).

Table 1
Demographic and clinical characteristics of the children and adolescents.

	Early-onset schizophrenia	Bipolar affective disorder	Obsessive-compulsive disorder	Controls
Demographics				
Number	43	13	17	29
Age (years, S.D.)	17.0 (1.8)	15.4 (2.1)	16.2 (1.6)	16.5 (2.0)
Sex (M/F)	24/19	6/7	9/8	15/14
Hand (R/L/both)	36/6/1	10/2/1	17/1/0	26/2/1
IQ	89.0 (16.1)	94.3 (15.5)	107.5 (13.0)	106.9 (15.4)
Clinical measures				
Age of onset	14.4 (1.6)	14.1 (2.1)	11.2 (3.3)	n/a
PANSS (positive)	21.8 (4.0)	19.5 (3.7)	n/a	n/a
PANNS (negative)	15.3 (4.3)	10.5 (2.9)		n/a
Chlorpromazine equivalents	352 (248)	210 (133)	0	n/a
	$n = 35$	$n = 13$		
Antipsychotics				
Aripiprazole	2		1	
Chlorpromazine	1			
Clozapine	6			
Fluphenazine	1			
Olanzapine	9	6		
Quetiapine	3	3		
Risperidone	6	1		
Sulpiride	1			
Mood stabilizers				
Valproate	1			
Lithium		3		
Serotonin reuptake inhibitors				
SSRIs				
Fluoxetine		1	5	
Fluvoxamine			4	
Sertraline			3	
None	6	1	4	29