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Abnormal frontostriatal connectivity in adolescent-onset schizophrenia and its relationship to cognitive functioning

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ABSTRACT

Background: Adolescent-onset schizophrenia (AOS) is associated with cognitive impairment and poor clinical outcome. Cognitive dysfunction is hypothesised, in part, to reflect functional dysconnectivity between the frontal cortex and the striatum, although structural abnormalities consistent with this hypothesis have not yet been demonstrated in adolescence.
Objective: To characterise frontostriatal white matter (WM) tracts in relation to cognition in AOS.
Design: A MRI volumetric and diffusion tensor imaging study.
Participants: Thirty-seven AOS subjects and 24 age and sex-matched healthy subjects.
Outcome measures: Using probabilistic tractography, cortical regions with the highest connection probability for each striatal voxel were determined, and correlated with IQ and specific cognitive functions after co-varying for age and sex. Fractional anisotropy (FA) from individual tracts was a secondary measure.
Results: Bayesian Structural Equation modeling of FA from 12 frontostriatal tracts showed processing speed to be an intermediary variable for cognition. AOS patients demonstrated generalised cognitive impairment with specific deficits in verbal learning and memory and in processing speed after correction for IQ. Dorsolateral prefrontal cortex connectivity with the striatum correlated positively with these measures and with IQ. DTI voxel-wise comparisons showed lower connectivity between striatum and the motor and lateral orbitofrontal cortices bilaterally, the left amygdalohippocampal complex, right anterior cingulate cortex, left medial orbitofrontal cortex and right dorsolateral prefrontal cortex.
Conclusions: Frontostriatal dysconnectivity in large WM tracts that can explain core cognitive deficits are evident during adolescence. Processing speed, which is affected by alterations in WM connectivity, appears an intermediary variable in the cognitive deficits seen in schizophrenia.

1. Introduction

Schizophrenia is a disorder of neurodevelopment [1] in which abnormalities give rise to psychotic symptoms and cognitive dysfunction. Functional neuroimaging studies strongly implicate the frontal cortex [2], yet few studies have found frontal cortical structural abnormalities in relation to cognition [3]. MRI diffusion tensor imaging (DTI) tractography studies have found abnormal WM tract integrity of the cingulum bundle [4], uncinate fasciculus [5], and superior longitudinal fasciculus [6] in relation to cognitive impairment. More specifically, in first-episode schizophrenia (FES) WM tract abnormalities (reduced FA and increased trace and radial diffusivity) between rostral medial frontal gyrus and rostral inferior frontal gyrus and the striatum have been found to be

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associated with executive dysfunction [7]. There have been fewer studies of structural abnormalities and cognition in early-onset schizophrenia. However, Epstein et al. [8] found that lower FA in left inferior fronto-occipital fasciculus and left inferior longitudinal fasciculus was associated with worse neurocognitive performance, a finding replicated in medication naive patients [9]. A combined DTI and fMRI study of working memory in adolescent-onset schizophrenia revealed fMRI changes within the anterior cingulate and ventrolateral prefrontal cortex (hyperactivation) and the cuneus (hypoactivation), whereas DTI findings were of consistently reduced FA in the splenium and posterior cingulum [10].

Altered functional connectivity and dopamine transmission in the striatum have been implicated in the cognitive impairment in schizophrenia [11]. It was hypothesized that altered structural integrity of frontostriatal white matter tracts (connectivity), contributes to the cognitive deficits seen in this disorder. In order to test this, we applied DTI probabilistic diffusion tractography [12], which has advantages over conventional streamlining techniques in that it allows characterization of tracts even in areas of low fractional anisotropy, e.g. near their cortical or subcortical GM targets. Furthermore, probability density function (PDF) can be used as a robust, quantitative measure of structural connectivity strength between GM regions [12,13].

Adolescent-onset schizophrenia is associated with more severe cognitive impairment and generally worse clinical outcomes than adult-onset schizophrenia [14,15]. It also offers the opportunity to test for clinico-pathological correlations without confounds from longer-term effects of medication and environmental factors of concern in adults. Here, we are testing for frontostriatal connectivity and their relationship to cognitive deficits in a well-characterised group of patients with AOS.

2. Methods

2.1. Subjects

Thirty-seven patients were recruited from adolescent units in the Oxford area. The Kiddie Schedule for Affective Disorders and Schizophrenia [16] was used to confirm a DSM-5 diagnosis of schizophrenia and the Positive and Negative Syndrome Scale [17] was used to assess symptom severity. All patients were receiving second-generation antipsychotics (SGAs) (Table 1). Although adolescent-onset, the duration of illness was quite long (average 1.8 years), and the duration of untreated psychosis was on average 0.37 years (Table 1). Twenty-four healthy participants were recruited as controls through their general practitioners and were screened using the K-SADS-PL for a history of emotional, behavioural or medical problems. None of family relatives of the controls suffered from a major mental illness. All participants attended mainstream schools.

Study exclusion criteria included moderate intellectual impairment (IQ < 60), a history of pervasive developmental disorder, significant head injury, substance misuse disorder, neurological disorder or major medical disorder. The Oxford Psychiatric Research Ethics Committee approved the study and written consent was obtained from all participants and parents.

2.2. Neuropsychological assessments

All participants were assessed for:

- full scale IQ (FSIQ) using the Wechsler Abbreviated Scale of Intelligence (WASI) Vocabulary, Similarities, Block Design, Matrix Reasoning subtests [18];
- verbal memory using the Word Lists subtests from the Children's Memory Scale in under 16s [19], and the Wechsler Memory Scale-III in over 16s (WMS/CMS) 1997 [20];
- visuospatial skill and visuospatial memory with the Rey Complex Figure Test (RCFT) [21];
- working memory with the Digit Span subtest from the Wechsler Intelligence Scale for Children-III UK [22] in under 16s and the Wechsler Adult Intelligence Scale-Revised [23];
- executive function using Letter and Category Fluency subtests from the Delis-Kaplan Executive Function System (DKEFS) [24];
- processing speed using the Coding subtest from the Weschler Intelligence Scale for Children-III UK in under 16s [22] and the Digit Symbol task from the Wechsler Adult Intelligence Scale-Revised in over 16s [23].

Table 1
Demographic and clinical details of adolescent-onset schizophrenia patients and healthy controls.

	Adolescent schizophrenia patients ($n = 37$)	Controls ($n = 24$)	Statistic	Significance
Gender (male/female)	23/14	12/12	Chi^2 0.88	$P = 0.34$
Age (mean ± SD)	16.3 ± 1.1	15.9 ± 1.4	t_{59} 1.2	$P = 0.22$
Range in years	(Range 13.9–18.0)	(Range 13.7–17.9)		
Handedness left/right	6/31	2/22	Chi^2 0.79	$P = 0.37$
Socio-economic class	I 2	I 4	Chi^2 3.6	$P = 0.16$
[The National Statistics Socio-economic Classification (NS-SEC)]	II 22	II 16		
	III 13	III 4		
Age at onset of symptoms in years (mean ± SD)	14.5 ± 1.5	–		
Range in years	(Range 11.0–17.0)			
Disease duration in years (mean ± SD)	1.8 ± 1.3	–		
Range in years	(Range 0.6–5.8)			
Duration of untreated psychosis in years (mean ± SD)	0.37 ± 0.18			
Range in years	(Range 0.1–0.8)			
PANSS positive (mean ± SD)	22.3 ± 2.8	–		
PANSS negative (mean ± SD)	15.6 ± 2.9			
Full scale IQ (FSIQ) (mean ± SD)	89.1 ± 15.3	108.8 ± 13.9	t_{59} 5.1	$P < 0.001$
Medication chlorpromazine equivalents	345.6 ± 230.1			
Medication (number of patients taking medication)				
Olanzapine	15			
Risperidone	9			
Quetiapine	5			
Arpipirazole	1			
Sulpiride	1			
Clozapine	6			

Numbers are mean [standard deviation (SD)].