Schizophrenia Research 159 (2014) 435–440

Contents lists available at ScienceDirect

Schizophrenia Research

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

A diffusion tensor imaging family study of the fornix in schizophrenia

Vina M. Goghari [a,*], Thibo Billiet [b], Stefan Sunaert [b], Louise Emsell [b]

[a] Clinical Neuroscience of Schizophrenia (CNS) Laboratory, Department of Psychology, Hotchkiss Brain Institute, University of Calgary, 2500 University Drive, NW Calgary, AB T2N 1N4, Canada
[b] Translational MRI, Department of Imaging and Pathology, KU Leuven and Radiology, University Hospitals Leuven, Belgium

ARTICLE INFO

Article history:
Received 2 August 2014
Received in revised form 18 September 2014
Accepted 22 September 2014
Available online 12 October 2014

Keywords:
Psychosis
Tractography
Fornix
Family study
Hippocampus
White matter

ABSTRACT

Diffusion tensor imaging (DTI) studies suggest abnormalities in the white matter microstructure of the fornix in schizophrenia patients. Research evaluating schizophrenia patient and relatives also suggests that the white matter microstructure of the fornix is heritable. However, previous studies have been hindered by limited DTI methodology. Therefore, the goal of this study was to assess whether fornix abnormalities were related to the genetic liability for schizophrenia using the novel methodological approach of assessing multiple metrics of along-tract measurements, in addition to whole-tract means. Twenty-five schizophrenia patients, 24 adult non-psychotic first-degree biological relatives, and 27 community controls underwent neuroimaging. No group differences were found for any of the DTI metrics using the classical whole-tract measures of the fornix. Along-tract analysis detected local increases in fractional anisotropy (FA) in the *right fimbria of the fornix* for relatives compared to patients and controls corrected for false discovery rate. No significant associations were found between symptoms, global functioning, or IQ and whole-tract FA means in schizophrenia patients or relatives. Increased FA in non-psychotic relatives could represent a compensatory mechanism to guard against psychosis or an abnormality associated with the genetic liability for the disorder. These findings underscore the importance of obtaining along-tract measurements, in addition to whole-tract measurements to fully understand white matter abnormalities in schizophrenia.

1. Introduction

Diffusion tensor imaging (DTI) metrics differentiate between schizophrenia patients and controls, and furthermore, appear to be useful vulnerability markers for schizophrenia (e.g., Camchong et al., 2009; Clark et al., 2011; Knochel et al., 2012; Skudlarski et al., 2013). Additionally, these measures are associated with symptoms of the disorder in both patients and relatives (Knochel et al., 2012). Although most white matter (WM) tracts have been investigated, most DTI studies of relatives have not assessed the fornix.

The fornix is a tract of key interest in schizophrenia, given it connects the hippocampus to the hypothalamus. Several studies in schizophrenia patients have found WM abnormalities in the fornix using voxel-based (e.g., Guo et al., 2012) and tract-based DTI analyses (e.g., Fitzsimmons et al., 2014). While tractography itself is not a quantitative technique (it is a way of virtually reconstructing WM fiber-like pathways), it is often used synonymously with the method used to extract mean quantitative values of tracts generated from tractography (Jbabdi and Johansen-Berg, 2011). However, it is known that DTI metrics vary along the length of tracts; therefore, taking a simple mean of all these values, as in classical tractography analysis, may be insufficient for capturing more subtle local differences (Colby et al., 2012). A more sophisticated approach that accounts for this variation is *along-tract analysis*, whereby focal differences in parameters manifest as local offsets between along-tract profiles (i.e., the plot of metric value at predetermined points along a tract) and whole-tract differences manifest as a global off-set between tract profiles. Abdul-Rahman et al. (2011) used along tract-based analysis and found specific loci for fractional anisotropy (FA) reductions and axial diffusivity (AD) and radial diffusivity (RD) increases in the left fornix. Furthermore, this study found decreased FA in the specific part of the left fornix that was related to increased psychotic symptoms in patients (Abdul-Rahman et al., 2011).

Along-tract methods have not been used in any family studies of schizophrenia patients. Using traditional methods, two large scale studies, including over 100 relatives and controls each, did not find FA differences in the fornix in relatives versus controls (Boos et al., 2013; Skudlarski et al., 2013). However, one study found that FA values of the fornix were heritable in schizophrenia patients and relatives (Skudlarski et al., 2013), suggesting that further investigation of the fornix with more sophisticated DTI methods, in relatives, is warranted.

Most previous studies investigating WM changes in schizophrenia have used voxel-based analysis, typically of a highly restricted WM skeleton (e.g., tract based spatial statistics), which is not an optimal approach for investigating a narrow tract such as the fornix (Bach et al.,

* Corresponding author at: Department of Psychology, University of Calgary, 2500 University Drive, NW Calgary, AB T2N 1N4, Canada. Tel.: +1 403 210 7344; fax: +1 403 282 8249.
E-mail address: vmgoghar@ucalgary.ca (V.M. Goghari).

http://dx.doi.org/10.1016/j.schres.2014.09.037
0920-9964/

2014). Other studies have used whole-tract mean values from tractography; thereby, losing anatomical specificity. The goal of this investigation therefore, was to use advanced DTI analysis to examine along-tract microstructural differences, in addition to whole-tract mean values, including measures of FA, mean diffusivity (MD), RD, and AD, in two subdivisions of the fornix in a family study of schizophrenia. We expected significant differences between all groups, with greater along-tract differences than whole-tract mean differences. We hypothesized that the largest differences would be found between patients and controls with non-psychotic relatives being intermediate. In terms of the individual metrics, we expected reduced FA and increased MD, RD, and AD in patients and relatives compared to controls in both parts of the fornix.

2. Materials and methods

2.1. Participants

A total of 76 individuals participated: 25 schizophrenia or schizoaffective patients (hereafter referred to as schizophrenia patients), 24 adult non-psychotic first-degree biological relatives, and 27 community controls. Demographic characteristics are shown in Table 1. Schizophrenia patients were recruited through outpatient clinics and through community support programs in Calgary, Canada. Research staff identified first-degree biological relatives by completing a pedigree with the proband. Not all probands met recruitment criteria for the study; however, to enhance the sample, all first-degree biological relatives of schizophrenia patients that met recruitment criteria were included. Seven relatives were related to probands in this sample and there were two families in which two relatives participated and one family in which three relatives participated. Community controls were recruited through flyers and advertisements around the community. The University of Calgary Ethics Board approved the protocol and informed written consent was obtained.

Inclusion criteria for all participants included: (1) age 18–65; (2) minimum IQ of 70; (3) no current diagnosis of drug/alcohol dependence/abuse; (4) no history of head injury or being unconscious for more than 20 min; (5) no history of electroconvulsive therapy; and (6) no history of stroke or other neurological condition. Further criteria for inclusion of first-degree relatives were no lifetime diagnosis of a psychotic disorder or bipolar disorder, or history of anti-psychotic medication use. Further criteria for inclusion of community controls were no personal or family history of a psychotic disorder or bipolar disorder, or personal use of an anti-psychotic medication.

2.2. Diagnosis and assessment

Participants were interviewed using the Structured Clinical Interview for DSM-IV Axis I Disorders. The Structured Interview for Schizotypy, with supplemental questions, was used to measure Axis II Cluster A disorders in relatives and controls (Kendler et al., 1989). Diagnoses were assigned according to DSM-IV-TR criteria via case conferences. No relatives or controls met criteria for a Cluster A disorder. Symptoms and functioning were measured using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987), Social Functioning Scale (Birchwood et al., 1990), the Global Assessment of Functioning (GAF) Scale (APA, 1994). Lastly, the vocabulary and matrix reasoning subtests of the Wechsler

Table 1
Participant characteristics: demographics, IQ measures, symptoms, functioning, and medication usage.

	Schizophrenia	Relative	Control
N	25	24	27
Age	41.3 (10.8)	40.2 (15.0)	40.7 (11.1)
Gender (% female)	48	58	52
Born in Canada (%)	92	88	81
Education (years completed)	14.2 (3.0)[a]	16.4 (2.6)	15.3 (2.4)
Annual income (%)[1]			
$0–$30,000	64	4	8
$30,000–$50,000	20	17	19
$50,000–$95,000	12	54	39
$95,000 +	4	25	35
Maternal education (years completed)	13.7 (2.8)	13.1 (3.8)	13.5 (3.4)
Paternal education (years completed)	14.0 (3.0)	12.6 (4.0)	13.7 (4.7)
Matrix reasoning raw score	26.3 (2.8)	27.6 (3.1)	27.0 (5.6)
Vocabulary raw score	57.1 (5.9)[a]	62.2 (5.8)	59.1 (7.8)
Handedness (% right handed)	92	79	96
PANSS negative: range	11.9 (3.6): 7–19	7.8 (1.1): 7–11[b]	7.2 (0.6): 7–10[b]
PANSS positive: range	14.4 (5.3): 7–24	8.8 (1.9): 7–14[b]	7.9 (1.3): 7–11[b]
PANSS general: range	26.8 (6.5): 16–39	20.5 (3.6): 16–29[b]	18.1 (37): 16–33[b]
Global assessment of functioning: range	53.4 (14.9): 30–83[a,c]	81.8 (5.7): 63–88	84.7 (5.1): 73–95
Social functioning scale: range			793.5 (53.1): 701–883
Axis I (% with any lifetime diagnosis)	–	33[2]	26[3]
Relative status — parent:sibling:offspring	N/A	9:12:3	N/A
Anti-psychotic (atypical, typical, both; % on)	96, 4, 4	0, 0, 0	0, 0, 0
Anti-depressants (% on)	40	8	8
Mood stabilizer (% on)	12	0	0
Anti-anxiety (% on)	8	4	0
Anti-parkinson (% on)	4	0	0
Other psychiatric (% on)	8	4	0

Note. Mean and standard deviation presented where appropriate.
The following notations were used for non-medication variables:
[a] Less than relatives.
[b] Less than patients.
[c] Less than controls.
[1] Overall chi-square demonstrated patients had more individuals in lower income brackets than controls or relatives.
[2] Some relatives had more than one lifetime Axis I disorder: 1 with alcohol dependence, 4 with alcohol abuse, 1 with cannabis abuse, 5 with major depressive disorder, 1 with dysthymia, 2 with post-traumatic stress disorder, 1 with panic disorder without agoraphobia, and 1 with generalized anxiety disorder.
[3] Some controls had more than one lifetime Axis I disorder: 1 with alcohol dependence, 1 with cocaine dependence, 3 with alcohol abuse, 1 with hallucinogen abuse, 1 with cannabis dependence, 3 with major depressive disorder, and 1 with social anxiety disorder.