Schizophrenia Research 130 (2011) 68–77

Contents lists available at ScienceDirect

Schizophrenia Research

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

Microstructural alterations of the arcuate fasciculus in schizophrenia patients with frequent auditory verbal hallucinations

A.D. de Weijer *, R.C.W. Mandl, K.M.J. Diederen, S.F.W. Neggers, R.S. Kahn, H.E. Hulshoff Pol, I.E.C. Sommer

Rudolf Magnus Institute of Neuroscience, Dept. of Psychiatry, University Medical Center Utrecht, The Netherlands

ARTICLE INFO

Article history:
Received 5 February 2011
Received in revised form 11 May 2011
Accepted 16 May 2011
Available online 8 June 2011

Keywords:
Schizophrenia
Arcuate fasciculus
Diffusion tensor imaging
Magnetization transfer imaging
Fiber tracking
White matter
Auditory verbal hallucinations
Language network
Tract-based analysis

ABSTRACT

Auditory verbal hallucinations (AVH) is a common and stressful symptom of schizophrenia. Disrupted connectivity between frontal and temporo-parietal language areas, giving rise to the misattribution of inner speech, is speculated to underlie this phenomenon. Disrupted connectivity should be reflected in the microstructure of the arcuate fasciculi (AF); the main connection between frontal and temporo-parietal language areas.

In this study we compared microstructural properties of the AF and three other fiber tracts (cortical spinal tract, cingulum and uncinate fasciculus), between 44 schizophrenia patients with chronic severe hallucinations and 42 control subjects using diffusion tensor imaging (DTI) and magnetic transfer imaging (MTI).

The DTI scans were used to compute fractional anisotropy (FA) and to reconstruct the fiber bundles of interest, while the MTI scans were used to compute magnetic transfer ratio (MTR) values.

The patient group showed a general decrease in FA for all bundles. In the arcuate fasciculus this decreased FA was coupled to a significant increase in MTR values. A correlation was found between mean MTR values in both arcuate fasciculi and the severity of positive symptoms.

The combination of decreased FA and increased MTR values observed in the arcuate fasciculi in patients suggests increased free water concentrations, probably caused by degraded integrity of the axons or the supportive glia cells. This suggests that disintegrated fiber integrity in the connection between frontal and temporo-parietal language areas in the schizophrenia patients is associated with their liability for auditory verbal hallucinations.

1. Introduction

Auditory verbal hallucinations (AVH) are a core symptom of schizophrenia, which underlying neurobiology is still largely unclear. Unraveling its pathophysiology may provide clues for new treatment strategies for the 25% of patients who fail to respond to current antipsychotic medication (Shergill et al., 1998).

Recent functional magnetic resonance imaging (fMRI) studies have revealed important aspects of the neurobiology of AVH. Several brain areas consistently showed activation during AVH (Jardri et al., 2010), such as the right and left temporo-parietal cortices and Broca's area and its right-sided homologue (Shergill et al., 2000; Sommer et al., 2003; Hoffman et al., 2007; Sommer et al., 2007; Sommer et al., 2008; Diederen et al., 2010). Temporo-parietal activation during AVH probably reflects the *perception* of speech, while activity in the bilateral inferior frontal areas suggests the *production* of language. Words produced in these areas may be experienced as AVH. It is unclear, however, why patients do not recognize these words as self-produced, but rather attribute them to an external source. Ford et al. (2007) pointed to malfunction of the corollary discharge mechanism: a neuronal circuit that suppresses the sensory consequences of self-generated actions. Such systems are well known in the visual system, but also serve the auditory language circuit (Paus et al., 1996). EEG and ERP studies showed that where healthy individuals suppress auditory perception areas during speech, this suppression is decreased in schizophrenia patients (Heinks-Maldonado et al., 2007; Ford et al., 2007). Insufficient corollary discharge in the language system could result from disrupted communication between frontal and temporo-parietal areas (Whitford et al., 2010). Such disturbed connectivity could result from microstructural alterations in the arcuate fasciculi, the most important fiber bundle between Broca's area and Wernicke's area (Lichtheim, 1885).

Diffusion tensor imaging (DTI) can measure structural connectivity in the human brain for specific white matter bundles. Fractional anisotropy (FA) is a measure of directionality of the axons forming the fiber bundles and is often used as an index of fiber integrity and, to a lesser extent, myelination (Beaulieu, 2002). Decreased FA, along with

* Corresponding author at: Rudolf Magnus Institute for Neuroscience, Dept. of Psychiatry, University Medical Center Utrecht, Heidelberglaan 100, Room B.01.1.43, 3584 CX Utrecht, The Netherlands. Tel.: +31 88 755 8672; fax: +31 88 755 5509.
E-mail address: a.d.deweijer@umcutrecht.nl (A.D. de Weijer).

0920-9964
doi:10.1016/j.schres.2011.05.010

increased diffusivity within prefrontal and temporal lobes, as well as abnormalities within the fiber bundles connecting these regions are frequent findings in schizophrenia (Kubicki et al., 2007). Three studies have specifically measured the arcuate fasciculus in hallucinating schizophrenia patients using DTI (Hubl et al., 2004; Seok et al., 2007; Shergill et al., 2007), reporting decreased FA values of this bundle.

More specific information about abnormalities of white matter tracts can be obtained by combining DTI with magnetization transfer imaging (MTI) (Kubicki et al., 2005). MTI is sensitive to macro molecules in tissue including myelin (Wolff and Balaban, 1994; van Buchem et al., 1999; Barkovich, 2000; Henkelman et al., 2001). A measure of this magnetization transfer is usually expressed as magnetic transfer ratio (MTR). However, sequences with relatively high T1 weighting (as used in this study) are also sensitive to free water concentrations (Henkelman et al., 2001). By combining the MTR results with the FA results we can differentiate between these two possible explanations. With increasing myelin concentration one would expect an increase in MTR as well as a *decrease* in radial diffusivity and an increase in FA (Gulani et al., 2001). However if the level of free water increases (e.g. as a result of degradation of its microstructure) then also an increase in MTR may be expected but no decreases in radial and axial diffusivity. In fact, if the increase in free water is for instance due to a less dense packing of axons then an *increase* in radial diffusivity and hence a reduction in FA may be expected. Thus, low values of both FA and MTR would point to decreased myelin, while low FA values associated with high MTR suggest increased free water concentrations, probably caused by degraded integrity of the axons or the supportive glia cells.

In this study we investigated microstructural connectivity between the frontal and temporo-parietal language areas in schizophrenia patients with chronic hallucinations and matched controls. Mean FA values and mean MTR were determined along the left and right arcuate fasciculi. In order to make inferences about specificity of our findings, the same measures were taken from three other tracts, namely the cortico spinal tract (CST), cingulum (CGL) and uncinate fasciculus (UF). These different tracts were chosen for anatomical reasons, because they share directional components with the AF, rather than their functional role in schizophrenia. We hypothesize that FA and MTR values integrated along the arcuate fasciculus are specifically affected in the patient group, which may underlie their predisposition for AVH.

2. Methods

2.1. Participants

Forty-four patients diagnosed with schizophrenia and 42 healthy controls, matched for age, gender and handedness participated in this study. All patients were recruited from the psychiatry department of the University Medical Center Utrecht. Patients were diagnosed using the Comprehensive Assessment of Symptoms and History interview (CASH) (Andreasen et al., 1992) according to DSM-IV criteria by an independent psychiatrist. The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) was used for the assessment of symptoms on the day of the MRI scan. All patients used typical or atypical antipsychotic medication in conventional dosages (Table 1 and Supplementary Table). All patients suffered from severe medication resistant auditory verbal hallucinations (AVH), defined as insufficient response to at least two antipsychotic agents, occurring at least once an hour (enquired with PSYRATS (Haddock et al., 1999)).

Absence of psychiatric disorder including substance abuse in the control group was checked using the CASH interview. Demographic details about the patient and control group are provided in Table 1. From all participants handedness was assessed with the Edinburgh Handedness Inventory (Oldfield, 1971). The study was approved by the medical ethical committee of the University Medical Center and after explanation to the participants; a written informed consent was obtained.

Table 1
Demographic data.

	Patient group	Healthy control group
	N = 44	N = 42
Male/female	25/19	23/19
Age (years)	36.9 (12.0)	38.4 (12.6)
Range (years)	18–61	21–66
Handedness (r/l)	39/5	37/5
Age of onset (years)	23 (11.4)	
Duration of illness (years)	13.6 (12.9)	
PANSS tot scores	62.1 (14.9)	
PANSS pos scores	15.6 (3.9)	
PANSS neg scores	16.0 (5.6)	
PANSS gen scores	30.3 (7.5)	
A-typical anti-psychotic medication	30	
Classic anti-psychotic medication	8	
No anti-psychotic medication	6	

2.2. Image acquisition

All MRI scans were acquired on a 3 T Philips Achieva using an 8 channel SENSE head-coil. For each participant a set of DTI scans, a T1-weighted scan for anatomical reference and a MTI scan were collected. To increase the signal to noise ratio the DTI set consisted of two transverse DTI scans. The second set was identical to the first but acquired with reversed k-space readout (anterior direction) which allowed us to correct for geometric EPI distortions in the image processing step. The DTI scans were used for reconstruction of the fiber tracts.

The 3D MTI scan consisted of 2 volumes, one without and one with a magnetization transfer prepulse. The anatomical scan was used for normalization of all scans to MNI space.

For acquisition parameters see Table 2.

2.3. Image processing

DTI image preprocessing was performed with in-house developed software (Mandl et al., 2010). All subsequent registration steps of images and fiber coordinates as well as fiber selection with ROIs were done in Matlab scripts developed in-house using SPM5 Matlab functions, among others.

The DTI data set was corrected for susceptibility artifacts by exploiting the fact that DTI was scanned twice and with reversed phase encoding direction (Andersson and Skare, 2002). Next the DTI

Table 2
Scan types and scan parameters used in experiment.

Scan type	MRI parameters
DTI scans	Single shot EPI-DTI scan consisting of 30 diffusion-weighted scans ($b = 1000$ s/mm^2) with non-colinear gradient directions and an average of 5 diffusion unweighted scans ($b = 0$ s/mm^2), TR/TE = 7035/68 ms, FOV 240 mm, matrix 128 × 128, 75 slices thickness 2 mm, no gap, SENSE factor 3, EPI factor 35, no cardiac gating.
MTI scan	First volume: TR/TE = 65.8/2.19 ms, FOV 240 × 190 × 180 mm, matrix 128 × 128, 95 slices, thickness 2.5 mm, flip angle = 18. Second volume: identical parameters with an additional off-resonance magnetization transfer prepulse (frequency offset 1100 Hz; 620°; three-lobe sync-shaped).
T1 anatomy	TR/TE = 9.87/4.6 ms, flip angle = 8°, FOV 224 × 160 × 168, matrix = 256 × 256, slice thickness 1 mm (no gap).