Psychiatry Research: Neuroimaging xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

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

Formal thought disorder is related to aberrations in language-related white matter tracts in patients with schizophrenia

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ARTICLE INFO

Keywords:
Diffusion tensor imaging (DTI)
Fractional anisotropy (FA)
psychosis
Arcuate fasciculus (AF)
inferior fronto-occipital fasciculus (IFOF)
inferior longitudinal fasciculus (ILF)
superior longitudinal fasciculus (SLF)
uncinate fasciculus (UF)

ABSTRACT

This study examined the hypothesis that a fronto-temporal disconnection in the language network underpins formal thought disorder (FTD) in schizophrenia. Forty-nine patients with a schizophrenia spectrum disorder (27 with mild FTD, 22 with severe FTD) and 26 healthy controls (HC) were included. Overall psychopathology and FTD were assessed by the Positive and Negative Syndrome Scale and the Thought, Language, and Communication scale, respectively. White matter (WM) microstructure was analysed using Tract-Based Spatial Statistics. In patients, severity of overall FTD (TLC Sum Score) was predicted by decreased fractional anisotropy (FA) in the right superior longitudinal fasciculus (SLF), and severity of negative FTD (TLC Emptiness subscale) was predicted by increased FA in the left SLF and arcuate fasciculus (AF). Notably, these results were no longer significant after correction for multiple comparisons. Compared with HC, patients showed lower FA in all the investigated language-related WM tracts as well as across the whole WM skeleton. No difference in FA was found between patients with severe and patients with mild FTD. Our results are compatible with earlier studies reporting impairments in widely spread WM tracts including those related to language processing in patients with schizophrenia.

1. Introduction

Formal thought disorder (FTD) is a severe language disturbance and a core syndrome of schizophrenia (Bleuler, 1958). This syndrome, however, is not only found in schizophrenia or schizoaffective disorders, but also in the general population, in people at high risk of developing psychosis, and in people with non-psychotic disorders (Roche et al., 2015). Therefore, FTD should be considered as both a dimensional entity of speech pathology and a categorical entity in terms of a trait marker for psychosis (Roche et al., 2015). Rather than being a single entity, FTD spans various abnormalities of speech, including organization, rate, impoverishment, and degree of idiosyncrasy. FTD can be distinguished into objective positive (e.g. derailment) and subjective positive (e.g. pressure/rush of thought) forms as well as objective negative (e.g. poverty of speech) and subjective negative (e.g. thought blocking) forms (Nagels et al., 2013), which have different neuropsychological correlates. For instance, positive FTD has been related to executive dysfunctions, and negative FTD to deficits in lexico-semantic retrieval (Nagels et al., 2016; Silverstein et al., 1991). Overall, FTD is as disabling as other symptoms of schizophrenia, limiting therapeutic relationship and psychological recovery (Cavelti et al., 2016), social and occupation functioning, wellbeing and life satisfaction (Sigaudo et al., 2014; Tan et al., 2014).

FTD in schizophrenia has been linked to structural and functional abnormalities in language-related brain regions. Structural studies found grey matter (GM) volume reductions in the left temporo-parietal junction (TPJ), including Wernicke's area (Horn et al., 2010, 2009; Rajarethinam et al., 2000), and both volume decrease (Horn et al., 2009; Sans-Sansa et al., 2013) and increase (Palaniyappan et al., 2015) in the left inferior frontal gyrus (IFG), overlapping with Broca's area, to be associated with FTD. Functional studies reported increased resting blood flow (Horn et al., 2009; Stegmayer et al., 2017) and increased

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https://doi.org/10.1016/j.pscychresns.2018.05.011
Received 21 November 2017; Received in revised form 20 April 2018; Accepted 21 May 2018

neural activity (Kircher et al., 2003, 2001a,b; McGuire et al., 1998) in the TPJ and the IFG to be associated with FTD. Interestingly, recent findings indicate that positive and negative FTD may be differently associated with structural and functional abnormalities in the language network (Palaniyappan et al., 2015; Sans-Sansa et al., 2013; Stegmayer et al., 2017; Viher et al., 2018). For instance, Sans-Sansa et al. (2013) found 'fluent disorganization' (a positive FTD symptom) to be correlated with volume reductions in both Brocca's and Wernicke's areas, whereas 'poverty of content of speech' (a negative FTD symptom) was correlated with reductions in the medial frontal/orbitofrontal cortex. This research has led to the hypothesis that a fronto-temporal disconnection in the language network may underlie FTD in schizophrenia (Cavelti et al., 2018; Horn et al., 2012; Kircher, 2008; Strik et al., 2017, 2008).

By examining white matter (WM) fibre bundles we can study the structural foundations of information transmission between distant brain regions of the language network. Yet, only few studies examined WM abnormalities in relation to FTD in schizophrenia so far. These studies found an inverse relation between FTD and FA in the right cingulum bundle (Bopp et al., 2017), the splenium of the corpus callosum along with the retrolenticular limb and the posterior limb of the internal capsule (Arnedo et al., 2015), the left cerebellum (Rigucci et al., 2013), and language-related tracts including the left middle longitudinal fascicle (MdLF) (Asami et al., 2013), inferior fronto-occipital fasciculi (IFOF) (Rigucci et al., 2013; Viher et al., 2018), inferior longitudinal fasciculi (ILF) (Rigucci et al., 2013; Viher et al., 2018), superior longitudinal fasciculi (SLF) (Viher et al., 2018), and uncinate fascicle (UF) (Viher et al., 2018). Zhou et al. (2017) reported a positive association between FA in the right SLF II, belonging to the MdLF, and FTD in patients with first episode psychosis. However, also non-significant correlations between disorganized speech and FA have been reported (Viher et al., 2016). The SLF, which includes the arcuate fasciculus (AF), represents the dorsal language pathway and is involved in sound-to-motor mapping. The IFOF, ILF, and UF are components of the ventral language pathway that is accountable for sound-to-meaning integration (Friederici, 2015). The MdLF has only recently been detected in humans (Makris et al., 2017), and its location and function for language processing remain a subject of debate (e.g., Kellmeyer et al., 2013; Wang et al., 2013).

In order to test the hypothesis of a fronto-temporal disconnection of the language network as neural correlate of FTD in schizophrenia (Kircher, 2008; Strik et al., 2008), the current study examined aberrations in language-related WM tracts in relation to FTD in patients with schizophrenia and healthy controls (HC). Thereby, we intended to overcome some of the methodological limitations of recent studies, such as the usage of a general psychopathology measure rather than a measure specifically developed to assess FTD, the lack of differentiating between subtypes of FTD such as positive and negative forms (Cavelti et al., 2018), the lack of specific hypotheses with regard to FTD (Sumner et al., 2017), and the usage of whole brain approaches that prevent drawing conclusions regarding the specificity of a region for a certain symptom/syndrome (Gelman and Stern, 2006). We employed tract-based spatial statistics (TBSS), which is currently considered one of the leading methods for diffusion tensor imaging (DTI) analysis. It is superior to traditional voxel-based morphometry (VBM) in terms of alignment and smoothing issues (Smith et al., 2006), and to tractography, because it provides a quantitative and objective measure of diffusion parameters for group comparisons (Jbabdi and Johansen-Berg, 2011; Smith et al., 2006). We investigated the SLF, AF, IFOF, ILF, and UF as regions of interest (ROIs), all major structures of the dorsal and ventral language pathways (Friederici, 2015). We assessed FTD by the Thought, Language and Communication (TLC) scale that allows to distinguish positive (Disorganization subscale) and negative (Emptiness subscale) FTD (Nagels et al., 2013). In accordance with recent studies (Asami et al., 2013; Rigucci et al., 2013; Viher et al., 2018; Zhou et al., 2017), we hypothesized that in patients with schizophrenia severity of FTD is predicted by lower FA in the ROIs. In addition, we conducted a subsequent whole-brain analysis in order to explore whether other brain areas than the *a-priori* ROIs were affected by FTD, too. We hypothesized that patients with schizophrenia show lower FA in the ROIs and in the whole brain than HC, with patients with severe FTD showing even lower FA than patients with mild FTD.

2. Methods

2.1. Subjects

The study was conducted at the University Hospital of Psychiatry in Bern, Switzerland, between 2011 and 2014. For the advantage of a bigger sample size, data from two studies with similar methods were combined. The final sample consisted of 75 subjects, including 49 patients with a schizophrenia spectrum disorder according to DSM-IV-TR (American Psychiatric Association, 2000) and 26 HC recruited among the employees of the University Hospital of Psychiatry and through personal contacts. For all participants, inclusion criteria were age between 18 and 65 years, good German language skills that allowed to understand the consent procedure and to undergo the clinical assessment, and right-handedness according to the Edinburgh Inventory (Oldfield, 1971). Participants were excluded if they were left-handed, pregnant, showed any contraindications for MRI (e.g. metal-containing implants such as pacemaker or cochlear implants, claustrophobia), had a history of serious neurological issues, or reported current abuse of alcohol and/or psychoactive substances (apart from nicotine). Diagnoses were confirmed by an experienced clinician (first sample) or the Mini-International Neuropsychiatric Interview (MINI) (Lecrubier et al., 1997) (second sample). Additionally, HC had no current major psychiatric DSM-IV Axis I diagnoses, as assessed with the screening questionnaire of the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1996) (first sample) or the MINI (second sample). Positive symptoms (Positive Syndrome subscale), negative symptoms (Negative Syndrome subscale), and general psychopathology (General Psychopathology subscale), and overall psychopathology (Total Score) were assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Severity of overall FTD was assessed using the TLC Sum Score, severity of positive FTD using the TLC subscale Disorganization, and severity of negative FTD using the TLC subscale Emptiness (Nagels et al., 2013). Patients were stratified according to their TLC Sum Score (which ranges between 0 and 63) into a mild (mFTD; TLC < 10; $N = 27$) and a severe (sFTD; TLC ≥ 10; $N = 22$) FTD group (see Table 1). A cut-off of 10 was chosen as predefined in the initial study proposal. For comparison, we also stratified patients based on a median split of the TLC Sum Score (mFTD: TLC < 8, $N = 24$; sFTD: TLC ≥ 8, $N = 25$; see Supplementary Fig. 1). Overall, the results did not differ depending on the cut-off used to stratify the patients. Thus, in the following, we are going to report the group comparisons based on the original cut-off of 10 only.

All subjects gave written informed consent. Assessments of psychopathology as well as magnetic resonance imaging (MRI) were conducted on the same day by a trained clinician. Both studies were approved by the ethics committee of the Kanton Bern, Switzerland.

2.2. DTI data acquisition

Diffusion tensor images were acquired from two different magnet resonance scanners at the Department of Neuroradiology of the University Hospital Bern, Switzerland. Both scanners used spin echo planar imaging with two 180° pulses at a minimum b-value of 0 s/mm^2 and a maximum b-value of 1300 s/mm^2 along 42 non-collinear directions. Thirty-nine subjects were scanned with a 3T Magnetom Verio SYNGO system (Siemens Erlangen, Germany) and a 12-channel array head coil. Following parameters were used: TR/TE = 9100/88 ms, matrix = 128*128, field of view (FOV) = 256*256 mm^2, slices = 55