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Structural correlates of formal thought disorder in schizophrenia: An ultra-high field multivariate morphometry study

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ABSTRACT

Background: Persistent formal thought disorder (FTD) is one of the most characteristic features of schizophrenia. Several neuroimaging studies report spatially distinct neuroanatomical changes in association with FTD. Given that most studies so far have employed a univariate localisation approach that obscures the study of covarying interregional relationships, the present study focussed on the multivariate systemic pattern of anatomical changes that contribute to FTD.
Methods: Speech samples from nineteen medicated clinically stable schizophrenia patients and 20 healthy controls were evaluated for subtle formal thought disorder. Ultra high-field (7 T) anatomical Magnetic Resonance Imaging scans were obtained from all subjects. Multivariate morphometric patterns were identified using an independent component approach (source based morphometry). Using multiple regression analysis, the morphometric patterns predicting positive and negative FTD scores were identified.
Results: Morphometric variations in grey matter predicted a substantial portion of inter-individual variance in negative but not positive FTD. A pattern of concomitant striato-insular/precuneus reduction along with frontocingular grey matter increase had a significant association with negative FTD.
Conclusions: These results suggest that concomitant increase and decrease in grey matter occur in association with persistent negative thought disorder in clinically stable individuals with schizophrenia.
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1. Introduction

Formal thought disorder (FTD) is one of the defining features of schizophrenia. FTD is closely related to the constructs of disorganisation syndrome and hebephrenia and has been reported in 80–90% of individuals with acute psychosis in some samples (Andreasen, 1979; Harrow et al., 1986; Harrow and Marengo, 1986). In particular, persistence of FTD is considered as a core feature of the long-term course of schizophrenia (Harvey et al., 1984). In a follow-up study persistent FTD was observed in 64% of patients with schizophrenia, while only 33% patients with non-schizophreniform psychosis displayed such persistence 7.5 years after the first psychotic episode (Marengo and Harrow, 1997).

Structural basis of persistent thought disorder has been a matter of interest for the last 20 years, but continues to be unclear. A large majority of studies have focused on the superior temporal gyrus (STG) as a region-of-interest (ROI) while examining the structural basis of FTD. Several (Menon et al., 1995; Shenton et al., 1992; Subotnik et al., 2003; Weinstein et al., 2007) but not all (Flaum et al., 1995; Kim et al., 2003; Molina et al., 2003) of these studies have found an association between reduced volume of STG and the severity of FTD. Morphometric abnormalities in other ROIs such as the inferior frontal gyrus (Suga et al., 2010), supramarginal gyrus (Palaniyappan and Liddle, 2012), orbitofrontal cortex (Nakamura et al., 2008), cerebellum (Kühn et al., 2012), amygdala (Rajarethinam et al., 2001) and parahippocampal gyrus (Prasad et al., 2004) have also been related to disorganisation or FTD. Whitford et al. (2005) and Lui et al. (2009) undertook whole brain voxelwise studies comparing patients and controls, but restricted the study of disorganisation to ROIs that showed significant effect of diagnosis, thus precluding unbiased inference on the spatial distribution of structural correlates of FTD. A small number of whole brain studies have investigated the association between disorganisation/FTD and morphometric changes across the entire brain without prior anatomical assumptions. STG volume reductions were noted in some (Horn et al., 2009, 2010; Leube, 2009; Sans-Sansa et al., 2013) but not all (Chua et al., 1997; Rigucci et al., 2013) studies. Other regions showing FTD-related morphometric changes in the whole brain studies include the

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cerebellum (Leube, 2009; Rigucci et al., 2013), insula (Leube, 2009; Sans-Sansa et al., 2013), OFC (Horn et al., 2010; Sans-Sansa et al., 2013), anterior cingulate cortex (Horn et al., 2009; Sans-Sansa et al., 2013), hippocampal region (Chua et al., 1997), lingual gyrus (Horn et al., 2010), occipital lobe (Horn et al., 2010; Rigucci et al., 2013), precuneus (Horn et al., 2009), angular gyrus (Horn et al., 2009) and temporal pole (Horn et al., 2010). In summary, morphometric studies to date implicate distributed brain regions to be relevant to the pathophysiology of FTD, though no consistent reports have emerged.

Inconsistent observations of structural changes in relation to FTD could be attributed to various factors. Firstly, previous morphometric studies have adopted a univariate approach in seeking the structural basis of FTD. These studies assume that between subjects, regional variations in brain structure are spatially distinct, and do not take into account the covariance or interrelationship that exists among distributed regions. This issue is especially important in the investigation of schizophrenia, where structural changes affecting distributed 'systems' in the brain, rather than single regions, are suspected to underlie the complex clinical symptoms observed in patients. Secondly, the prominence of FTD varies with the clinical stage of the psychotic illness (Arndt et al., 1995; Russo et al., 2013). It is possible that only a small portion of the variance in such state-related symptom severity could be related to the structural variations in the brain (Mathalon and Ford, 2012). In contrast, morphometric changes might relate better to persistent, trait-like FTD seen in clinically stable subjects despite adequate treatment. Moreover, subtle aspects of FTD are often missed during the course of clinical interactions (De Bruin et al., 2007); an adequate assessment of FTD requires unstructured, freely generated speech samples (Johnston et al., 1986; Liddle et al., 2002a; Kircher et al., 2014). Finally, most structural MRI studies (except Sans-Sansa et al., 2013) have sought the neural correlates for overall severity of FTD as a single construct, though functional imaging studies indicate that the pathophysiology of positive FTD characterized by looseness and peculiar word, sentence or logic usage may differ from negative FTD characterized by poverty of speech and weakening of goal (Kircher et al., 2001, 2003; McGuire et al., 1998a,b).

A multivariate statistical approach called source-based morphometry (SBM) offers a novel means to study the patterns of morphometric variations in grey matter in relation to disease states (Xu et al., 2009). In this approach, the term 'source' refers to independent spatial components derived without any a-priori assumptions that have similar patterns of morphometric variability between subjects. Due to its multivariate nature, SBM reveals linked sub-systems or 'macrocircuits' in the brain that relate to a clinical phenotype (Caprihan et al., 2011). Several recent studies have utilized this approach to investigate clinical features (Kubera et al., 2013; Wolf et al., 2014) in psychotic disorders. In the present study, we aimed to identify spatially independent, SBM-derived grey matter components at a whole brain level that predict positive and negative FTD in clinically stable subjects with schizophrenia. To this end, we quantified FTD using freely generated speech sample. Further, we collected structural scans from an ultra high field 7-Tesla MRI scanner. 7 T MRI offers higher signal-to-noise resolution compared to lower field scans (Metcalf et al., 2010), and offers superior accuracy in discriminating structural changes seen in patients with schizophrenia (Iwabuchi et al., 2013). Given the inconsistency of previous structural studies, we made no a priori assumptions as to the brain regions implicated in FTD, but hypothesized the presence of structural alterations across distributed anatomical 'subsystems' in relation to the variations in severity of persistent FTD in clinically stable patients with schizophrenia.

2. Methods

2.1. Participants

The characteristics of the sample used in this study have been described previously (Iwabuchi et al., 2013). 20 patients and 21 healthy controls aged between 18–55 years were recruited, of which 19 patients and 20 controls had scans of adequate quality for morphometric analyses. Patients satisfied the diagnostic criteria for schizophrenia according to DSM-IV criteria assessed on the basis of a consensus procedure based on a review of case files, information from the psychiatrists providing direct clinical care and a structured clinical interview (Signs and Symptoms of Psychotic Illness, (Liddle et al., 2002b)) to assess clinical features. Patients were specifically recruited in a stable phase of illness (defined as a change of no more than 10 points in their Global Assessment of Function (GAF, DSM-IV) score, assessed six weeks prior and immediately prior to study participation). Patient recruitment was carried out in Nottinghamshire, from cases registered with generic community mental health teams, first episode teams or rehabilitation teams. The mean duration of illness was 7.7 years (SD = 8.3). Subjects with neurological disorders, current substance dependence, or IQ < 70 using Quick Test (Ammons and Ammons, 1962) were excluded. Healthy controls group-matched for age, gender and parental socioeconomic status were recruited from the local communities. Controls had no personal or family history of psychosis and were free of neuropsychiatric disorders as assessed by a research psychiatrist. The study was conducted in Nottinghamshire, UK with ethical permission obtained from the National Research Ethics Committee, Nottingham. All participants gave written informed consent and received monetary compensation for their time in accordance with the ethical approval.

2.2. MRI data acquisition

Scanning was performed on a 7 T Philips Achieva system with 32-channel receive coil. T1 weighted images were acquired using a 3D Magnetization Prepared-Turbo Field Echo (IR-TFE) with 0.6 mm isotropic resolution, 192 × 180 × 140 mm matrix, TR = 15 ms, TE = 5.6 ms, shot interval = 3 s, and flip angle 8°. An optimized inversion pulse (adiabatic pulse) was used at 7 T to reduce bias field inhomogeneity. One patient and one control were excluded due to significant movement artefacts. T1 weighted images were resliced (1 mm isotropic) and segmented into grey, white and CSF tissue using the SPM8 Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL) algorithm (Ashburner, 2007) using a study-specific template. To correct for variation due to field inhomogeneity, the images were bias field corrected using 60 mm FWHM setting using SPM8 (Uwano et al., 2013). Further precautions taken to reduce bias field inhomogeneity are described in our previous work (Iwabuchi et al., 2013). Modulated grey matter images were normalized to MNI space using DARTEL's high-dimensional normalization protocol and smoothed using a 8 mm isotropic Gaussian kernel in line with recent SBM studies (Kubera et al., 2013; Wolf et al., 2014). Intracranial volume was calculated as a sum of the partial volumes derived from grey matter, white matter and CSF tissue images.

2.3. Assessment of thought disorder

Subjects were interviewed on the same day as the scan to assess seven features of formal thought disorder (poverty of speech, weakening of goal, perseveration, looseness, peculiar word usage, peculiar sentence usage and peculiar logic) in line with the validated procedure for administering Thought Language Index (Liddle et al., 2002a). To generate free speech samples, 3 pictures from Thematic Apperception Test (Murray, 1943) were used as in the study by Sommer et al. (2010). Speech samples were audio recorded by two research psychiatrists (LP and VB) and transcribed and rated by a single author (JM) blind to the diagnostic status, symptom burden of the subjects and neuroimaging findings. During the training phase, several meetings were organized among the authors to develop consensus on how to interpret and score FTD using previously collected speech samples. Further, we used the examples from the original author (PFL) for reference. In keeping with the original description of the scale, the summed scores of looseness, peculiar word, peculiar sentence and peculiar logic were classified as positive FTD (disorganised thinking) and the summed scores of

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