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# Association of formal thought disorder in schizophrenia with structural brain abnormalities in language-related cortical regions☆

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ABSTRACT

*Background:* Formal thought disorder (FTD) in schizophrenia has been found to be associated with volume reductions in the left superior temporal cortex. However, there have been negative findings and some studies have also found associations in other cortical regions.
*Method:* Fifty-one schizophrenic patients were evaluated for presence of FTD with the Thought, Language and Communication (TLC) scale and underwent whole-brain structural MRI using optimized voxel-based morphometry (VBM). Fifty-nine matched healthy controls were also scanned.
*Results:* Compared to 31 patients without FTD (global TLC rating 0 or 1), 20 patients with FTD (global TLC rating 2–5) showed clusters of volume reduction in the medial frontal and orbitofrontal cortex bilaterally, and in two left-sided areas approximating to Broca's and Wernicke's areas. The pattern of FTD-associated volume reductions was largely different from that found in a comparison between the healthy controls and the patients without FTD. Analysis of correlations within regions-of-interest based on the above clusters indicated that the 'fluent disorganization' component of FTD was correlated with volume reductions in both Broca's and Wernicke's areas, whereas poverty of content of speech was correlated with reductions in the medial frontal/orbitofrontal cortex.
*Conclusions:* The findings point to a relationship between FTD in schizophrenia and structural brain pathology in brain areas involved in language and executive function.


Structural brain changes, taking the form of lateral ventricular enlargement, a 2% reduction in whole brain volume, and somewhat more marked reductions in the frontal lobe, hippocampus and amygdala, are well established in schizophrenia (Wright et al., 2000). Less well established is how these changes relate to the clinical features of the disorder. One early proposal was that lateral ventricular enlargement and by implication other brain changes were associated with deteriorating course and poor response to treatment (Crow, 1980). However, subsequent studies failed to support this view, and current evidence suggests that patients with good and poor outcome schizophrenia show only at most subtle differences in lateral ventricular and brain volume (Mitelman and Buchsbaum, 2007). Nor have studies on the closely related distinction between deficit and non-deficit schizophrenia yielded any clear evidence of differences in regional brain structure (Galderisi and Maj, 2009).

Another possibility is that regional structural brain alterations are associated with the presence of certain schizophrenic symptoms. Here, a relationship has been found between negative symptoms and volume reductions in the ventromedial prefrontal cortex (Chua et al., 1997), and between hallucinations and reductions in the superior temporal cortex (Barta et al., 1990; Flaum et al., 1995; Levitan et al., 1999) and the anterior cingulate cortex (Noga et al., 1995). However, by far the most investigated relationship of this type has been that between formal thought disorder (FTD) and volume reductions in the superior temporal cortex, where a significant association has been reported in eight studies (Shenton et al., 1992; Menon et al., 1995; Barta et al., 1997; Holinger et al., 1999; Matsumoto et al., 2001; Anderson et al., 2002; Subotnik et al., 2003; Weinstein et al., 2007), although there have also been negative findings (Flaum et al., 1995; Vita et al., 1995; Chua et al., 1997; Gur et al., 2000; Sanfilipo et al., 2000; Kim et al., 2003). Such an association is of considerable theoretical interest because the left superior temporal cortex houses Wernicke's speech area posteriorly (Bogen and Bogen, 1976), and

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dysphasia-like phenomena are seen in FTD (Chaika, 1974; Faber et al., 1983; Hoffman and Sledge, 1984; for a review see McKenna and Oh, 2005).

Most studies examining correlations between FTD and brain morphology have used conventional MRI volumetric analysis, which is limited in terms of sensitivity and also by the fact that regions of interest have to be selected on a priori grounds. Recently, however, Horn and co-workers (Horn et al., 2009; Horn et al., 2010) have re-examined the association using voxel-based morphometry (VBM) (Ashburner and Friston, 2000), which maps clusters of significant change in grey matter volume across the whole brain. In two samples of 13 and 20 schizophrenic patients, they found a significant negative correlation between FTD scores and clusters of volume reduction in the left superior temporal cortex. However, they also found additional clusters of association in the anterior cingulate gyrus bilaterally, the left angular gyrus and the precuneus bilaterally (Horn et al., 2009), and in the right cuneus, the right orbitofrontal cortex and the left temporal pole (Horn et al., 2010).

One factor which might account for the heterogeneity in the above findings is that FTD is not a unitary construct, but rather encompasses a range of different clinical phenomena. Thus, Andreasen (1979) found empirical support for 18 different elements of FTD in the study which led to the development of her widely used Thought, Language and Communication (TLC) scale. Some of these elements, such as derailment, tangentiality, loss of goal and incoherence, appear to form a tightly intercorrelated cluster (Andreasen, 1979; Harvey et al., 1992). However, one item, poverty of content of speech – speech that is adequate in quantity but conveys little information – occupies a more ambiguous position, having been found to be correlated with core features of FTD such as derailment, tangentiality and loss of goal (Andreasen, 1979; Liddle, 1987), but also with poverty of speech (Harvey et al., 1992), a symptom which is no longer considered to form part of the syndrome of FTD. Two studies (Andreasen and Grove, 1986; Peralta et al., 1992) which examined the factor structure of TLC scores both isolated a 'fluent disorganization' factor with loadings on items such as derailment, tangentiality and incoherence, illogicality and circumstantiality, as well as a second factor which loaded on poverty of content of speech and poverty of speech (plus perseveration in one of the studies).

The aim of this study was to further delineate the pattern of structural brain changes associated with FTD in schizophrenia. We used VBM and a whole-brain approach to examine grey matter volume, and applied this to a relatively large sample of patients selected for showing a wide range of severity of FTD. We also investigated whether fluent disorganization and poverty of content of speech were differentially associated with the grey matter volume changes found.

## 1. Method

### 1.1. Subjects

The patient sample consisted of 51 adults with schizophrenia. All subjects were right-handed. They were recruited from the in-patient units and supported housing facilities of a psychiatric hospital. They all had chronic illnesses (i.e. duration >2 years, mean 23.84 ± 7.83 years). They were not preselected on symptomatic criteria, apart from the fact that we made efforts to recruit patients who showed severe forms of FTD, who are relatively uncommon.

All patients met DSM-IV (APA, 1994) criteria for schizophrenia, based on psychiatric interview by their treating psychiatrist and a member of the research team. Patients were excluded if they were younger than 18 or older than 65, had a history of neurological disease or brain trauma, or had shown alcohol/substance abuse within 12 months prior to participation. They were also required to have a current IQ in the normal range (i.e. 70+), as measured using 4 subtests from WAIS III (Wechsler, 1997) (vocabulary, similarities, block design and matrix reasoning). All were taking antipsychotic medication at the time of the study (typical [N = 5], atypical [N = 25], both kinds [N = 20]; detailed medication information not available for one patient).

The controls consisted of 59 healthy right-handed adults meeting the same exclusion criteria as the patients. They were recruited from relatives and acquaintances of staff working in the hospital and also by advertisement in the community. They were questioned and excluded if they reported a history of mental illness and/or treatment with psychotropic medication.

The patients underwent a videotaped semistructured interview for the purpose of rating FTD. In this they were first asked to talk about their childhood, then interpreted five Rorschach pictures and finally recounted one or more well-known fairy tales (techniques used by Rochester and Martin, 1979 and Oh et al., 2002). The interview lasted 15–25 min, depending on the quantity of speech elicited. FTD was scored using the TLC (Andreasen, 1979) by two clinicians, a psychologist (BS-S) and a psychiatrist (EP-C), both of whom were experienced in its use. Ratings were discussed in case of disagreement and a consensus was reached. For the reasons given in the introduction, the item 'poverty of speech' was not included.

Other symptomatology was rated in both patients groups using the Positive and Negative Syndrome Scale (PANSS). Scores for positive, negative and disorganization syndromes were calculated based on factor analytic studies of the PANSS (Bell et al., 1994; Lindenmayer et al., 1995). Premorbid IQ was estimated using the Word Accentuation Test (TAP) (Del Ser et al., 1997; Gomar et al., 2011). This is conceptually similar to the National Adult Reading Test (NART) (Nelson and Willison, 1991) and requires pronunciation of low-frequency Spanish words whose accents have been removed.

The study was approved by the hospital ethics committee and written informed consent was obtained from all participants.

### 1.2. Procedure

All subjects underwent structural MRI scanning using a 1.5 Tesla GE Signa scanner (General Electric Medical Systems, Milwaukee, Wis) located at the Sant Joan de Déu Hospital in Barcelona (Spain). High resolution structural T1 MRI data were acquired with the following acquisition parameters: matrix size 512 × 512; 180 contiguous axial slices; voxel resolution 0.47 × 0.47 × 1 $mm^3$; echo (TE), repetition (TR) and inversion (TI) times, (TE/TR/TI) = 3.93 ms/2000 ms/710 ms respectively; flip angle 15°.

Structural data were analyzed with FSL-VBM, an optimized voxel-based morphometry style analysis (Ashburner and Friston, 2000; Good et al., 2001) carried out with FSL tools. This yields a measure of local grey matter volume. First, structural images were brain-extracted. Next, tissue-type segmentation was carried out. The resulting grey-matter partial volume images were then aligned to MNI152 standard space, followed by nonlinear registration. The resulting images were averaged to create a study-specific template, to which the native grey matter images were then non-linearly re-registered. The registered partial volume images were then modulated by dividing by the Jacobian of the warp field. The modulated segmentated images were smoothed with an isotropic Gaussian kernel with a sigma of 4 mm (For technical details see www.fmrib.ox.ac.uk/fsl/fslvbm/index.html).

Statistical inference of spatially distributed patterns was carried out with the *randomize* function implemented in FSL, using a cluster-based correction method with initial threshold $t > 2.3$ and 10,000 iterations. This analysis was conducted across the whole brain grey matter volume. All statistical tests were performed with a statistical threshold of $p < 0.05$, corrected for multiple comparisons, using the null distribution of the max (across the image) voxelwise test statistic — a permutation-based non-parametric inference method implemented in FSL as part of the *randomize* function.