White Matter Integrity in Treatment-Refractory Schizophrenia: A Diffusion Tensor Imaging Study

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BACKGROUND

It is commonly estimated that at least 20-30% of schizophrenia patients fail to respond adequately to antipsychotic treatment[1]. We are yet to understand the exact mechanisms contributing to this treatment-resistance. Reduced white matter fractional anisotropy (FA) – a marker of disrupted microstructural integrity detected by diffusion tensor imaging (DTI), is a well-established finding in schizophrenia, particularly in frontal and temporal regions[2].

Existing studies have largely utilised a voxel-based morphometry (VBM) approach, which is prone to alignment and smoothing drawbacks. In order to overcome these, this study used tract-based spatial statistics (TBSS), a relatively new technique deploying non-linear registration projecting FA values onto a mean FA skeleton.

METHODS

Subjects: This study pooled existing datasets of in- & outpatients meeting DSM-IV criteria for schizophrenia recruited into several studies at the Institute of Psychiatry, Psychology & Neuroscience, King's College London (UK). Subjects, aged 18-60, were divided into treatment refractory (n=34) and non-refractory (n=44) groups; the former included subjects who had been registered at any time with a mandatory UK clozapine monitoring service up until autumn 2011, the latter included subjects who had not been registered with these. Subjects were matched according to age, gender, handedness, duration of illness, and intelligence (using NART and WAIS-III scores).

Diffusion tensor data acquisition: DTI acquisition sequence was identical to Kanaan et al. (2009)[3], using a 1.5 T GE Signa LX system with actively shielded magnetic field gradients (maximum amplitude 40 mT/m). At each slice location, seven images were acquired with no diffusion gradient applied, together with diffusion-weighted images in 64 gradient directions uniformly distributed in space as per Jones et al. (2002)[4].

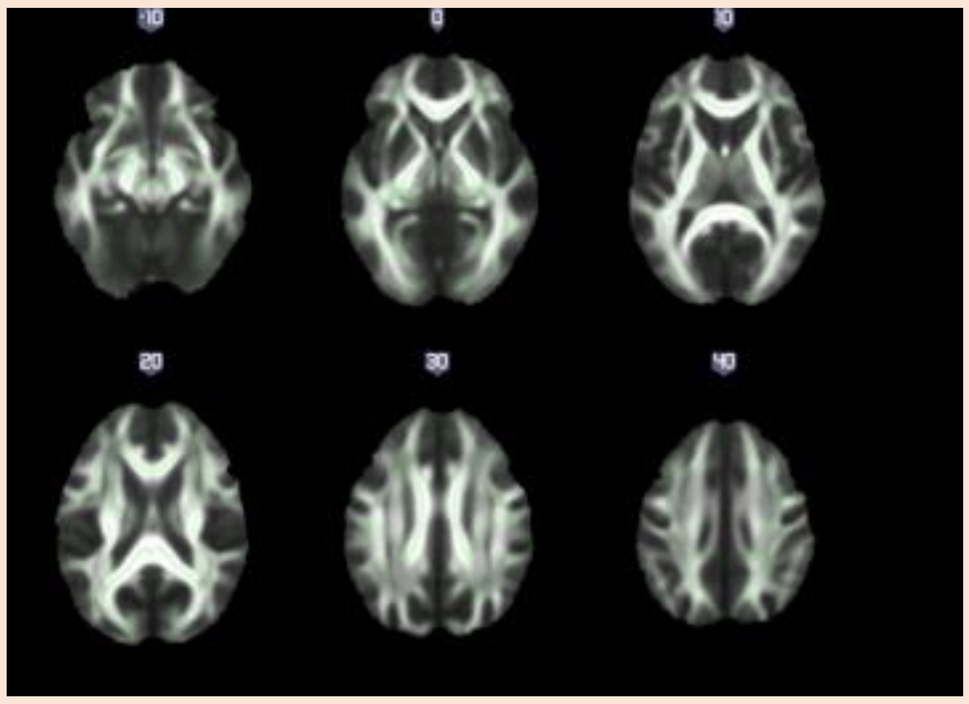
Image analysis: Diffusion data were processed with ExploreDTI. DTI source data were corrected for eddy current distortions and head motion. B-matrix was subsequently reoriented per subject to improve accuracy of tensor orientation estimations. Diffusion tensor was estimated by applying a non-linear least squares approach, with FA calculated from the diffusion tensor. TBSS v1.2 was utilised to conduct the voxel-wise statistical analysis of FA data and compare groups. FA images from all subjects were registered to standard Montreal Neurological Institute (MNI) space using the non-linear registration tool in FSL (FNIRT). A voxel-wise average across all subjects was calculated to create a mean FA image, which was 'skeletonised'. An FA threshold of 0.3 was applied to the skeleton, optimised to correspond to major fibre bundles, generating a mean FA skeleton, which formed a representation of the tract centres common to all subjects. Aligned FA maps were then projected onto the mean FA skeleton to facilitate voxel-wise cross-subject statistics.

Statistical analysis: Whole-brain statistical analyses identifying group differences in the skeletonised voxel-wise diffusion metrics were performed using Randomise v.2.1 (FSL). Differences in FA were assessed between refractory and non-refractory patients. The analysis utilised the threshold-free cluster enhancement (TFCE), using a nonparametric permutation test, in which group membership was permuted 5000 permutations for each contrast in order to generate voxelwise p-values corrected for multiple testing (significant at $p<0.05$, familywise error corrected). Age and gender were de-meaned prior to analysis and used as covariates of no-interest within the voxel-based statistical analysis.

RESULTS

Whilst approaching significance level, differences in FA / white matter integrity detected between treatment refractory and non-refractory groups following voxel-wise analysis were not significant ($p=0.05$). Further analysis of the results did not reveal any trend level differences in white matter integrity. Age, gender, handedness, duration of illness, and intelligence were controlled for in these analyses.

[A] Mean group FA map - TBSS determined major fibre tracts



CONCLUSIONS

To our knowledge, this is the first study investigating white matter differences between treatment-respondent and treatment-refractory schizophrenia patients using DTI/TBSS[2]. Our results suggest that white matter integrity does not differ significantly between these groups. Whilst some differences in brain structure have been associated with outcome in schizophrenia, there is a general lack of consistent neuroimaging correlates of treatment resistance[5], supporting our lack of positive findings.

A multitude of possible confounders are likely to contribute to this paucity, ranging from the limited sensitivity of contemporary neuroimaging methods to inconsistent definitions of treatment-resistance. A multi-dimensional classification of treatment-resistance, including factors such as lifetime antipsychotic doses, quality of life measures, and social/occupational functioning, is likely to provide a more accurate representation of this population and thereby enable a more distinct detection of treatment response correlates using neuroimaging methods.

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