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White matter microstructure and volitional motor activity in schizophrenia: A diffusion kurtosis imaging study

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ABSTRACT

Avolition is a core feature of schizophrenia and may arise from altered brain connectivity. Here we used diffusion kurtosis imaging (DKI) to investigate the association between white matter (WM) microstructure and volitional motor activity. Multi-shell diffusion MRI and 24-h actigraphy data were obtained from 20 right-handed patients with schizophrenia and 16 right-handed age and gender matched healthy controls. We examined correlations between fractional anisotropy (FA), mean diffusivity (MD), mean kurtosis (MK), and motor activity level, as well as group differences in these measures. In the patient group, increasing motor activity level was positively correlated with MK in the inferior, medial and superior longitudinal fasciculus, the corpus callosum, the posterior fronto-occipital fasciculus and the posterior cingulum. This association was not found in control subjects or in DTI measures. These results show that a lack of volitional motor activity in schizophrenia is associated with potentially altered WM microstructure in posterior brain regions associated with cognitive function and motivation. This could reflect both illness related dysconnectivity which through altered cognition, manifests as reduced volitional motor activity, and/or the effects of reduced physical activity on brain WM.

1. Introduction

Avolition is a core feature of the negative syndrome in schizophrenia (Messinger et al., 2011). The motor inactivity associated with avolition has been objectified in studies using actigraphy to measure the activity level (AL) of participants. In these studies, AL has been consistently reported to be lower in patients than healthy controls (e.g. Bracht et al., 2013; Docx et al., 2013; Walther et al., 2011; Wichniak et al., 2011). Abnormalities in the white matter (WM) networks of the brain may underlie altered volition. This hypothesis is supported by recent diffusion tensor imaging (DTI) studies that have linked volitional motor activity measures to WM microstructure in schizophrenia (Brach et al., 2013; Walther et al., 2011), major depressive disorder (Bracht et al., 2012; Walther et al., 2012) and neurological conditions such as multiple sclerosis (Gow et al., 2012), as well as in healthy adults (Walther et al., 2010) and normal aging (Shaurya Prakash et al., 2010; Marks et al., 2007; Tseng et al., 2013).

In schizophrenia, motor activity levels have been found to correlate with reduced fractional anisotropy (FA) values in the posterior cingulum and right ventral primary motor cortex and supplementary motor area (Walther et al., 2011). Furthermore, the correlations in these regions differed significantly between patients and healthy controls, suggesting that aberrant WM organization is involved in reduced motor activity in schizophrenia. Supporting evidence for this hypothesis was provided in a later probabilistic fibre tracking study by the same research group. In contrast to controls, where a significant correlation between AL and cortico-basal ganglia pathways was found, the AL of schizophrenia patients were related to cortico-cortical pathways (Bracht et al., 2013).

Although DTI studies are widely used in the context of identifying non-specific differences in tissue microstructure, they can only provide limited neurobiological insights into the origin of these differences. This is because DTI cannot characterise WM microstructure as comprehensively as more advanced diffusion MRI approaches (Jones

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et al., 2013). DTI is based on a Gaussian model (Basser et al., 1994) that does not make a distinction between hindered and restricted water diffusion. Hindered diffusion occurs when unconfined molecules interact with structural boundaries, such as in extra-axonal spaces, whereas diffusion is restricted if molecules are confined within a bounding structure, e.g. within axons. A typical diffusion-weighted MRI voxel ($2.5\times2.5\times2.5$ mm^3) contains water moving within and between innumerable cellular boundaries and compartments, and thus contains a mixture of hindered and restricted diffusion. It is therefore important to use techniques which account for this when investigating white matter microstructure (Assaf and Basser, 2005; Assaf et al., 2004).

DKI is an extension of DTI that additionally allows the quantification of non-Gaussian diffusion (Jensen et al., 2005), and thus also captures the contribution of restricted diffusion to the measurement. As such, DKI provides additional complementary measures alongside standard DTI metrics (FA, Mean Diffusivity (MD), radial diffusivity (RD) etc.) that relate more closely to the underlying tissue microstructure. Specifically, DKI provides the dimensionless metric 'mean kurtosis' (MK), which describes the amount of deviation from Gaussianity (Jensen et al., 2005). Emerging clinical studies suggest that DKI is complementary to DTI (Billiet et al., 2015), Coutu et al., 2014 and may even be more sensitive than DTI for detecting WM microstructural change (Falangola et al., 2008; Gong et al., 2013; Grossman et al., 2012; Helpern et al., 2011; Kamagata et al., 2013; Yoshida et al., 2013; Zhang et al., 2013) To date, only one study (Zhu et al., 2015) has applied DKI to investigate group differences in schizophrenia and found reduced FA and increased diffusivity (MD, RD), as well as decreased kurtosis metrics in patients compared to controls. Moreover, they identified differential sensitivity between DTI and DKI to WM changes depending on the complexity of the affected fibre pathways, thus demonstrating the complementary nature of the two approaches.

Here we present findings from the first DKI study specifically investigating volitional motor activity in schizophrenia patients. The aims of this study were twofold. First, we aimed to investigate the association between WM microstructure and volitional motor activity in schizophrenia. Second, we aimed to investigate if DKI is more sensitive than and/or complementary to DTI to study this association.

2. Materials and methods

2.1. Participants

We included 20 patients with a DSM-IV diagnosis of 'Schizophrenia' and 16 healthy control participants in the study. All participants were right handed. Patients were recruited within three major in- and outpatient treatment facilities in Belgium. We included 14 inpatients and 6 outpatients. All patients were being treated with antipsychotic medication (6 patients received monotherapy with atypical antipsychotics, 2 patients received monotherapy with conventional antipsychotics, 6 patients received polypharmacy with atypical agents and 6 patients were treated with a combination of atypical and conventional antipsychotics) and there had been no major changes in their medication regime for at least 2 weeks prior to inclusion (for chlorpromazine equivalent dose, see Table 1). Other psychopharmacological agents used were benzodiazepines (N=6), mood stabilizers (N=5) and antidepressants (N=9). DSM-IV diagnosis of schizophrenia was based on a clinical interview performed by an experienced psychologist (LD) and supporting case histories. All diagnoses were additionally confirmed by treating psychiatrists. Current psychopathology was assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Participants who had neurological disorders, a current diagnosis of alcohol and/or drug dependence or contraindications to MRI were excluded from the study. The study was approved by the Ethical Committees of the participating hospitals and all participants provided signed informed consent.

2.2. Actigraphy

The motor activity level of participants was assessed by means of actigraphy. Participants wore an actigraphy (Actiwatch® AW7, Cambridge Neurotechnology, Inc., UK) on their left wrist for 24 consecutive hours. The measurements were performed during the weekend in order to assess volitional motor activity in a natural environment that was minimally influenced by external motivators such as therapy, work or school. Inpatients were all allowed to leave the ward at the time of testing. Activity counts were stored in 2 s intervals. Actiwatch Activity & Sleep Analysis 7® software (Cambridge Neurotechnology, Inc., UK) was used to read and extract data. Activity level (AL) during wake time (i.e. average cumulated activity per hour) was calculated using in-house Excel® templates made for this purpose.

2.3. Imaging

2.3.1. Data acquisition

All MRI data were acquired on a 3 T MRI scanner (Siemens Trio, Erlangen, Germany) at the Antwerp University Hospital, Antwerp, Belgium. A multi-slice, single-shot EPI, spin echo sequence (TR/TE=7700/139 ms) was used to obtain 40 axial slices without slice gap and 2.2 mm nominal isotropic resolution (FOV=220×220 mm). Diffusion weighting was applied according to an optimized diffusion gradient encoding scheme that consisted of 25, 40, and 75 diffusion weighted gradients isotropically distributed over three shells with b=700, 1000, 2800 s/mm^2 respectively. In addition, 10 non-diffusion weighted images (b_O) were acquired. The acquisition time was 16 min

2.3.2. Image processing

Motion and distortion correction was performed by aligning all diffusion-weighted images with an affine transformation to the non-diffusion-weighted image. Thereafter, a b-matrix rotation was performed to preserve ensure the orientation information of the diffusion tensors in each voxel (Leemans and Jones.2009).

The diffusion and kurtosis tensors were then calculated in every voxel using a weighted linear least squares method (Veraart et al., 2011, 2013). Subsequently, quantitative maps of FA, MD, and MK were calculated. In order to perform voxel-wise comparisons, all subjects were aligned to a common template. This population specific DTI atlas was constructed from the participant datasets using a viscous fluid based non-rigid coregistration algorithm that was adopted to include all tensor information during the iterative alignment procedure (Van Hecke et al., 2007; Sage et al., 2009). All aligned images were smoothed by an adaptive, anisotropic smoothing kernel (FWHM=6 mm) (Alexander et al., 2001; Van Hecke et al., 2010). This spatially dependent, anisotropic kernel was estimated from the FA maps and subsequently applied to all the parameter maps.

2.3.3. Statistical analysis

Voxel-based correlations between AL and the parameters FA, MD and MK were carried out using multiple regression as implemented within the general linear model framework in "statistical parametric mapping" (SPM)8 (http://www.fil.ion.ucl.ac.uk/spm/) with age as a covariate. The analysis was restricted to WM voxels using a custom made mask based on an FA threshold of 0.2 in the population specific atlas space. Group differences between patients and controls were assessed using independent two-sample *t*-tests. SPM maps were thresholded at p=0.001(unc) to control family-wise error, and clusters were deemed significant below cluster-level pFWE-value =0.05. When highly significant clusters were detected (pFWE < 0.0001), we reanalysed the data with SPM maps thresholded at pFWE=0.05, and clusters were deemed significant below cluster-level pFWE-