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Comparing free water imaging and magnetization transfer measurements in schizophrenia

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ABSTRACT

Diffusion weighted imaging (DWI) has been extensively used to study the microarchitecture of white matter in schizophrenia. However, popular DWI-derived measures such as fractional anisotropy (FA) may be sensitive to many types of pathologies, and thus the interpretation of reported differences in these measures remains difficult. Combining DWI with magnetization transfer ratio (MTR) – a putative measure of white matter myelination – can help us reveal the underlying mechanisms. Previous findings hypothesized that MTR differences in schizophrenia are associated with free water concentrations, which also affect the DWIs. In this study we use a recently proposed DWI-derived method called free-water imaging to assess this hypothesis. We have reanalyzed data from a previous study by using a fiber-based analysis of free-water imaging, providing a free-water fraction, as well as mean diffusivity and FA corrected for free-water, in addition to MTR along twelve major white matter fiber bundles in 40 schizophrenia patients and 40 healthy controls. We tested for group differences in each fiber bundle and for each measure separately and computed correlations between the MTR and the DWI-derived measures separately for both groups. Significant higher average MTR values in patients were found for the right uncinate fasciculus, the right arcuate fasciculus and the right inferior-frontal occipital fasciculus. No significant results were found for the other measures. No significant differences in correlations were found between MTR and the DWI-derived measures. The results suggest that MTR and free-water imaging measures can be considered complementary, promoting the acquisition of MTR in addition to DWI to identify group differences, as well as to better understand the underlying mechanisms in schizophrenia.

1. Introduction

Although the etiology of schizophrenia is still unknown there is compelling evidence that white matter in the brain is implicated (Flynn et al., 2003; Friston and Frith, 1995; Hulshoff Pol et al., 2004; Kubicki et al., 2007; Shenton et al., 2001; Voineskos et al., 2010). Magnetic resonance imaging (MRI) techniques such as diffusion weighted imaging (DWI) (Le Bihan and Breton, 1985; Stejskal and Tanner, 1965) — or when a tensor is used to model the diffusion profile of the water molecules, referred to as diffusion tensor imaging (DTI) (Basser, 1995) — have been extensively used to study schizophrenia, with varying results. These differences in results may be due to differences in patient populations, MRI field strengths, MRI acquisition sequences used, and/or analysis techniques, but most likely are a result of a combination of these factors (Kubicki et al., 2013).

Although differences in the diffusion profile are reported for virtually all brain regions, the overall consensus is that these differences are most prominent in fiber bundles connecting to the fronto-temporal parts of the brain (Shenton et al., 2010). To compare diffusion profiles between subjects, a number of scalar measures have been introduced to describe certain aspects of the diffusion profile. These include fractional anisotropy (FA) (Basser and Pierpaoli, 1996) and mean diffusivity (MD), which represent the two most frequently measures used. Using these methods reductions in FA and increases in MD in patients with schizophrenia have been reported in several studies (Ellison-Wright et al., 2014; Kubicki et al., 2013; Shenton et al., 2010). However, the interpretation of reported differences in FA and MD is complicated because there are a number of possible underlying mechanisms that may be responsible. For instance, differences in fiber directionality, level of myelination and axonal diameter and, importantly, the degree of partial volume between different tissue types, will all result in differences in FA as well as MD (De Santis et al., 2014).

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One way to increase the specificity of DWI measures is to compare them with other imaging contrasts (Kubicki et al., 2005b). In previous studies, DWI measurements were combined with magnetization transfer imaging (de Weijer et al., 2011, 2013; Kubicki et al., 2005a; Mandl et al., 2010, 2013b; Palaniyappan et al., 2013; van den Heuvel et al., 2010), which measures the amount of signal that is transferred from macromolecules (including myelin) to the water molecules in the free water pool (Henkelman et al., 2001; Laule et al., 2007; Wolff and Balaban, 1994). Magnetization transfer ratio (MTR), a measure derived from the magnetization transfer images, is a putative measure of myelination because in white matter the myelin molecules form a large fraction of the macromolecules present. Since both FA and MTR are (amongst others) sensitive to myelin content, combining both imaging contrasts can help us to understand better the underlying mechanisms. Many studies used MTR to study white matter in schizophrenia albeit with varying results. Several studies reported on lower MTR values in schizophrenia (Bohner et al., 2012; Du et al., 2013; Foong et al., 2000; Kubicki et al., 2005a; Palaniyappan et al., 2013; Price et al., 2010), one study reported no differences (Antosik-Biernacka et al., 2006) while other studies reported on higher MTR signal in schizophrenia (de Weijer et al., 2011, 2013; Mandl et al., 2010, 2013b). Of particular relevance here, in our previous study (Mandl et al., 2010) we combined MTR and FA with a focus on prefrontal fiber bundles, i.e., left and right uncinate fasciculus and the genu of the corpus callosum. These three fiber bundles were reconstructed using fiber tracking (Jones, 2008; Mori et al., 1999) and FA, MD and MTR values were measured along the reconstructed fiber bundles. The main finding was a statistically significantly higher MTR along the right uncinate fasciculus in schizophrenia patients, which was not accompanied by a higher FA. Since the MTR changes did not overlap with the FA changes, and since MTR is sensitive, but not specific to myelin changes, we speculated that the increased MTR finding is not related to myelin changes. It is also known that MTR is influenced by other mechanisms such as changes in T1 relaxation time, and modulation of neuroinflammation (Laule et al., 2007). Accordingly, we speculated that this higher MTR may reflect differences in the free water pool (e.g., water in the extracellular space) between groups. Our rationale was that an increase in free water in patients with schizophrenia would lead to prolonged T1 relaxation times (Kalus et al., 2005), which could then explain the measured increase in MTR.

Here, our goal was to further test the hypothesis that differences in bulk water contribute to the observed increased MTR by incorporating free-water imaging, which is a recently proposed post processing method that operates on DWI data and can estimate the fractional volume of free water in each voxel (Pasternak et al., 2009). In line with our hypothesis, a previous free-water study in schizophrenia found that there was an increase in the volume of the extracellular space in schizophrenia patients following their first psychotic episode (Pasternak et al., 2012). For this reason we reanalyzed the data from Mandl et al. (2010) to obtain free-water measures, and we added nine more major fiber bundles (Boos et al., 2013) (Fig. 1A) to the three bundles tested earlier. By combining the measures we tested whether differences in free water concentrations could indeed be an alternative explanation for the higher MTR values measured in patients with schizophrenia.

2. Materials and methods

2.1. Subjects

Forty patients with schizophrenia and 40 healthy participants, matched for age, gender, handedness and parental education participated in this study. The healthy participants were recruited by means of local newspaper advertisements. The study was approved by the medical ethics committee for research in humans (METC) of the University Medical Center Utrecht, the Netherlands. All subjects participated after written informed consent was obtained. All participants underwent extensive psychiatric assessment procedures using the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al., 1992). Patients met the DSM-IV criteria for schizophrenia. "Age of onset of illness" was defined here as the age at which the patients experienced psychotic symptoms for the first time, as obtained from the CASH interview, and Schedule for Affective Disorder and Schizophrenia Lifetime version (SADS-L) assessed by two independent raters. Diagnostic consensus was achieved in the presence of a psychiatrist. "Duration of illness" was defined as time between age of onset of illness and age at the time of the MRI scan. All healthy participants met Research Diagnostic Criteria for "never mentally ill" and had no first-degree family member with a mental illness or second-degree relatives with a psychotic disorder. Drug use was assessed with the Composite International Diagnostic Interview (CIDI). Four patients and one healthy participant met criteria for drug abuse, one patient met criteria for drug dependency. Drugs used included cannabis (in all 6 subjects) and others (3).

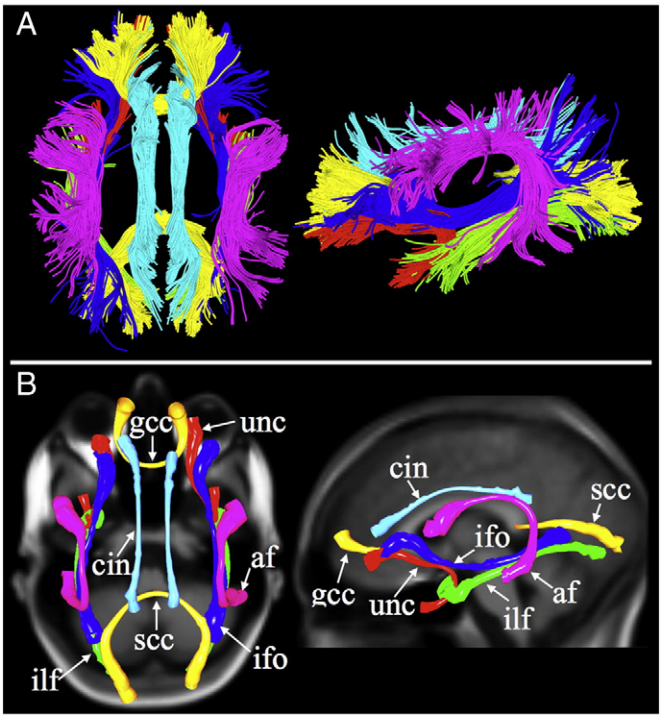

Fig. 1. Twelve major fiber bundles and corresponding model average fiber bundles. A) The twelve major fiber bundles reconstructed for one single subject. B) Average model fiber bundles used to compute the mean FA_c, MD_c MTR and free water signal along the fiber bundles for all subjects. The use of these average model fiber bundles allows us to perform a point-by-point comparison between subjects along a fiber bundle. gcc = genu of the corpus callosum, scc = splenium of the corpus callosum, ilf = inferior longitudinal fasciculus, cin = cingulum bundle, af = arcuate fasciculus, unc = uncinate fasciculus, ifo = inferior fronto-occipital fasciculus. The diameter of the model fibers represents the variability of the positions of the individual fiber bundles that were used to construct the model fiber.

All patients were receiving typical, or atypical antipsychotic medication at the time of the scan. A table from the Dutch National Health Service (Commissie Farmaceutische Hulp van het College voor Zorgverzekeringen, 2002) was used to calculate the cumulative dosage of typical antipsychotics during the scan interval and to derive the haloperidol equivalents. For atypical antipsychotics the respective pharmaceutical companies suggested how to convert dosage into haloperidol equivalents (clozapine, 40:1; olanzapine, 2.5:1; risperidone, 1:1, sulpiride, 170:1; quetiapine, 50:1; and sertindole, 2:1). See Table 1 for demographics.

2.2. Image acquisition

Magnetic resonance imaging (MRI) scans were obtained on a 1.5 Tesla Intera Achieva Philips System using a six-element SENSE