White Matter Microstructure Correlates of Visual Working Memory in Schizophrenia Patients and Healthy Controls

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Introduction

Schizophrenia patients consistently show lower scores in visual working memory (VWM) tasks. As compounding evidence strongly implies that schizophrenia is associated with disordered anatomical and functional connectivity [1] it seems reasonable to assume that VMW poor performance may be in part related to altered microstructural features of white matter pathways that connect different brain regions. Traditionally white matter microstructure has been characterized using the Diffusion Tensor Imaging (DTI), which assumes that water diffusion in tissues is Gaussian. This assumption is not valid in complex tissues like the brain [2]. Diffusion Kurtosis Imaging (DKI) is an extension to DTI that estimates the deviation of diffusion from the Gaussian model and gives a measure of tissue complexity, the mean kurtosis (MK) [3]. Using DKI and based on a bi-exponential water diffusion model, other parameters like the axonal water fraction (*AWF*) and tortuosity of the extra axonal space (*Ex-Tort*) are estimated [4]. The objective of this study was to investigate the relationship between VWM scores in schizophrenia (SZ) patients and healthy comparison controls (HC) and several Gaussian and non-Gaussian diffusion metrics. We hypothesized that different relationships between behavioral measures and neuroimaging data will be found in the two groups reflecting different VMW neural mechanisms.

Methods

Sixteen male schizophrenia patients and twenty one male healthy controls with ages between 30 and 55 years old participated in the study. The Visual Working Memory Index of the Wechsler Memory Scale – IV [6], comprised of the Spatial Addition and Symbol Span subtests, was used to assess working memory in both SZ and HC participants. Imaging data was obtained using 3T Trio MRI (Siemens Medical Solutions, Erlangen, Germany). Diffusion weighted data were acquired for a total of 64 uniformly distributed gradient directions and for three b values (b = 0, 1000, and 2000 s/mm^2) and 64 uniformly distribute encoding directions, with an isotropic voxel size of 2.3x2.3x2.3mm^3. Diffusion images were first co-registered and corrected for field inhomogeneity distortions. Subsequently, the diffusion and kurtosis tensor elements [5], as well as *AWF* and *Ex-Tort* [4] were estimated. Statistics were performed using Tract Based Spatial Statistics (TBSS) [7] for fractional anisotropy (FA), MK, AWF, and Tort. Within-group correlations were used to measure the association between each of the four diffusion metrics and VWM scores.

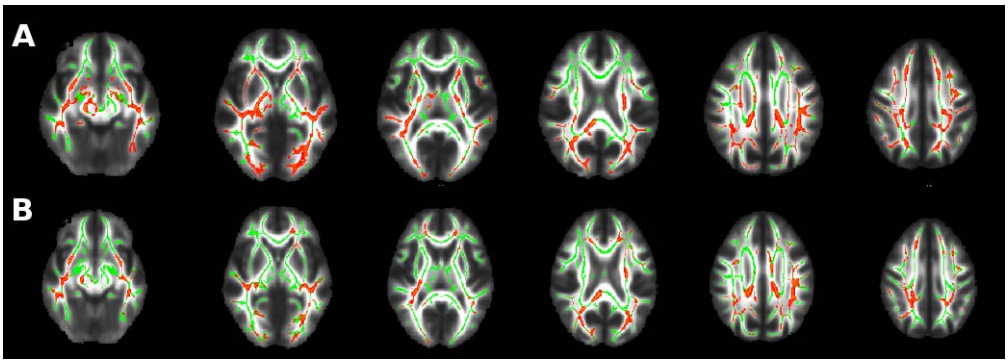

Figure 1. Regions where VWM is significantly correlated with MK (top) and *AWF* (bottom) in HC ($p<0.05$, corrected for multiple comparisons using Threshold-Free Cluster Enhancement). No correlations were found in the SZ group for any of the investigated measures.

Results

FA and *Ex-Tort* do not show any correlation with VWM performance in either group. MK and *AWF* are significantly correlated with VWM index in healthy controls, but not in patients. The correlation for MK is observed in several tracts, including inferior fronto-occipital fasciculus, the optic radiations, the posterior thalamic radiations, posterior areas of corpus callosum, and superior longitudinal fasciculus (Figure 1A). *AWF* is correlated with VWM score in controls in similar but somewhat more restricted regions (Figure 1B).

Discussion and Conclusions

Non-Gaussian diffusion metrics predict VWM performance in healthy controls. In particular, *AWF* of white matter relates to the axonal density, whereas *Ex-Tort* was suggested to relate primarily to myelination [4]. Thus, these preliminary data suggest that VMW performance in healthy adult population is primarily driven by axonal density. The correlation is mainly observed in white matter tracts which connect frontal to occipital and parietal brain regions, areas whose communication is known to be a key factor in VWM tasks. This association noted in HC was not observed in SZ patients, which confirm our original hypotheses of atypical neural mechanisms of VMW and white matter involvement. The VMW - white matter relationship was not observed for Gaussian diffusion parameters like FA, which merits further exploration given that FA differences are widely reported in SZ and were also observed in this data along with *Ex-Tort* differences [8]. Thus employing more specific metrics of white matter microstructure appears to be essential to better understand the various mechanisms of brain disorders like schizophrenia.

References: [1] Ragland JD, et al. 2010. Curr Top Behav Neurosci 4: 181 – 214. [2] Clark CA, et al. 2000. Magn Reson Med 44(6): 852 – 859. [3] Jensen J, et al. 2005. Magn Reson Med 53(6): 1432 – 1440. [4] Fieremans E, et al. 2011. Neuroimage 58(1): 177 – 188. [5] Tabesh A, et al 2011. Magn Reson Med 65(3): 823 836. [6] Wechsler, D. (2009). *Wechsler Memory Scale - Fourth Edition.* San Antonio, TX: The Psychological Corporation. [7] Smith SM, et al. 2006. Neuroimage 31(4): 1487 – 1505. [8] Lazar et al., submitted to ISMRM 21st Annual Meeting.