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Axonal deficits in young adults with High Functioning Autism and their impact on processing speed

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ABSTRACT

Microstructural white matter deficits in Autism Spectrum Disorders (ASD) have been suggested by both histological findings and Diffusion Tensor Imaging (DTI) studies, which show reduced fractional anisotropy (FA) and increased mean diffusivity (MD). However, imaging reports are generally not consistent across studies and the underlying physiological causes of the reported differences in FA and MD remain poorly understood. In this study, we sought to further characterize white matter deficits in ASD by employing an advanced diffusion imaging method, the Diffusional Kurtosis Imaging (DKI), and a two-compartment diffusion model of white matter. This model differentially describes intra- and extra-axonal white matter compartments using Axonal Water Fraction (f_{axon}) a measure reflecting axonal caliber and density, and compartment-specific diffusivity measures. Diagnostic utility of these measures and associations with processing speed performance were also examined. Comparative studies were conducted in 16 young male adults with High Functioning Autism (HFA) and 17 typically developing control participants (TDC). Significantly decreased f_{axon} was observed in HFA compared to the control group in most of the major white matter tracts, including the corpus callosum, cortico-spinal tracts, and superior longitudinal, inferior longitudinal and inferior fronto-occipital fasciculi. Intra-axonal diffusivity (D_{axon}) was also found to be reduced in some of these regions. Decreased axial extra-axonal diffusivity (AD_{extra}) was noted in the genu of the corpus callosum. Reduced processing speed significantly correlated with decreased f_{axon} and D_{axon} in several tracts. f_{axon} of the left cortico-spinal tract and superior longitudinal fasciculi showed good accuracy in discriminating the HFA and TDC groups. In conclusion, these findings suggest altered axonal microstructure in young adults with HFA which is associated with reduced processing speed. Compartment-specific diffusion metrics appear to improve specificity and sensitivity to white matter deficits in this population.

1. Introduction

Autism Spectrum Disorders (ASD) are complex developmental disorders that are characterized by a series of deficits in social interaction, language, behavior, and cognitive functions. Current ASD prevalence is estimated at 1 in 50 children (Blumberg et al., 2013). The disease symptoms are typically apparent in early infancy around 2–3 years of age, however subtle symptoms and brain deficits are likely to be present at earlier ages (Tager-Flusberg, 2010; Wolff et al., 2012).

Findings in the last decade have suggested that ASD involves pervasive brain abnormalities and dysfunction across multiple functional domains (Belmonte et al., 2004). However these brain abnormalities as well as their relationship to disease symptoms are far from being completely understood. Several lines of evidence have implicated abnormalities in the white matter pathways connecting different brain regions. For example, morphological studies have shown abnormal white matter growth patterns (Courchesne, 2004), with abnormal enlargement of the white matter in young autistic children but decreased volume in autistic adolescents. Moreover, task-based or resting-state functional MRI (FMRI) experiments (Just et al., 2007) have indicated atypical functional connectivity, suggesting impaired communication between different brain regions, potentially driven by anatomical substrates, i.e., white matter pathways.

More recently, the advent of Diffusion Tensor Imaging (DTI) has allowed the characterization of some of the microstructural properties of white matter using fractional anisotropy (FA) and diffusivity (mean (MD), axial (AD), and radial diffusivity (RD)) metrics. Most studies have reported reduced FA and/or increased diffusivity in ASD; however these findings were not always replicated, with either no differences or

Abbreviations: f_{axon}, Axonal Water Fraction; D_{axon}, Intra-axonal diffusivity; AD_{extra}, Axial extra-axonal diffusivity; RD_{extra}, Radial extra-axonal diffusivity; FA, Fractional anisotropy; MD, Mean diffusivity; AD, Axial diffusivity; RD, Radial diffusivity; HFA, High Functioning Autism; ASD, Autism Spectrum Disorders; TDC, Typically developing control; DigitSC, Digit Symbol-Coding; DTI, Diffusion Tensor Imaging; DKI, Diffusional Kurtosis Imaging.

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even increases in FA also reported (Travers et al., 2012). These inconsistencies have been partially attributed to differences in the age ranges of the populations under consideration and differences in methodology across studies (Travers et al., 2012). In particular, FA and MD differences between ASD and control groups have been more consistently reported in children populations (Jou et al., 2011), but not in adult ones (Kleinhans et al., 2012). Most importantly, recent reports have highlighted the lack of specificity of the DTI metrics as one of their chief limitations (Travers et al., 2012; Walker et al., 2012). In particular, both FA and MD differences may arise from a variety of factors including differences in myelination, axonal fiber density and caliber, and fiber tract homogeneity, making it difficult to interpret the underlying pathology of the observed differences.

Novel advanced diffusion imaging approaches have sought to improve white matter characterization by employing multi-compartment models to more independently describe different white matter features (Panagiotaki et al., 2012). One such approach is a two-compartment model of white matter (Fieremans et al., 2011) based on the Diffusional Kurtosis Imaging (DKI) technique. This model, valid in homogeneous white matter regions of similarly oriented fibers, separates MR signal contributions from the intra-axonal and the extra-axonal water (Fig. 1) with myelin water contributions being neglected, as they are not detectable for imaging parameters that are employed in typical diffusion imaging experiments. Thus, diffusion in each compartment is described by a different diffusion tensor. A first parameter that can be obtained is the Axonal Water Fraction (f_{axon}), which represents the volume of intra-axonal water relative to the total intra and extra-axonal water volume. In addition, the model also provides diffusivity metrics that describe properties of the two compartments: the intra-axonal diffusivity, D_{axon}, considered to primarily occur along the axial direction (i.e., along the axonal axis), and the extra-axonal axial (AD_{extra}) and radial (RD_{extra}) diffusivities (Fig. 1). f_{axon} is generally assumed to relate to axonal density and caliber (Barazany et al., 2009; De Santis et al., 2012; Fieremans et al., 2012), with more dense and/or larger axons resulting in larger values of this parameter. D_{axon} reflects intra-axonal microscopical organization and thus its changes may reflect variations in the size and/or number of intra-axonal structures such as microfilaments, microtubules, or mitochondria. AD_{extra} and RD_{extra} describe the extra-axonal space; changes in these parameters might reflect loss of extra-axonal structures such as oligodendrocytes and astrocytes or may be related to extracellular inflammation (Fieremans et al., 2013). RD_{extra}, which describe diffusion in the extra-axonal space in the direction perpendicular to axonal direction, may also reflect changes in axonal packing (i.e., sparser versus more compact arrangements) due to either dysmyelination or reduced axonal caliber or density. These metrics have been recently shown to improve upon the understanding of white matter changes in pathologies such as Alzheimer's disease (Benitez et al., 2013), schizophrenia (Lazar et al., 2013), and stroke (Hui et al., 2012).

Thus, in this study we employed the DKI approach to investigate differences in the white matter intra- and extra-axonal diffusion properties in a group of young adults with High Functioning Autism (HFA) compared to a control group of typically developing (TDC) young adults. The diagnostic utility of these new metrics has also been tested. The DKI approach also allows estimation of the DTI parameters from the same set of images. Thus, differences between the two groups in the DTI parameters (FA, MD, AD, and RD) were examined in order to allow comparison of our data with previous published work. Finally, given the primary role of white matter in the information flow between different brain regions, we examined the relationship between white matter diffusion properties and a metric describing information processing capacity and speed. Processing speed is generally found to be impaired in autism (Hedvall et al., 2013; Oliveras-Rentas et al., 2012; Roberts et al., 2011). However, there is still a limited understanding of the neural substrates of this deficit.

2. Methods and materials

2.1. Participants

Behavioral and diffusion imaging data were obtained for 17 typically developing control (TDC) young adults and 16 young adults with a diagnosis of High Functioning Autism (HFA). HFA was defined in this study by a diagnosis of autism disorder and a Full IQ > 80. All participants were males between 18 and 25 years old recruited by advertising the study in the New York City area. All participants were right handed except for one participant in each group with mixed handedness. A summary of demographical variables is presented in Table 1.

TD participants had no history of any psychiatric, neurological, or developmental disorders. None of the participants (TDC or HFA) reported a history of head injury or of organic brain disorder. All participants included in the study had unremarkable MRI data, with no gross brain abnormalities noted on the radiological examination, performed by members of the Neuroradiology Section as part of the standard workflow in our department. The study was approved by the Institutional Review Board at the New York University Langone Medical Center.

2.2. Diagnostic and behavioral characterization

Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 2000) and Autism Diagnostic Interview—Revised (ADI-R) (Lord et al., 1994)

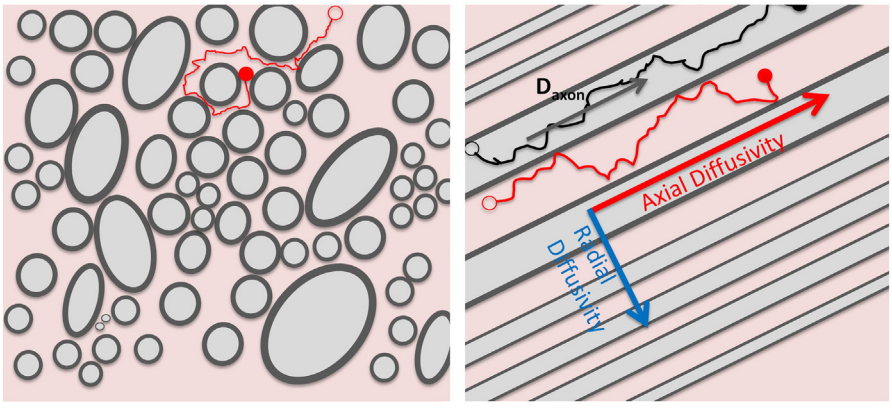

Fig. 1. Water diffusion in white matter is modeled using a two-compartment approach that assumes that the diffusion signal arises from intra-axonal (light gray) and extra-axonal (light pink) water. Axonal density and caliber are described by Axonal Water Fraction (f_{axon}), which represents the ratio of intra-axonal (light gray regions) and total intra- and extra-axonal water (light gray + light pink regions). The measured intra-axonal diffusivity (D_{axon}) is assumed to be primarily axial for typical axonal sizes and diffusion imaging parameters and for areas of high anisotropy where axons are similarly oriented. Axial (along the axons) and radial (perpendicular to axonal direction) diffusivities (AD_{extra}, respectively RD_{extra}) describe water diffusion within the extra-axonal compartment. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)