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White matter integrity and cognitive performance in school-age children: A population-based neuroimaging study

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ABSTRACT

Child and adolescent brain development are typically accompanied by marked improvements in a wide range of cognitive abilities. However, limited information is available surrounding the role of white matter in shaping cognitive abilities in children. The current study examined associations between white matter microstructure and cognitive performance in a large sample ($n = 778$) of 6- to 10-year-old children. Results show white matter microstructure is related to non-verbal intelligence and to visuospatial ability, independent of age. Specificity was demonstrated, as white matter associations with visuospatial ability were independent of general intellectual ability. Associations between white matter integrity and cognition were similar in boys and girls. In summary, results demonstrate white matter structure–function associations are present in children, independent of age and broader cognitive abilities. The presence of such associations in the general population is informative for studies examining child psychopathology

Introduction

Magnetic resonance imaging (MRI) studies demonstrate significant neurodevelopmental changes throughout childhood and adolescence, into young-adulthood. These neurodevelopmental changes occur concurrently with observed improvements in a wide range of cognitive abilities. White matter development, including myelination, continues throughout childhood and adolescence and is thought to play a key role in cognitive function. As distant brain regions become more efficiently interconnected, it is expected that the ability to utilize and manipulate information also becomes more efficient. The role of white matter in shaping cognitive abilities has been previously explored, however the literature in children, especially studies with large sample sizes, remains limited. Furthermore, while such structure–function associations seem intuitive, current *in vivo* neurobiological measures of the brain do not always demonstrate a straightforward link with neuropsychological performance, especially in the absence of severe neurological or psychiatric symptoms.

White matter maturational effects have been studied *in vivo* for over a decade using morphological information (i.e., volume, density) and, more recently, using measures of microstructural integrity (Lenroot and Giedd, 2006; Schmithorst and Yuan, 2010). Diffusion tensor imaging (DTI) is a non-invasive technique that provides such microstructural information related to white matter status (Basser et al., 1994). White matter integrity is inferred from DTI based on its ability to measure patterns of water diffusion in the brain. The water diffusion profile in white matter is distinct from that of gray matter due to the myelin sheath, axonal arrangement and packing, and axonal diameter (Beaulieu, 2002). Common parameters describing white matter integrity from DTI include fractional anisotropy (FA) and mean diffusivity (MD). Fractional anisotropy, ranging from 0 to 1, describes the degree of anisotropic diffusion, with 0 being completely isotropic (equal in all directions) and 1 being completely anisotropic (diffusion along only one axis). Mean diffusivity simply describes the average diffusion in all directions (Basser and Pierpaoli, 1996). Various cytoarchitectural features contribute to the diffusion signal by creating boundaries that impede or facilitate free water diffusion (e.g., axonal packing and myelin), and it has been shown that FA and MD (in addition to other scalar metrics) can contribute unique information (Beaulieu, 2002).

Beginning with morphological information from structural imaging, and more recently with DTI, white matter development in children and

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adolescents has been examined using both cross-sectional and longitudinal designs (Barnea-Goraly et al., 2005; Giedd et al., 1999; Giorgio et al., 2008; Lebel et al., 2008; Schmithorst et al., 2002; Schmithorst and Yuan, 2010). The majority of literature in children demonstrates that with age, both white matter volume and microstructural integrity increase. The precise determinant of these maturational effects has yet to be fully delineated, however the primary hypothesis suggests a combination of increases in myelination coupled with an optimized structural organization of axons (Paus, 2010). Interestingly, studies have demonstrated differential developmental trajectories in white matter between boys and girls (Erus et al., 2015; Simmonds et al., 2014), which may underlie some of the subtle cognitive differences (Maitland et al., 2000).

While studied to a lesser extent than white matter maturation, associations between white matter and cognitive performance have also been examined in children (Erus et al., 2015; Fryer et al., 2008; Johansen-Berg et al., 2007; Muetzel et al., 2008; Navas-Sanchez et al., 2014; Schmithorst et al., 2005). In an early study of roughly 50 children, 5 to 18 years old, Schmithorst et al. (2005) found positive associations between white matter microstructure (i.e., DTI metrics) and intelligence, irrespective of age and sex. A more recent study of 36 children and adolescents 11 to 15 years of age also showed a positive association between white matter microstructure and intelligence (Navas-Sanchez et al., 2014). These studies show IQ to be linked to white matter microstructure in multiple regions, including frontal, parietal and occipital lobes, and the corpus callosum. In general, available studies of white matter microstructure and cognitive ability demonstrate brain–behavior associations that suggest white matter integrity is linked to better cognitive performance.

The current study aims to describe associations between white matter microstructure and cognition across a wide range of neuropsychological domains in a large sample of 6- to 10-year-old children. We hypothesized age-independent associations between DTI measures and cognitive performance across all domains. Based on developmental literature, fractional anisotropy and axial diffusivity are hypothesized to associate positively with cognition, whereas mean diffusivity and radial diffusivity will associate negatively. Given substantial evidence for involvement of widespread brain regions in general intellectual ability (Jung and Haier, 2007), we hypothesize global associations across multiple white matter areas. For more specific cognitive functions, we also hypothesize involvement from multiple regions, but to a lesser extent than with general intelligence. As previous work has already demonstrated distinct patterns of white matter maturation in boys and girls, we also hypothesize differential structure–function associations in boys and girls, specifically in cognitive domains where differences in ability have been demonstrated (e.g., language and spatial ability).

Methods

Participants

The current study is embedded within the Generation R Study, which is a large, population-based cohort investigating children's health from fetal life onwards in Rotterdam, the Netherlands (Jaddoe et al., 2012). A sub-sample of 1070 children visited the research center for neuropsychological testing and MRI scanning. Further details of the selection and recruitment of subjects, the research protocol, and overall design of this MRI sub-study are described elsewhere (White et al., 2013). Of the 1070 children who visited the research center for an MRI, 1033 received a DTI scan. Of the 1033 DTI scans, 255 (25%) were excluded due to excessive motion/artifact (described below), leaving 778 datasets for analysis. The Medical Ethics Committee of the Erasmus Medical Center approved all study procedures, and parents provided written informed consent.

Cognitive and behavioral assessments

Intelligence assessment

General intellectual functioning was assessed during the age-6 assessment wave using an abbreviated version of the Snijders-Oomen Niet-verbale Intelligentie Test-Revisie (SON-R 2½-7) (Tellegen et al., 2005; Tiemeier et al., 2012). The SON-R 2½-7 is a measure of nonverbal intelligence for children between 2.5 and 7 years of age and was selected in order to minimize language-dependent confounds that may be present in a large, ethnically diverse sample such as the Generation R Study. An intelligence quotient (IQ) was estimated from the two SON-R performance subtests that were administered (*Mosaics* and *Categories*), which is highly correlated with estimates resulting from the complete version (Basten et al., 2014).

Neuropsychological assessment

Neuropsychological functioning was assessed using the NEPSY-II-NL, a Dutch translation and adaptation of the NEPSY-II (Brooks et al., 2010). Due to time constraints, a selection of tests from the NEPSY-II-NL was chosen in order to examine five areas of cognitive ability: attention and executive functioning, language, memory and learning, sensorimotor functioning, and visuospatial processing (Mous et al., in press). In order to limit the number of statistical tests performed, and because the NEPSY-II-NL does not provide domain-specific summary scores, a data reduction technique was utilized to derive empirical scores. Initially, a confirmatory factor analysis was applied to create domain scores, however model fit indices were very low, which is potentially a reflection of the abbreviated neuropsychological test battery used in the current study. Thus, an overall performance score was derived by using a principal component analysis (PCA) on all raw (i.e., non-age-normed) summary scores from the NEPSY-II-NL and selecting only the first unrotated factor score. Next, for the Attention & Executive Function, Language, Learning and Memory, and Visuospatial domains, a similar approach was utilized. NEPSY-II-NL test items belonging to a given domain were submitted to PCA, and again only the first unrotated factor score was selected as the summary score for that cognitive domain. Given the nature of the summary scores in the Sensorimotor domain, namely that the completion time and error scores together can reflect a particular strategy (e.g., fast with many errors vs. slow with few errors) making interpretations in isolation difficult, a different approach was employed. For this domain, a simple trade-off score was generated by computing the standardized product of the completion time and errors. Of note, as the overall domain was constructed using a standard PCA, certain test domains that are overrepresented in the test battery are similarly overrepresented in the overall PCA score. However, this is not the case with the other domain scores.

Assessment of behavioral problems

Behavioral problems in children were assessed using the Child Behavior Checklist (CBCL/1½-5) from the age-6 assessment wave (Tiemeier et al., 2012). All children were assessed with one instrument; the preschool CBCL was selected because many children were younger than 6 years of age at the time of the assessment, and the other versions are inappropriate for such young children. The CBCL is a 99-item parental report inventory that utilizes a Likert response format ("not true", "somewhat true", "very true") for a variety of behaviors. A simple sum of all items was used to create a total behavioral problems score, which was square root transformed to approximate a normal distribution (Achenbach and Rescorla, 2000).

MRI

MR-image acquisition

Prior to neuroimaging, all children underwent a 30-min mock scanning session in order to acclimate them to the MR-environment (White et al., 2013). Magnetic resonance imaging data were acquired on a 3 T