Myelin Water Fraction in Relation To Fractional Anisotropy and Reading in 10-Year-Old Children

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Short Report

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Abstract

Diffusion-weighted imaging studies have repeatedly shown that white matter correlates with reading throughout development. However, the neurobiological interpretation of this relationship is constrained by the limited microstructural specificity of diffusion imaging. A critical component of white matter microstructure is myelin, which can be investigated noninvasively using MRI. Here, diffusion-weighted as well as myelin water imaging were applied to examine the links of myelin water fraction (MWF) with fractional anisotropy (FA; a common diffusion index) and reading ability in 10-year-old children (n = 69). The results replicate previous reports on a positive relationship between FA and MWF, which is significant in dorsal but not ventral tracts. Moreover, our findings revealed a negative correlation between word reading and MWF in left reading-related white matter tracts. Altogether, this study contributes important insights into the role of myelin-related processes in the relationship between reading and white matter structure.

Introduction

Skilled reading relies on coordinated processing across a widespread network of cortical areas. The white matter tracts connecting these areas play a key role in facilitating rapid signal transmission across the reading network. White matter properties can be studied noninvasively using diffusion-weighted imaging (DWI), which yields, among others, the fractional anisotropy (FA) index, a quantitative measure of the directionality of water diffusion used to characterize white matter organization.

There is ample evidence consolidating the involvement of white matter organization in relation to reading. Several DWI studies provide evidence of significant associations between white matter properties (as measured by FA) and reading ability in adults (for a review see Vandermosten et al. 2012b). Although a converging finding seems to be positive correlations in left frontal and temporo-parietal white matter (Lebel et al. 2013), studies have also reported negative associations between FA and reading measures (Yeatman et al. 2012). In addition, evidence from studies in pre-reading children suggests that an early link between literacy-related skills and white matter is present before the onset of reading acquisition (Vanderauwera et al. 2018; Walton et al. 2018). There is also strong evidence to support a link between white matter and reading throughout development (Yeatman et al. 2012), as well as predictive power of early white matter organization for later reading-related skills (Vanderauwera et al. 2017; Zuk et al. 2021).

What factors or processes might be driving the observed relationships between diffusion properties such as FA and reading? One of the original hypotheses put forward is myelination (Klingberg et al. 2000), a critical component of human white matter with a known role in cognitive functions and plasticity (Kaller et al. 2017). While early experiments have shown that anisotropy is primarily influenced by axonal membranes, including the density (packing) and diameter of axons, there is evidence that it is to a certain extent also modulated by myelination (Beaulieu 2009). Indeed, FA is sensitive to both microscopic and macroscopic aspects of tissue properties, but has demonstrably low specificity for any single neurobiological process (Jones et al. 2013), and therefore cannot inform us on the specific role of myelin-related processes. Myelin water imaging (MWI) is an approach that allows a more specific *in vivo* investigation of myelin, relying on the principles of varying T2 relaxation in the different cell compartments (reviewed in MacKay and Laule 2016). A quantitative index of MWI is myelin water fraction (MWF), which can be used as a proxy measure of cortical myelination. This measure represents a quantification of myelin water, based on the short relaxation rate of water trapped within the myelin bilayer (Whittall et al. 1997). Previous histology and imaging studies have validated the use of MWF as an indirect, yet specific measure of brain myelin using both qualitative and quantitative methods (Moore et al. 2000; Laule et al. 2006).

Few studies have investigated the link between MRI myelin measures and reading. Kraft et al. (2016) reported higher T1 intensities, interpreted as reduced myelin concentration, in the left anterior arcuate fasciculus of preliterate children at familial risk for developing dyslexia compared to children without a risk. Notably, the opposite pattern was reported in adults, whereby increased myelinated cortical thickness ratio is observed in the auditory cortex of dyslexic compared to typical readers (Skeide et al. 2018). To date, only one study has directly investigated the relationship between MWF and reading ability. In a sample of 20 participants aged 10-18 years old, Beaulieu et al. (2020) reported positive correlations between reading and MWF, as well as lower MWF in poor (n=7) compared to good readers (n=11) in several regions including bilateral thalamus, centrum semiovale, anterior and posterior limbs of the internal capsule and splenium of the corpus callosum. This study offers new insights into the relationship between myelin water and reading, however replication of these findings is warranted given the small sample size, the wide age range and the selection of regions which are not typically considered part of the core reading circuitry.

An important factor in interpreting associations between white matter and cognitive measures, is our understanding of how MWF relates to conventional DWI metrics such as FA. While some studies report an overall positive relationship between FA and MWF (Mädler et al. 2008; Friedrich et al. 2020), others find little evidence for shared variance between the two (Bells et al. 2011; Billiet et al. 2015). Notably, Mädler et al. (2008) reported that the relationship between FA and MWF differed across regions of interest. This finding is further corroborated by De Santis et al. (2014), who showed that the correlation between FA and MWF was only significant when regions with single fiber populations were considered, as compared to regions with multiple fiber populations. Altogether, these divergent findings suggest that a positive relationship between FA and MWF may exist, but is rather dependent on the underlying fiber architecture and potentially influenced by other microstructural factors as well. Importantly, most of the aforementioned studies were conducted using adult data. Given that white matter development is still ongoing throughout childhood and adolescence (Lebel and Beaulieu 2011), it is important to uncover whether the observed relations in adults also hold in children. In children, one study reported no significant correlation between MWF and FA (Morris et al. 2020), however the literature here is very limited.

The goal of the present work is to elucidate the relationship between white matter microstructure and reading ability in children. First, we extend previous work on the relationship between FA and the MWI-derived myelin water fraction (MWF) index, in order to better understand the shared relationship between the two metrics in our sample. Second, we investigate the relationship between MWF and reading in school-aged children. We focus on bilateral white matter tracts involved in reading processes, such as the dorsal direct temporo-parietal segment of the AF (AF_{direct}), dorsal anterior fronto-parietal segment of the AF ($AF_{anterior}$) and the ventral inferior fronto-occipital fasciculus (IFOF).

Methods

Participants

The participants of this study were 72 children aged 10-11 years old (mean age 10.6 y.o.). The data reported here were collected in the framework of a larger longitudinal project (*N*=87) investigating the neuroanatomical and neurophysiological correlates of dyslexia (for initial cohort description see Vandermosten et al. 2015). In the original sample, children with and without a familial risk were matched based on school, sex, age, non-verbal intelligence and parental educational level. The following inclusion criteria were applied: non-verbal intelligence ≥ 80 based on Raven's Coloured Progressive Matrices (Raven et al. 1984), normal hearing (pure tone average at 0.5, 1, 2 and 4 kHz below 20 dB HL), monolingual native Dutch speakers, no history of brain damage, vision or articulatory problems and no increased risk for developing ADHD. The current report focuses on data from 63 children from the initial cohort, who took part in an MRI examination during spring of fifth grade. An additional nine children who were not part of the longitudinal project, were recruited to participate in the MRI measurements in order to reach a larger sample. Therefore, the sample of this study comprises 72 children, 36 of whom had a familial risk of dyslexia, defined by having at least one first-degree relative with dyslexia, while 36 children had no familial risk.

Cognitive assessment

The behavioral assessment took place at school during the spring of fifth grade of primary school. Reading ability was assessed using a standardized test for word reading, during which words are presented and the participant is asked to read them as accurate and fast as possible (Brus and Voeten 1979). Reading scores were calculated based on the number of words correctly read in one minute. Raw scores were used in subsequent analyses.

MRI data acquisition

All participants underwent MRI scanning during spring of fifth grade. Images were acquired on a 3T MRI Philips Achieva scanner using a 32-channel head coil. A DWI sequence was acquired using single shot EPI with SENSE (parallel imaging). Following parameters were used: repetition time = 7600 ms, echo time = 65 ms, flip angle = 90 ° , voxel size = 2.5 × 2.5 × 2.5 mm, 60 non-collinear directions with b-value = 1300 s/mm^2, 6 nondiffusion-weighted images. In the same session, MWI data were acquired using a whole-cerebrum multi-echo 3D gradient spin echo (GRaSE) sequence (Prasloski et al. 2012). The acquisition scheme consisted of 48 slices for which 32 echoes were acquired with echo time = 10 ms, repetition time = 1000 ms, EPI factor = 3, flip angle = 90 ° and 2 mm isotropic voxel size.

MRI data processing

Pre-processing steps for DWI data are described in previous publications of the original cohort (Vandermosten et al. 2015; Vanderauwera et al. 2017). Briefly, the diffusion-weighted images were pre-processed using the software ExploreDTI (version 4.8.3) (Leemans et al. 2009). Images were corrected for subject motion and eddy current-induced distortions followed by fitting the diffusion tensor model and calculation of voxelwise FA maps. Subsequently, whole-brain deterministic tractography was performed using the following parameters: minimum FA threshold = 0.20, step length between calculations = 1 mm, maximum turning angle = 40°. Individual white matter pathways (AF_{direct}, $AF_{anterior}$, IFOF) were delineated in TrackVis (Wang et al. 2007) by an experienced rater (JV) by manual placement of anatomical regions-of-interest in native space (details outlined in Vandermosten et al. 2012a). The right AF_{direct} could not be identified in 14 participants, the left AF_{direct} could not identified in 4 participants and the left $AF_{anterior}$ could not be identified in 1 participant. This inability to detect the right AF_{direct} in certain individuals is consistent with previous reports (Eluvathingal et al. 2007; Lebel and Beaulieu 2009) and has been attributed to methodological limitations rather than gross anatomical abnormalities (Yeatman et al. 2011). Head motion during DWI acquisition was quantified by calculating the absolute displacement of each volume relative to the first volume of the DWI series. Datasets from subjects whose average translational motion exceeded 2.5 mm (acquisition voxel size) were excluded from further analysis due to excessive motion. Note that no datasets were removed according to this criterion (median translational displacement = 0.43, range = 0.21-1.30).

MWI data were pre-processed in MATLAB 2016b using in-house scripts, following a protocol previously outlined in Billiet et al. (2015). Briefly, a multiexponential decay curve was fit in each voxel and then transformed into a continuous T2 distribution of mono-exponential T2 decay curves using a non-negative least squares algorithm (Whittall and MacKay 1989). The extended phase graph algorithm was used to account for possible stimulated echoes (Prasloski et al. 2012). To assure smooth T2 amplitude distributions, a 1.02 regularization factor was applied during the fitting procedure. From the T2 distributions, metrics were derived on a voxelwise basis. Maps of MWF were obtained for each participant, with MWF defined as the area fraction between 10 and 40 ms relative to total T2 distribution area.

To achieve alignment between the two modalities, the first non-diffusion-weighted image (b0) of the DWI acquisition was registered to the first echo (TE1) of the MWI acquisition using a rigid transformation with six degrees of freedom as implemented in Advanced Normalization Tools (ANTs; Avants et al. 2011). The inverse transformation was then applied on the MWF map to achieve alignment with native DWI space. Binarized masks of all delineated white matter tracts were constructed and superimposed on FA and

MWF parameter maps. For each subject, average FA and MWF measures were extracted from each corresponding tract by calculating the metric average across all mask voxels in native space.

Statistical analysis

All reported analyses were performed in R (version 4.0.0) (R Core Team 2020). All subjects are included in the analyses except one participant, for whom MWI data were not available and two datasets where the MWI pre-processing pipeline could not be successfully completed (analyzed $N = 69$). Linear mixed-effects regression using the *lme4* package (Bates et al. 2020) was employed to assess the shared variance between metrics, with FA as the dependent variable and MWF, tract and the MWF-by-tract interaction modelled as fixed predictors. Three different models (random intercept for subject, random intercept for tract, or random intercept for both subject and tract) were compared to determine the best random-effects structure. The model with the lowest Akaike Information Criterion (AIC) was chosen as the one with the best fit. Estimated linear trends and confidence intervals were calculated using the R package *emmeans* (Lenth 2020). The overall variance explained by the best fitting model was summarized using marginal R^2 and conditional R^2 (representing fixed effects only and both fixed and random effects respectively) (Nakagawa and Schielzeth 2013). Pearson correlations were used to investigate the association between word reading and MWF in each tract. Significance was set at alpha = .05 for all analyses.

Results

Participant demographic characteristics are shown in Table 1. The model with by-subject random intercept was the best fitting model as indicated by the lowest AIC value and had a conditional R^2 of 73.1% and a marginal R^2 of 55.0%. Model assumptions were confirmed by visual inspection of diagnostic plots. This model revealed a significant positive relationship between MWF and FA ($F(1, 371)$ 33.30, $p = < .001$), with varying intercepts for the different tracts (see Figure 1A). We found no evidence of a MWF-by-tract interaction effect ($F(5, 327) = 0.95$, $p = .448$). As shown in Figure 1A, the estimated linear relationship between FA and MWF was significantly different from zero (assessed using 95% confidence intervals) in bilateral AF_{direct} and $AF_{anterior}$, but not the IFOF.

Table 1
Group demographic characteristics

Variable	N = 69[a]
Sex (female/male)	24/45
Familial risk for dyslexia (yes/no)	36/33
Age at MRI (years)	10.6 (10.1 - 11.2)
Socio-economic status[b]	6 (2 - 8)

[a] Occurrence (N) or Median (Range)

[b] Assessed with the Family Affluence Scale (Boudreau and Poulin, 2009)

Reading scores were negatively correlated with MWF in the left $AF_{anterior}$ ($r(66) = -.31$, $p = .011$) and left IFOF ($r(67) = -.38$, $p = .001$). No additional correlations were observed in the other investigated pathways. The corresponding scatter plots for the correlation analysis are shown in Figure 1B. Note that the results remain the same after controlling for the false discovery rate ($q = .05$).

Discussion

In this report, we investigated the relationship between reading ability and myelin water fraction (MWF) in 10-year-old children. In a first step, we examined how MWF relates to FA, a commonly used index of white matter organization in studies of reading and language. Next, we examined the relationship between reading scores and MWF in three bilateral white matter tracts relevant for reading. We found an overall positive relationship between FA and MWF bilaterally, with varying intercepts and slopes among tracts. Moreover, MWF was negatively correlated with reading scores in left dorsal and ventral tracts, but not their right-hemispheric counterparts.

Understanding how MWF relates to diffusion anisotropy measures enables a more comprehensive interpretation of the associations reported between white matter properties and reading. Our analysis revealed a positive relationship between FA and MWF, a finding that is in agreement with some previous studies investigating associations among white matter microstructure metrics (Friedrich et al. 2020), but in contrast to others (Billiet et al. 2015; Morris et al. 2020). In the present study, the relationship between FA and MWF was significant in bilateral dorsal pathways such as the AF_{direct} and $AF_{anterior}$, but not the ventral IFOF. The observation that the linear relationship between myelination and anisotropy may vary depending on the investigated region has been suggested in previous studies as well (Mädler et al. 2008; De Santis et al. 2014) and helps explain the mixed literature. When interpreting the findings of the current study, it is important to acknowledge that previous research was almost solely conducted using adult data, whereas here we report on data from 10-year-old children. Given that most tracts are undergoing both myelination and increases of axonal packing during late childhood and adolescence (Geeraert et al. 2019), it is possible that the relationship between myelination and anisotropy is driven by different factors in children than it is in adults. Overall, our results provide evidence for shared variance between the two metrics in children and support the observation that the FA-MWF relationship is influenced by regional anatomy, among other factors.

The present study contributes to a fairly sparse literature on how reading relates to white matter structure beyond the classical DWI metrics. Here, our results support a negative correlation between reading skill and myelin measures in left-hemispheric tracts. This finding contradicts earlier hypotheses suggesting that lower or poor myelination might contribute to compromised conduction speed along axons and in turn to impaired reading (Klingberg et al. 2000). Moreover, this finding comes in contrast to previous DWI studies in which a positive association between reading and FA is found (Lebel et al. 2013; Zhang et al. 2014). The only direct comparison with the literature is the study by Beaulieu et al. (2020), where myelin water measures were linked to reading scores, revealing positive correlations in bilateral anterior, thalamic and callosal regions. Distinct methodological differences should be considered when comparing the conflicting results observed between our study and that of Beaulieu and colleagues, such as i) the choice and method of extracting regions of interest (atlas vs tractography and manual delineations), ii) the sample size (n=71 in our study, n=20 in the study by Beaulieu et al.), and most importantly iii) the population characteristics (narrow vs wide age range).

With respect to the latter point, the influence of age/developmental effects on the correlation between reading and MWF is likely a major contributor. More specifically, Beaulieu and colleagues reported a positive correlation between MWF and reading in a relatively wide age range (10-18 years old) and did not find significant correlations between age and MWF within their sample. However, reading measures were standardized for age while MWF was not, which can be problematic for interpreting this correlation, given that previous studies have reported age-related increases in myelin volume fraction and thus ongoing myelination across a similar age span (Geeraert et al. 2019).

The negative correlation between reading and MWF can also be discussed in the context of developmental brain-behavior dynamics. For instance, it has been suggested that the nature of the associations between reading and white matter properties (e.g. FA) changes throughout development (Yeatman et al. 2012; Wandell and Yeatman 2013). This variability is presumably a result of individual differences in the rate and timing of processes such as pruning and myelination, and influenced by experience, genetic and environmental factors, among others. Hence, in line with this view, we can hypothesize that the direction of the correlation between reading and MWF does not remain stable throughout reading development and that the current cross-sectional investigation only captures a snapshot of this dynamic relationship. A longitudinal design including two or more assessment points, in combination with a sample that is similar in age, would be better suited and is recommended for future studies aiming to disentangle these developmental influences (Atteveldt et al. 2021).

To conclude, this study used myelin water imaging in combination with diffusion imaging aiming to elucidate the relationship between white matter microstructure and reading ability. The study contributes new insights into the shared relationship between myelination and anisotropy in children. In addition, our findings support associations between myelin water and reading scores in school-aged children, which were observed specifically in the left hemisphere.

Declarations

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Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Author contributions

ME and MV designed this study. ME conducted the data processing, data visualization, statistical analysis and drafted the manuscript. TB provided software for image processing, contributed to the methodology and revised the manuscript. JW, PG, JV and MV revised the manuscript, were involved in conceptualization, data curation, project administration, funding acquisition and supervised the project. All authors read and approved the final version of this manuscript.

Data availability

The conditions of our ethics approval do not permit public archiving of anonymised study data, since consent had only been obtained for the participation in the study, and not to share data with third parties. Researchers seeking access to the study data should contact the last author (maaike.vandermosten@kuleuven.be) explaining the purpose of their request. In accordance with the EU general data protection regulation (GDPR), data will be released to requestors upon the following conditions: consent of the representative of the minor and a formal agreement between parties. Please note that the MRI data cannot be shared under any circumstance, as MRI data are person-specific and therefore cannot be considered anonymous.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Medical Ethical Committee of the Leuven University Hospital (B322201214607).

Consent to participate

Written informed consent was obtained from the parents/guardians of the children participating in this study. Verbal assent was obtained from the children before participation.

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Figures

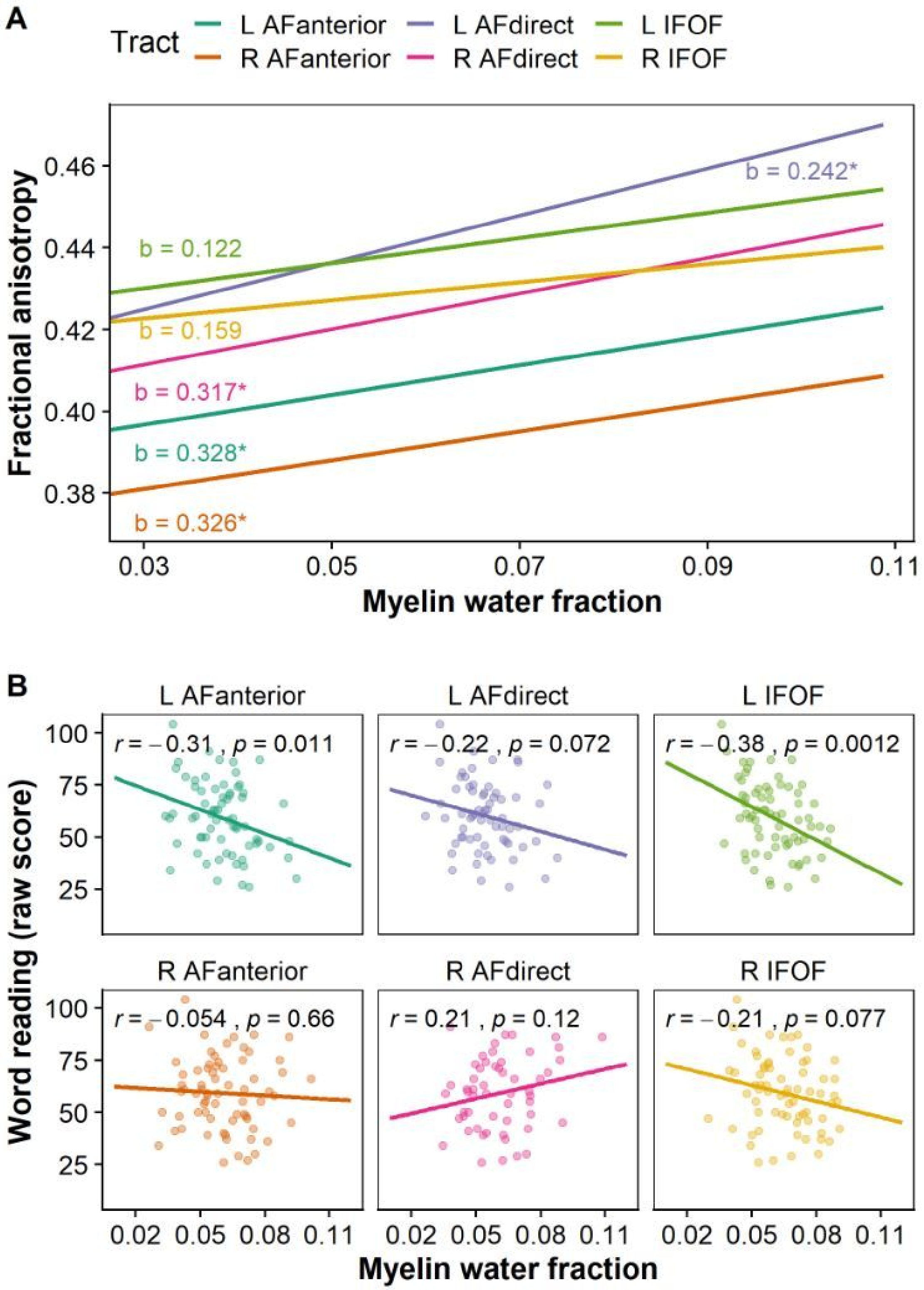

Figure 1

A Linear trend estimates (beta) assessing the effect of myelin water fraction on fractional anisotropy per tract. The asterisks indicate whether the estimated slope is significantly different from zero (assessed using 95% confidence intervals). B Scatter plots and correlation coefficients for the relationship between myelin water fraction and raw reading scores.