NeuroImage 241 (2021) 118426

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

Neurite density and arborization is associated with reading skill and phonological processing in children

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ARTICLE INFO

Keywords:
Neurite density
Neurite orientation
Tractography
Diffusion measures
Reading disability
School-aged children

ABSTRACT

Background: Studies exploring neuroanatomic correlates of reading have associated white matter tissue properties with reading disability and related componential skills (e.g., phonological and single-word reading skills). Mean diffusivity (MD) and fractional anisotropy (FA) are widely used surrogate measures of tissue microstructure with high sensitivity; however, they lack specificity for individual microstructural features. Here we investigated neurite features with higher specificity in order to explore the underlying microstructural architecture.

Methods: Diffusion weighted images (DWI) and a battery of behavioral and neuropsychological assessments were obtained from 412 children (6 – 16 years of age). Neurite indices influenced by orientation and density were attained from 23 major white matter tracts. Partial correlations were calculated between neurite indices and indicators of phonological processing and single-word reading skills using age, sex, and image quality metrics as covariates. In addition, mediation analysis was performed using structural equation modeling (SEM) to evaluate the indirect effect of phonological processing on reading skills.

Results: We observed that orientation dispersion index (ODI) and neurite density index (NDI) were negatively correlated with single-word reading and phonological processing skills in several tracts previously shown to have structural correlates with reading efficiency. We also observed a significant and substantial effect in which phonological processing mediated the relationship between neurite indices and reading skills in most tracts.

Conclusions: In sum, we established that better reading and phonological processing skills are associated with greater tract coherence (lower ODI) and lower neurite density (lower NDI). We interpret these findings as evidence that reading is associated with neural architecture and its efficiency.

1. Introduction

Individuals vary widely in reading ability, and various sensory, cognitive and neurobiological factors have been associated with variation in reading ability (D'Mello and Gabrieli, 2018; Norton et al., 2015). Decoding-based reading disabilities (RD) are used to classify those who have persistent difficulties with accuracy and/or fluency of word-level reading (Snowling and Hulme, 2012). Phonological processing has been shown to consistently predict reading performance and is thus considered a foundational skill for reading development (Foy and Mann, 2006; Hulme, 2002; Kovelman et al., 2012; Tanaka et al., 2011). At the neurobiological level, previous neuroimaging studies using diffusion data have explored neuroanatomical and neurobiological correlates of reading ability and have revealed various white matter tissue properties to be associated with reading ability and with the componential skills of reading (e.g., phonological and other related skills) (De Vos et al., 2020; Deutsch et al., 2005; Klingberg et al., 2000; Vandermosten et al., 2012b). Diffusion measures, particularly fractional anisotropy (FA), mean diffusivity (MD), axial and radial diffusivity have been used to identify white matter traits characteristic of RD (Arrington et al., 2017; Hasan et al., 2012) and associate the white matter structural alterations to individual differences in various reading skill measures in school-aged children and pre-readers (De Vos et al., 2020; Niogi and McCandliss, 2006). These diffusion markers have been predominantly identified in dorsal and ventral reading pathways (e.g., superior longitudinal, arcuate, inferior fronto-occipital, uncinate, and inferior longitudinal fasciculi) and the splenium of the corpus callosum (Dougherty et al., 2007; Odegard et al., 2009; Vandermosten et al., 2012a; Yeatman et al., 2012). Furthermore, longitudinal and intervention studies have shown that gains in reading skills have been associated with changes in diffusion measures (FA and MD),

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https://doi.org/10.1016/j.neuroimage.2021.118426.
Received 25 March 2021; Received in revised form 25 June 2021; Accepted 21 July 2021

mostly in left temporal-parietal regions or tracts identified as reading related along with the posterior corpus callosum and bilateral corona radiata (Huber et al., 2018; Keller and Just, 2009; Lebel et al., 2019).

Although these well-studied diffusion measures are sensitive to different tissue properties, such as axonal dispersion, axonal density, degree of myelination, membrane permeability, and intra-voxel orientational coherence (among others), they are not specific to any one of them (Beaulieu, 2002; Jones et al., 2013). For example, the computation of FA does not distinguish between anisotropy arising from the intra-axonal compartment (restricted) or extra-axonal compartment (hindered) diffusion which could be modulated by intra-voxel orientational dispersion, myelination, fiber density, membrane permeability, and partial volume effects, in addition to the number of axons (Beaulieu, 2009). Thus, a change in FA could reflect changes in one or more of these aspects but could not be precisely linked to any single tissue property and/or direction of change. Similarly, differences in MD could reflect variations within the intra- and extracellular space and/or index global increases in CSF (Beaulieu, 2002). The increased value in radial diffusivity could similarly reflect limited hindrance of transmembrane water transport by the myelin sheath or more diffusion in extracellular spaces by axonal loss, and thus could be interpreted both as myelin loss and/or axonal degeneration (Song et al., 2002; Wimberger et al., 1995). Hence, measures with higher specificity are desired. The neurite orientation dispersion and density imaging (NODDI) model based on advanced acquisition techniques alleviates these specificity constraints by being able to model neurite (collectively consisting of dendrites and axons) features (Jespersen et al., 2007; Zhang et al., 2012). NODDI models the diffusion signals by combining three tissue compartments: neurites, extra-neurites, and cerebrospinal fluid (CSF), each with different properties of diffusion motion. The model then generates the neurite measures (e.g., neurite density, orientation index, volume fraction of isotropic diffusion) by measuring the restriction of the movement of water molecules in those intra-neurite spaces determined by the neuronal architecture of dendrites and axons (Fukutomi et al., 2019; Jespersen et al., 2007; Zhang et al., 2012). These features, mainly neurite density and orientation dispersion, have been demonstrated to enable specific differentiation of cortical microarchitecture and the variation of these estimates has been utilized for characterizing various neuropsychological and neurological disorders (Chang et al., 2015; Colgan et al., 2016; Fukutomi et al., 2019; Kamagata et al., 2017). Moreover, a recent study has performed a direct validation of NODDI models and has shown a significant match of neurite density and orientation dispersion to those measures obtained from histological samples (Grussu et al., 2017). One of the notable methodological benefits of NODDI over diffusion tensor modeling (DTI) is that free water diffusion is isolated into a separate biophysical compartment; therefore, partial volume averaging with cerebrospinal fluid does not contaminate estimates of tissue microstructure as it often does in case of DTI (Metzler-Baddeley et al., 2012; Vos et al., 2011).

One recent study applied this novel approach to examine neural correlates of reading and showed that these measures can index individual differences in reading skills (Huber et al., 2019). However, another study using multimodal white matter imaging failed to identify significant relationships between reading skills and principal components derived using white matter measures (Geeraert et al., 2020). A similar study, which explored both reading and math skills in children who had been born preterm, also failed to identify any significant associations between NODDI metrics and reading (Collins et al., 2019). Notably, in two of these three studies (Huber et al., 2019) and (Geeraert et al., 2020), the NODDI metrics and traditional white matter imaging methods were only explored in a limited set of tracts. These studies represent an important first step in exploration of these measures in relation to reading, however there are some inconsistent findings between studies, which may be due to: relatively small samples, heterogenous samples in terms of age and reading skill profiles, use of different diffusion measures, and variation in the methods used for definition and selection of tracts of interest. The authors of a recent meta-analysis of diffusion tensor imaging [DTI] studies investigating white matter correlates of dyslexia via voxel-based analyses (VBA) of FA pointed to concerns about inconsistency in these findings and argued similar reasons (Moreau et al., 2018a). Hence, these factors motivate a more comprehensive whole brain study in a large sample with a range of reading skill. In the current study, we used NODDI coefficients to assess the association between white matter microarchitecture and reading skills in a large sample of children and adolescents with a broad range of reading abilities. Further, we also examine associations to phonological processing in order to identify potential intermediate phenotypes that may underlie relations between white matter microstructure and reading skills. Reading and phonological processing are explored independently and also using a mediation model to test for intermediary effects. Finally, for comparison to existing literature, and to empirically assess whether NODDI measures are providing unique information, we also examine associations between traditionally used white matter metrics (FA and MD) and reading in tracts where we observed associations using NODDI coefficients.

We hypothesized that we would find significant associations between NODDI measures, reading and phonological processing in tracts that have previously been linked to these skills (e.g., Superior Longitudinal Fasciculus (SLF), Arcuate Fasciculus (AF), Inferior Longitudinal Fasciculus (ILF), Inferior Fronto-Occipital Fasciculus (IFOF)). Based on previous literature that has examined NODDI metrics and their relationship to various cognitive and neurodevelopmental characteristics, we further predicted that these associations would be negative, with increased skill being associated with lower neurite orientation dispersion and neurite density, which have been linked to greater neural efficiency. However, given limited previous reports using NODDI measures with a whole brain approach in studies of reading, these hypotheses were somewhat speculative. We also predicted, given potentially tighter links between some of the previously identified tracts and phonological processing (vs. reading), that phonological processing would mediate the relationship between white matter microstructure and reading, at least in some tracts (e.g., AF). Previous studies have shown that phonological processing development begins prior to reading acquisition and is a well-established behavioral predictor of reading ability, e.g. (Schatschneider et al., 2004). Thus, we expected that the organization of dorsal pathways (arcuate fasciculus, superior longitudinal fasciculus) that link brain areas that support phonological processing (i.e. superior temporal gyrus, inferior frontal gyrus), would be related to phonological processing ability, and in turn, reading.

2. Methods and materials

2.1. Participants

Whole brain Magnetic Resonance Imaging (MRI) data and a battery of behavioral and neuropsychological measures were obtained from 412 children (6 – 16 years of age) included in the Florida Learning Disabilities Research Center (FLDRC) mega analysis from two different sites (Cornell Brain Imaging center, CBIC: N = 103 and Rutgers University, RU: N = 309], both included in the Healthy Brain Network Biobank (Alexander et al., 2017). Participants who were diagnosed with Autism (N = 39), intellectual disability (N = 8) and/or had Wechsler Intelligence Scale for Children WISC-FSIQ scores less than 70 (N = 78) were excluded along with those having poor MRI quality (N = 33, based on the lower edge outliers of average CNR, absolute and relative motion obtained using distribution visualization and Rosner's test for outliers; 9 subjects based on CNR and 24 based on motions) and/or incomplete behavioral assessments (N = 10), yielding N = 244 [mean age: 10.22 ± 2.76 years; sex: 150 females, 94 males; mean FSIQ: 100.55± 14.41; ADHD: 49.18% (120/244); RD: 15.98% (39/244)] participants for the statistical analysis. We did not eliminate children diagnosed with ADHD, given the high comorbidity between ADHD and RD (in the selected sample, 15.98% (39/244) were diagnosed with RD among which 48.71%

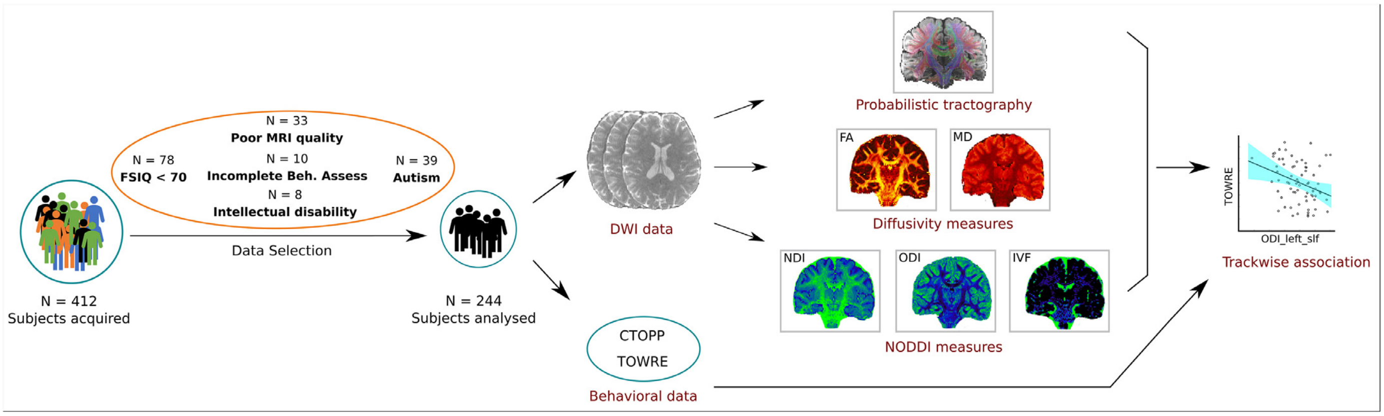

Fig. 1. Data selection and methodological pipeline carried out in the study. *Note: The numbers presented in data selection includes the comorbidities between autism, intellectual disability only in one group for ease. FSIQ: Wechsler intelligence scale for children, DWI: Diffusion weighted imaging, CTOPP: Comprehensive test of phonological processing, TOWRE: Test of word reading efficiency, FA: Fractional anisotropy, MD: Mean diffusivity, NDI: Neurite density index, ODI: Orientation dispersion index, IVF: Cerebrospinal fluid (CSF) volume fraction.*

(19/39) were also diagnosed with ADHD). The data selection and the methodological pipeline is illustrated in Fig. 1. The data acquisition procedure was approved by the Chesapeake Institutional Review Board (https://www.chesapeakeirb.com/). Prior to acquiring the data, written informed consent was obtained from their legal guardians and written assent obtained from the participant (Alexander et al., 2017).

2.2. MRI Data acquisition

Diffusion weighted images (DWI) and anatomical MPRAGE-T1 images were obtained for all participants with an identical data acquisition sequence in two 3T Siemens scanners. Diffusion weighted magnetic resonance imaging (dMRI) data was obtained with 64 directions; bvals = 0, 1000, 2000; and with isotropic voxels of 1.8 mm and anatomical MPRAGE-T1 images were obtained with Repetition time (TR) = 2500 ms, Echo time (TE) = 3.15 ms, voxel size = 0.8 mm (isometric) and flip angle = 8°.

2.3. Behavioral Assessments

We selected standardized assessments of reading and phonological processing skills from the larger Healthy Brain Network behavioral battery (Alexander et al., 2017) for our analysis; these included the Test of Word Reading Efficiency (TOWRE-2) and the Comprehensive Test of Phonological Processing (CTOPP-2) (Torgesen et al., 2012; Wagner et al., 2013). The TOWRE-2 includes two timed sub-tests: one assessing sight word reading fluency (SWE) and the other - pseudoword decoding fluency (PDE). A reading composite score was obtained by averaging raw scores from the TOWRE-2 sub-tests (mean scores, TOWRE - PDE: 31.58 ± 15.66, TOWRE - SWE: 65 ± 19.60). To create a phonological processing composite score, we averaged raw scores from two sub-tests of the CTOPP-2, Elision (EL) and Blending Words (BW) (mean scores, CTOPP - BW: 20.82 ± 4.84, CTOPP - EL: 23.59 ± 6.53). Raw scores were used because we were interested in identifying links between white matter microstructure and individual differences in reading and phonological processing ability, rather than ability relative to others of the same age. Both scores used were tested for outliers using Rosner's test for outliers using the R function 'RosnerTest'. No outliers were detected for the sample analyzed further. The demographics and the behavioral assessments data distribution is illustrated in Fig. 2.

2.4. MRI data processing, NODDI and diffusion tensor modeling

The imaging quality metrics of the obtained dMRI data - Contrast to Noise Ratio (CNR), Average Absolute and Relative Motion (AM & RM) of each volume were computed using the Quality Assessment of dMRI (QUAD) toolbox in Functional Magnetic Resonance Imaging of the Brain Software Library FSL, version 6.1.0 (Bastiani et al., 2019). These data were then processed using inbuilt functionality and different toolboxes in FSL described in detail elsewhere (Behrens et al., 2007; Jenkinson and Smith, 2001; Koirala et al., 2018). In brief, the data was preprocessed for artefact correction (susceptibility, eddy currents and head movements) and individual masks were generated for each brain using the Brain Extraction Toolkit (BET) to isolate the brain from the skull. DTIfit - diffusion tensor modeling tool in FSL was applied to obtain diffusion measures including fractional anisotropy (FA), and mean diffusivity (MD). Crossing fibers distribution was estimated using BEDPOSTX and the probability of major fiber directions were calculated. A multi-fiber model was fit at each voxel for tracing fibers through regions of crossing or complexity. Tractography was then computed using a recently developed XTRACT toolbox which reads the standard space protocols and performs probabilistic tractography (using curvature threshold: ±80° and max streamline steps: 2000) in the participant's native space to obtain 23 major tracts in human brain (Warrington et al., 2020). The toolbox embedded in FSL software package presents a library of standardized tractography protocols devised for the automated extraction of white matter tracts, both in the human and the non-human primate brain. The seed and target regions for each tract are detailed in (Warrington et al., 2020). The normalized fiber probability distribution obtained is then thresholded and binarised using fslmaths to get a tract mask. The threshold values applied here ranged from (0.001 to 0.005) and the mask generated was inspected for accuracy and the value was adapted accordingly to ensure correct segmentation. The obtained binary mask is then multiplied by the subject's NODDI and diffusion maps to get a tract specific distribution of those values. All tracts along with their abbreviations are listed in Supplementary table 1. Note: The SLF1 and SLF2 presented in the study are two (out of three) branches of SLF as explained in (Thiebaut de Schotten et al., 2011; Warrington et al., 2020). For SLF1, the seed mask was in the region of the central sulcus within the frontal/parietal cortex and two target masks were in superior frontal gyrus and superior parietal lobule, immediately posterior to the margin of the cingulate gyrus. For SLF2, the seed mask was the same as SLF1 with two target masks being in middle frontal gyrus and angular gyrus.

The neurite orientation dispersion and density imaging (NODDI) model was fitted using the NODDI toolbox (Zhang et al., 2012) and the

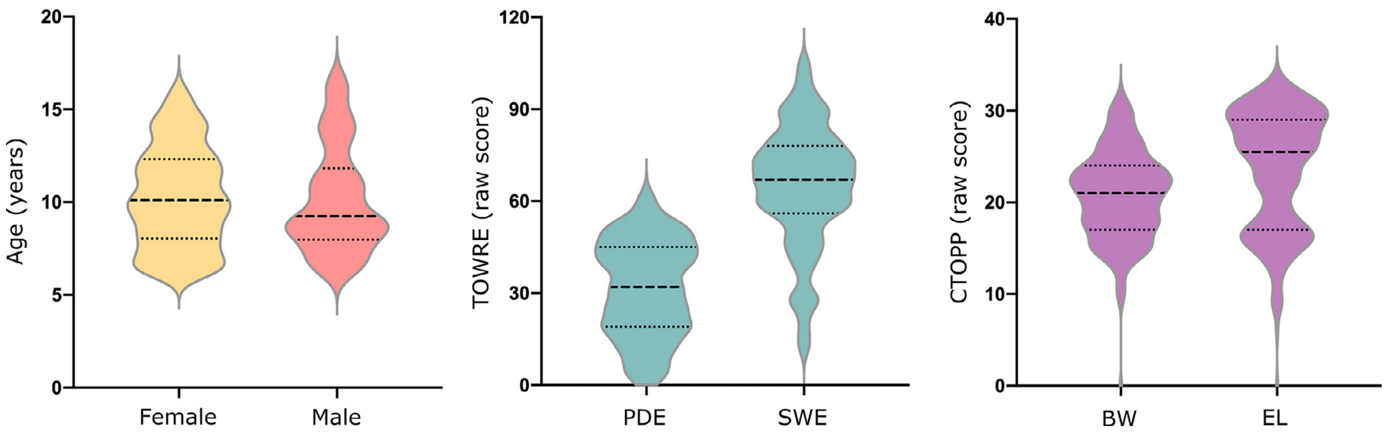

Fig. 2. The violin plot illustrates the age and sex distribution in the first sub-Fig. and TOWRE and CTOPP raw scores with the subtests used in the study. Here, PDE and SWE are pseudoword decoding and sight word reading TOWRE sub-tests and BW and EL are Blending words and Elision CTOPP sub-tests. Please refer to supplementary materials for the results from Standardized scores.

coefficients - neurite orientation dispersion index (ODI), neurite density index (NDI) and cerebrospinal fluid (CSF) - volume fraction (IVF) were obtained from all the participants. NODDI is an advanced multi-compartment, non-Gaussian, biophysical tissue model that can quantitatively evaluate specific microstructural changes and can distinguish three different microstructural environments intracellular, extracellular and CSF compartments (Zhang et al., 2012). Based on the amount of diffusion in each of these compartments, we can infer the density and the orientation distribution of neurites - a collective terminology for axons and dendrites (Grussu et al., 2017; Jespersen et al., 2010). The coefficients computed using this model include ODI, which is influenced by dispersion of neurites (0 to 1; 0 = well-aligned neurites, 1 = highly dispersed neurites), NDI, which is influenced by the amount of neurites (0 to 1; 0 = most extracellular diffusion (low neurite density), 1 = most intracellular diffusion (high neurite density), and IVF which is influenced by the free water compartments within the tissue (0 to 1; 0 = least free water diffusion/low extra axonal space and 1 = most free water diffusion/high extra axonal space) (Fukutomi et al., 2019; Gatto et al., 2018). As detailed above these NODDI coefficients (ODI, NDI and IVF) and diffusion measures (FA and MD) were then mapped along all the fiber tracts and mean values were obtained for each tract for subsequent data analysis.

2.5. *Statistical analysis of reading and phonological skills*

Partial correlation with NODDI metrics (ODI, NDI and IVF). Initially, partial correlation was computed using age, sex, site and image quality metrics (CNR, AM and RM) as covariates between NODDI coefficients and measures of reading and phonological skills (TOWRE and CTOPP). The multiple comparison correction was performed using Benjamini and Hochberg procedure for controlling the false discovery rate (fdr_bh, q-value threshold 0.05) of a family (between all tracts and imaging metrics) of hypothesis tests (Benjamini and Hochberg, 1995). Moreover, statistical post-hoc power analysis was performed to make sure that the study is sufficiently powered to avoid type two error. Details of this analysis are provided in supplementary materials. Given that we did not exclude participants with ADHD (120 out of 244), we additionally examined whether presence or absence of this disorder impacted the obtained results by adding ADHD diagnosis as a covariate.

Partial correlation with diffusion metrics (FA and MD). To better compare and understand the association of the NODDI measures and reading scores obtained above to existing literature, we performed partial correlation analyses for commonly used diffusion measures, fractional anisotropy (FA) and mean diffusivity (MD) to reading and phonological processing skills in the tracts which were significantly correlated to ODI and NDI measures. The covariates and multiple comparison correction were the same as for NODDI analysis.

Mediation analysis. To study the potential mediation effect of phonological processing (CTOPP) between white matter properties (NODDI and diffusion measures) and single-word/pseudoword reading (TOWRE), mediation analysis was performed using structural equation modelling (Gunzler et al., 2013). The technique implemented used the lavaan R package, (https://cran.r-project.org/web/packages/lavaan/index.html) for latent variable analysis. For this analysis, residuals values were estimated considering age, sex and image quality measures (CNR, AM and RM) as covariates. We predicted that white matter microstructure would be related to reading skills via phonological processing, at least for some tracts, because previous studies have shown that weaknesses in phonological processing predict and predate poor reading skills (Hulme et al., 2012). Moreover, other studies have shown that, phonological deficits are linked to connections among brain regions, which may implicate white matter (Boets et al., 2013). In particular, we expected to observe mediation for tracts such as the superior longitudinal fasciculus that connect to brain regions that are involved in phonological processing and phonologic-orthographic integration, such as the superior temporal gyrus, inferior frontal gyrus, and temporo-parietal cortex. We explored this relationship in all tracts that showed significant correlations with phonological processing. A summary of the mediation models is depicted in Fig. 5.

3. Results

3.1. *NODDI*

We observed that NODDI measures, density (NDI) and orientation dispersion (ODI) index, were negatively correlated with both reading (TOWRE) and phonological processing (CTOPP) composites in several tracts in the brain, predominantly in the left hemisphere and including those previously shown to have structural correlates with reading efficiency.

Specifically, the reading composite was significantly ($p < 0.05$ after fdr_bh correction) negatively correlated with ODI in Middle Cerebellar Peduncle (MCP), bilateral - Inferior Fronto-Occipital Fasciculus (IFOF), Middle Longitudinal Fasciculus (MDLF), Optic Radiation (OR), Uncinate Fasciculus (UF), Ventral Occipital Fasciculus (VOF), left - Arcuate Fasciculus (AF), Peri-genual Cingulum (CBP), Inferior Longitudinal Fasciculus (ILF), Superior Longitudinal Fasciculus (SLF2*) and right

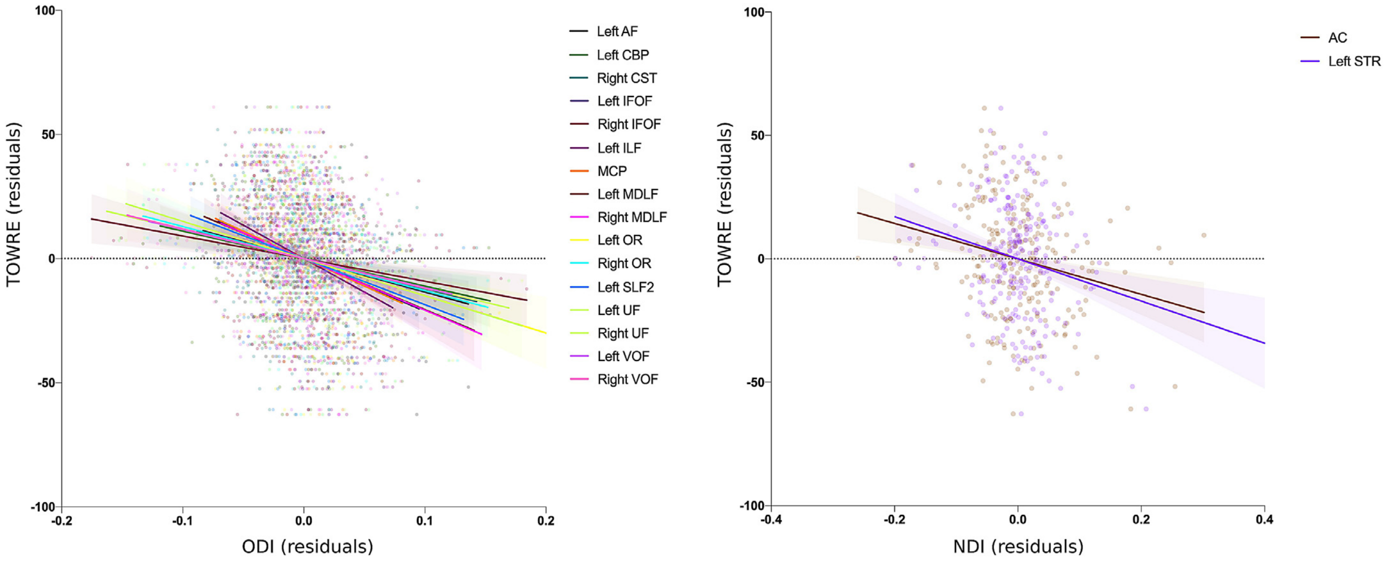

Fig. 3. The graphs depict unambiguous negative partial correlations which were significant ($p < 0.05$, fdr_bh corrected) in the mentioned tracts between NODDI measures and the reading composite score (TOWRE). All correlation coefficients and corrected p-values are presented in table 2. **The scatter plot separately for each individual tract is provided in supplementary Fig. 1a and 1b.** *NOTE: TOWRE: Test of word reading efficiency, NDI: Neurite density index, ODI: Orientation dispersion index, AF: Arcuate Fasciculus, CBP: Peri-genual Cingulum, CST: Corticospinal Tract, IFOF: Inferior Fronto-Occipital Fasciculus, ILF: Inferior Longitudinal Fasciculus, MCP: Middle Cerebellar Peduncle, MDLF: Middle Longitudinal Fasciculus, OR: Optic Radiation, SLF2: Superior Longitudinal Fasciculus, UF: Uncinate Fasciculus, VOF: Ventral Occipital Fasciculus, AC: Anterior Commissure, STR: Superior Thalamic Radiation.*

Table 1
NODDI Associations with Reading (TOWRE).

Orientation dispersion index (ODI)			
Tracts	$r_{partial}$	Tracts	$r_{partial}$
Left ILF	-0.30**	Left AF	-0.25**
Left IFOF	-0.29**	Right CST	-0.23**
Left SLF2	-0.29**	Right UF	-0.23**
Left MDLF	-0.29**	Left VOF	-0.23**
MCP	-0.28**	Right VOF	-0.21**
Right MDLF	-0.26**	Left CBP	-0.21**
Left UF	-0.26**	Right IFOF	-0.21**
Left OR	-0.26**	Right OR	-0.20$^{\phi}$
Neurite density index (NDI)			
Left STR	-0.23**	AC	-0.23**

Partial correlation coefficients between TOWRE and NODDI measures, shown for the tracts where they are significant as depicted in Fig. 3. Here, ** indicates the correlation coefficient with pval < 0.001 and $^{\phi}$ indicates those with pval < 0.05.

Table 2
NODDI Associations with Phonological Processing (CTOPP).

Orientation dispersion index (ODI)			
Tracts	$r_{partial}$	Tracts	$r_{partial}$
Left MDLF	-0.35**	Left STR	-0.25**
MCP	-0.33**	Left FX	-0.24**
Left IFOF	-0.32**	AC	-0.23*
Left ILF	-0.32**	Left CBP	-0.22*
Left SLF2	-0.31**	Right ILF	-0.21*
Left AF	-0.29**	Right VOF	-0.21*
Left UF	-0.28**	Right OR	-0.21*
Left VOF	-0.27**	Right CST	-0.21*
Left CBD	-0.26**	Right STR	-0.21*
Left OR	-0.25**	Right UF	-0.20*
Neurite density index (NDI)			
Left STR	-0.28**	Left CST	-0.22*
Right MDLF	-0.24*	Left ILF	-0.22*
AC	-0.24*	Right SLF1	-0.21*
Left CBD	-0.24*	Left AF	-0.21*
FMI	-0.23*	Right STR	-0.21*
Left CBP	-0.23*	Right CBD	-0.21*

Partial correlation coefficients between CTOPP and NODDI measures, shown for the tracts where they are significant as depicted in Fig. 4. Here, ** indicates the correlation coefficient with pval < 0.001 and * indicates those with pval < 0.009.

Corticospinal Tract (CST). Moreover, the reading composite was also negatively correlated with NDI in Anterior Commissure (AC) and left Superior Thalamic Radiation (STR). All correlation plots are illustrated in Fig. 3 with correlation coefficients and corrected p-values in Table 1.

Similarly, phonological processing was significantly ($p < 0.05$ after fdr_bh correction) negatively correlated with ODI in MCP, AC, bilateral - ILF, OR, STR, UF, VOF, left - AF, CBP, dorsal Cingulum (CBD), fornix (FX), IFOF, SLF2, MDLF and right CST. In addition, phonological processing was also negatively correlated to NDI in AC, Forceps minor (FMI), bilateral - STR, CBD, left - AF, CBP, CST, ILF and right - MDLF and SLF1. All correlation plots are illustrated in Fig. 4 with correlation coefficients and corrected p-values in Table 2.

3.2. FA and MD

We found significant ($p < 0.05$ after fdr_bh correction) correlations with FA and MD only in handful of tracts that showed NODDI associations and only for phonological processing. A positive correlation between phonological processing and FA was found in left - IFOF, MDLF, SLF2, VOF, CBD and FX. MD was positively correlated with phonological processing in Left UF. No correlations were significant between reading and diffusion measures in any of the tracts with NODDI associations. All correlation coefficients with corrected p-values are presented in Table 3.

3.3. Analyses with ADHD status as a covariate

For the partial correlation analysis, performed by coding ADHD as a covariate along with age, sex, and imaging quality metrics, the

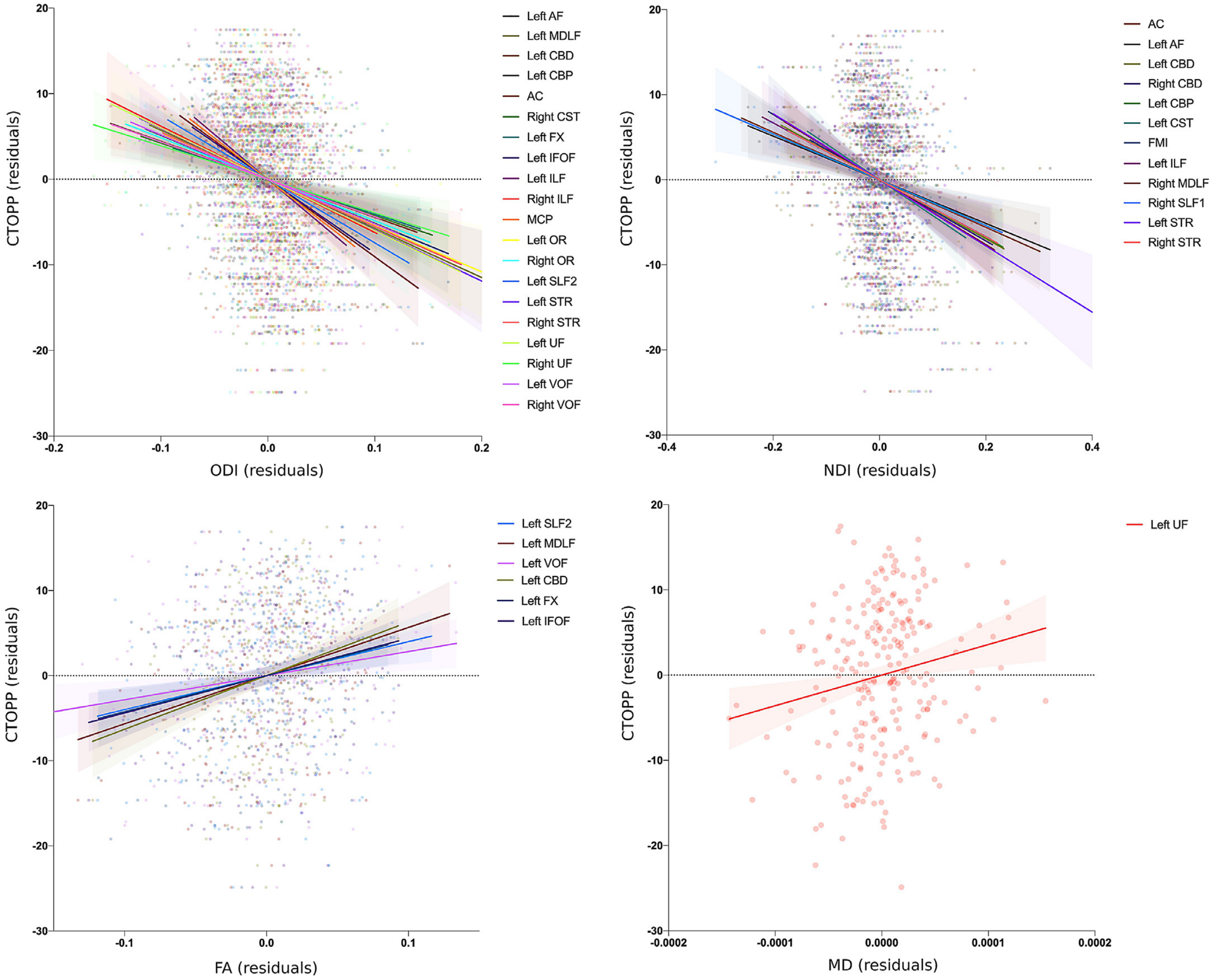

Fig. 4. The graphs illustrates partial correlations which were significant ($p < 0.05$, fdr_bh corrected) in the mentioned tracts between NODDI, diffusion measures and phonological processing composite score (CTOPP). All correlation coefficients and corrected p-values are presented in table 3. **The scatter plot separately for each individual tract is provided in supplementary Fig. 2a, 2b and 2c**. *Note: CTOPP: Comprehensive Test of Phonological Processing, NDI: Neurite density index, ODI: Orientation dispersion index, FA: Fractional anisotropy, MD: Mean diffusivity, AF: Arcuate Fasciculus, MDLF: Middle Longitudinal Fasciculus, CBD: Dorsal Cingulum, CBP: Peri-genual Cingulum, AC: Anterior Commissure, CST: Corticospinal Tract, FX: Fornix, IFOF: Inferior Fronto-Occipital Fasciculus, ILF: Inferior Longitudinal Fasciculus, MCP: Middle Cerebellar Peduncle, OR: Optic Radiation, SLF1 & SLF2: Superior Longitudinal Fasciculus, STR: Superior Thalamic Radiation, UF: Uncinate Fasciculus, VOF: Ventral Occipital Fasciculus, FMI: Forceps Minor.*

Table 3
Diffusion Measure Associations with Phonological Processing (CTOPP)

Fractional anisotropy (FA)			
Tracts	$r_{partial}$	Tracts	$r_{partial}$
Left MDLF	0.25^{*}	Left SLF2	0.21^{ϕ}
Left CBD	0.23^{*}	Left FX	0.20^{ϕ}
Left IFOF	0.21^{ϕ}	Left VOF	0.18^{ϕ}
Mean diffusivity (MD)			
Left UF	0.19^{ϕ}		

Partial correlation coefficients between TOWRE and NODDI measures, shown for the tracts where they are significant as depicted in Fig. 4. Here, * indicates the correlation coefficient with pval < 0.009 and $^{\phi}$ indicates those with pval < 0.05.

tracts obtained remained significant for both NODDI measures with negligible change in the strength of correlation for both composite reading scores and phonological processing (TOWRE and CTOPP). Similarly, the results for both diffusion measures (FA and MD) also remained the same with negligible changes in the strength and significance of correlation. The tables with detail of correlation from the analysis is provided as supplementary Table 2 (a, b and c).

3.4. Analyses using Standard scores of CTOPP and TOWRE

We used raw scores in the study, but to characterize individual's skills in the context of what is expected for their age and to compare them with the results from raw scores, we performed additional analysis using the standard scores (mean scores, TOWRE - PDE: 97.30 ± 15.54, TOWRE - SWE: 101.74 ± 15.97, CTOPP - BW: 8.27 ± 2.96, CTOPP - EL: 9.14 ± 2.74). We observed that the tracts showing the significant asso-

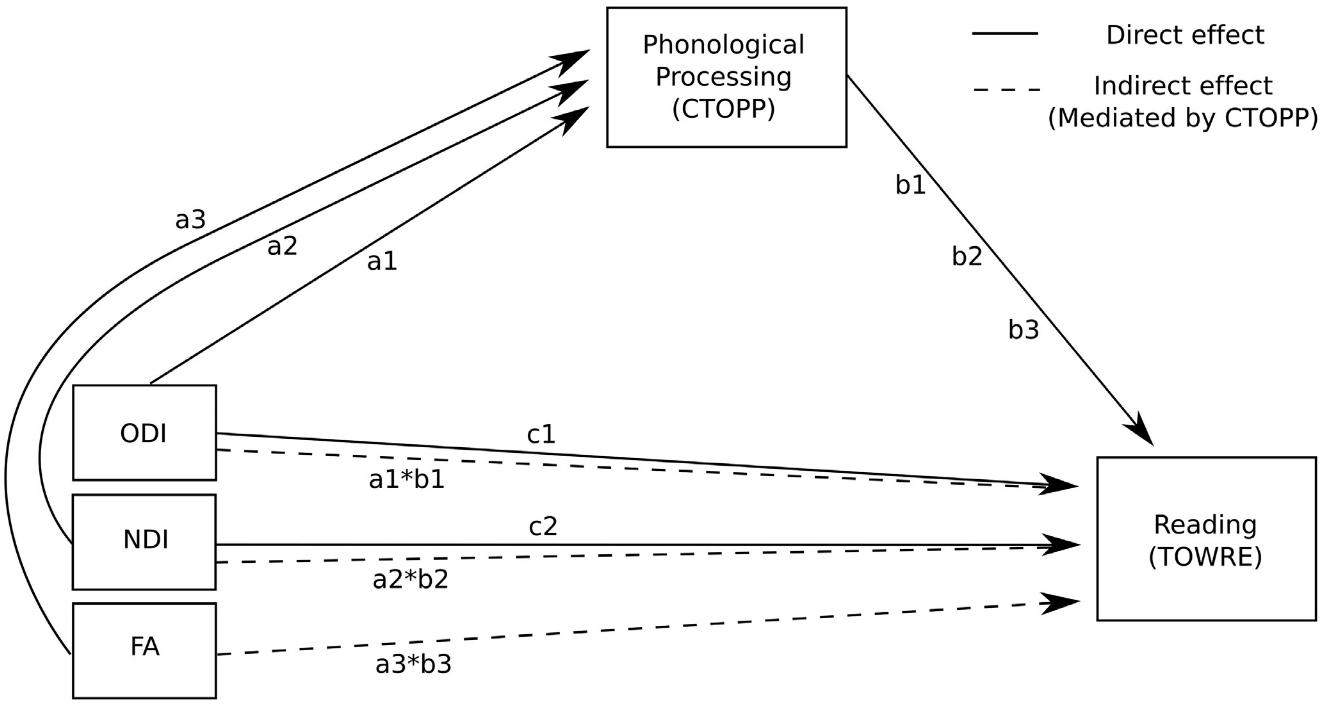

Fig. 5. The Fig. illustrates the models: model 1 = ODI -> CTOPP -> TOWRE, model2 = NDI -> CTOPP -> TOWRE, model 3 = FA -> CTOPP -> TOWRE, implemented for each tract separately to analyze mediation effect of phonological processing. The indirect effect (shown as dotted lines) represents the significant mediation effect of phonological processing for the association of NODDI and diffusion measures to reading (TOWRE). Here, a, b, c represents direct effect whereas the product of a and b represent the indirect effect. The values of indirect effect (a*b) are presented in table 4 and all other parameters as mentioned in the Fig. along with the statistical significance is presented in supplementary table 2.

ciation with ODI and NDI with CTOPP raw scores remained almost the same, except for some tracts (anterior thalamic radiation (ATR), right AF and right SLF2) which were not significant after the FDR correction with raw scores but were significant with standard scores. Similarly, some tracts in which the association was significant for raw scores were missing with the standard scores after FDR correction (Right CST and Right SLF1). Similarly, for TOWRE, except for Right ATR all other tracts remained the same. We found that these changes were mostly driven by multiple comparison correction, but the association observed between NODDI measures and phonological and reading measures remained the same with minimal difference in correlation for both raw and standard scores. For the analysis using diffusion measures (FA and MD), we found new associations using TOWRE standard scores (MD in Left UF, Right - IFOF, OR and UF) and only two associations observed using CTOPP raw scores survived (MD in Left UF and FA in Left FX). The details of all correlation statistics from analysis of standard scores are presented in supplementary Table 3 (a, b, c, and d).

3.5. Mediation analysis

A mediation analysis was performed to determine whether NODDI and diffusion measures have indirect effects on reading that are mediated by phonological processing skills. For this analysis, all tracts were used that showed significant associations with phonological processing, although these tracts did not necessarily demonstrate direct associations to reading, we wanted to test if an indirect effect (via partial mediation) exists for those which did not show a direct effect (Mackinnon and Fairchild, 2009; Rucker et al., 2011). We hypothesized that this analysis would yield additional indirect associations to reading from white matter metrics via phonological processing. Given that reading is a complex behavior, we expected that links between white matter structure and phonological processing, a componential skill for reading, could account for links between WM structure and reading ability. For all NODDI and diffusion measures analyzed, the comparative fit index (CFI) and Tucker–Lewis index (TLI) was 1 indicating good model fit using the Maximum Likelihood method (Hu and Bentler, 1999). The mediation effect was observed in all tracts (except for mean diffusivity in left UF) that had a significant association to phonological processing at $p < 0.003$. The model implemented is illustrated in Fig. 5 and shows the direct and indirect effects. Regression estimates, standard error and p-values are presented in Table 4 (details of all direct and indirect effects from all parameters and the results obtained using the standardized scores for CTOPP and TOWRE are provided in supplementary Tables 4 and 5). We observed that white matter is related to both phonological processing and reading in the same way. In particular, both the correlations between ODI and phonological processing and between ODI and reading are negative (likewise for NDI) and both the correlations between FA and phonological processing and FA and reading are positive. This is consistent with the observations of negative direct effects between ODI and phonological processing and positive direct effects between phonological processing and reading. Indirect effects involving FA were positive, which is consistent with the observation of positive direct effects between FA and phonological processing and between phonological processing and reading.

4. Discussion

In this study, we observed that the density and orientation of neurites were significantly associated with indicators of reading and phonological processing in several tracts in a large sample of children with a range of reading-related skills. Specifically, we found negative associ-

Table 4
Mediation effects.

ODI		NDI		FA	
Tracts	TOWRE ~ ODI + CTOPP (a1*b1)*Estimate [SE]*	Tracts	TOWRE ~ NDI + CTOPP (a2*b2)*Estimate [SE]*	Tracts	TOWRE ~ FA + CTOPP (a3*b3)*Estimate [SE]*
AC	-65.76 [19.40]	AC	-39.46 [11.11]	Left IFO	63.29 [20.03]
Left AF	-80.18 [19.13]	Left AF	-37.69 [11.87]	Left MDLF	82.02 [21.91]
Left CBD	-83.51 [21.60]	Left CBD	-49.67 [14.10]	Left SLF2	58.22 [18.53]
Left CBP	-60.26 [18.43]	Right CBD	-52.40 [16.76]	Left VOF	41.29 [15.41]
Right CST	-57.32 [18.45]	Left CBP	-50.03 [14.54]	Left CBD	92.76 [26.76]
Left FX	-74.73 [21.09]	Left CST	-61.99 [18.75]	Left FX	64.22 [21.43]
Left IFO	-117.76 [25.79]	FMI	-55.02 [15.71]		
Left ILF	-142.43 [31.37]	Left ILF	-48.81 [14.80]		
Right ILF	-89.41 [28.05]	Right MDLF	-55.08 [15.41]		
MCP	-133.08 [28.34]	Right SLF1	-38.89 [12.08]		
Left MDLF	-124.01 [25.68]	Left STR	-55.02 [13.24]		
Left OR	-75.17 [20.17]	Right STR	-48.36 [15.37]		
Right OR	-69.18 [22.24]				
Left SLF2	-101.34 [22.58]				
Left STR	-88.09 [23.75]				
Right STR	-78.87 [25.42]				
Left UF	-83.35 [20.29]				
Right UF	-55.21 [17.90]				
Left VOF	-73.91 [18.52]				
Right VOF	-62.15 [19.56]				

The indirect effects (unstandardized beta values) of phonological processing to reading score from the mediation analysis is presented in the table as shown in the model in Fig. 5 (path a*b). All results presented are significant with $p < 0.008$. A more detailed table with all direct effects from all parameters is provided as supplementary table 2.

ations with neurite orientation predominantly for the tracts in the left hemisphere (AF, CBP, CBD, ILF, SLF2, IFOF, MDLF) along with bilateral IFOF, MDLF, OR, UF and VOF. Similarly, we found negative associations with neurite density in bilateral AC, STR, CBD, left AF, CBP, CST, ILF and right MDLF and SLF. The negative associations obtained in the study between NODDI and reading-related indicators demonstrated that better reading and phonological skills are associated with higher coherence (where lower ODI values reflect higher coherence) and lower density of neurites (where lower NDI values reflect lower neurite density) in the obtained fibers. These NODDI indices are able to depict the components of the white matter microstructure (intra- and extra-neurite compartments) and their (axon and dendrite) geometrical organization, density and dispersion level (Billiet et al., 2015). Moreover, previous studies have also shown that these metrics are sensitive to a range of neurobiological properties, such as bending and fanning of axons, crossing fibers, glial infiltration and neurite pruning (Friedrich et al., 2020; Grussu et al., 2017; Sepehrband et al., 2015). Hence, the higher coherence and lower density observed here most likely indicates smaller and less dispersed axonal organization, which reflects a microstructural architecture that restricts synaptic connections to a cost-effective minimum and facilitates the energy efficient differentiation of signals from noise (Genc et al., 2018; Sporns et al., 2000). These efficient networks with lower ODI and NDI have previously been associated with higher IQ scores and cognitive functioning (Cragg, 1975; Genc et al., 2018; Tang et al., 2014). Other studies have shown that networks characterized by higher NDI and ODI (possibly due to reduced neurite pruning or abnormal myelination during development) are associated with learning difficulties and impaired cognitive abilities (Hawes et al., 2015; Matsuoka et al., 2020; Riccomagno and Kolodkin, 2015). Hence, our findings with reading and phonological processing are consistent with NODDI findings in other domains of cognition and further support a link between lower ODI and NDI and neural efficiency.

The tracts where we observed an association between neural architecture and reading skills in this study overlap with many of those identified in previous studies using more widely used diffusion measures of anisotropy and diffusivity; notably, our findings in the SLF and ILF are consistent with these previous findings (Vandermosten et al., 2012a; Wang et al., 2017; Yeatman et al., 2012). However, we found significant associations in a greater number of tracts than are typically identified in individual studies of white matter architecture and reading, possibly because our sample size afforded a whole brain exploratory approach and utilized measures that may be more sensitive than conventional diffusion metrics (Vandermosten et al., 2012b). It's also worth noting that recent studies using NODDI measures that have found associations between white matter microstructural alterations and reading have had variable findings. In one study, Huber and colleagues (2019) identified associations with reading skills in the posterior corpus callosum, anterior callosal tract, and right arcuate fasciculus (Huber et al., 2019). However, two other studies in typically developing children and adolescents failed to identify any significant relationships between NODDI measures and reading (Geeraert et al., 2020). Our findings reveal much more widespread and significant effects than (Huber et al., 2019) found and contradict the null effects observed in the two other studies (Collins et al., 2019; Geeraert et al., 2020).

We found the strongest negative correlations of ODI with reading and phonological processing in Middle Cerebellar Peduncle (MCP) and in left hemispheric tracts including Middle Longitudinal Fasciculus (MDLF), Inferior Fronto-Occipital Fasciculus (IFOF), Inferior Longitudinal Fasciculus (ILF) and Superior Longitudinal Fasciculus (SLF). Previous studies using tractography and diffusion measures (mainly FA and MD) have shown many of these fiber tracts to be affected in children with RD, including the IFOF, ILF and SLF (Su et al., 2018; Vandermosten et al., 2012a). Moreover, longitudinal and intervention studies have found a positive association with higher FA in left ILF, AF and SLF in better readers and following reading intervention (Borchers et al., 2019; Huber et al., 2018; Yeatman et al., 2012). Similarly, FA in MCP has also been linked to reading, although not consistently (Bruckert et al., 2020; Travis et al., 2015). Moreover, higher FA and lower MD values from bilateral IFOF, left UF and genu of Corpus Callosum in pre-school aged children have been shown to be significantly correlated with phonological processing, indicating that these associations are present before formal acquisition of reading begins (Vandermosten et al., 2015; Walton et al., 2018). It's also worth noting that phonological processing (CTOPP scores) was associated with more tracts (particularly with the density index, ODI) than reading (TOWRE scores). This could be because phonological processing is an intermediate phenotype for reading and is thus more closely related to brain measures. Indeed, this is consistent with our mediation findings which are discussed below.

With respect to comparisons between NODDI and traditional diffusion measures in our sample, we found that only a few of the tracts identified using NODDI metrics also had associations to phonological processing and FA or MD, and we observed no correlations between FA or MD and reading. Furthermore, the correlations (all positive) between FA and MD and phonological processing were only observed in left hemispheric tracts. This finding is not too surprising however, given that many previous associations to reading with these metrics are in the left hemisphere, and moreover, given that there is significant variability for FA and MD findings across the literature (Borchers et al., 2019; Hoeft et al., 2011; Huber et al., 2018; Huber et al., 2019; Lebel et al., 2019; Moreau et al., 2018b; Vanderauwera et al., 2017; Vandermosten et al., 2015; Wang et al., 2017; Yeatman et al., 2012). It's also possible that the NODDI metrics, which index specific microstructural properties, are more sensitive and thus more likely to capture widespread changes beyond traditional diffusion measures like FA and MD, which may explain why we observe a greater number of associations with these metrics.

With respect to our mediation analyses, as predicted, these revealed an indirect association of both NODDI and diffusion measures to reading that was mediated by phonological processing. The negative coefficients of the indirect effects involving NODDI measures indicate that lower neurite dispersion and density are associated with high phonological processing scores, which in turn are associated with higher reading scores. The positive coefficients of the indirect effects involving FA indicate that greater white matter integrity is associated with higher phonological processing scores, and in turn higher reading scores. Interestingly, we observed these indirect effects for all tracts in which we observed positive associations between white matter integrity and phonological processing. This finding is consistent with extensive work linking phonological processing with reading (Arrington et al., 2017; Lebel et al., 2019; Martin et al., 2015; Ramus et al., 2018; Saksida et al., 2016; Walton et al., 2018) and work suggesting that white matter connectivity and integrity may be particularly important for phonologically mediated aspects of reading (Boets, 2014; Boets et al., 2013). Further, this widespread effect, involving various cortical and subcortical structures, underscores the distributed nature of the reading network and importance of long-range connectivity to support reading and related skills.

These neurite indices, with their greater specificity and potentially higher sensitivity (relative to more commonly used anisotropy and diffusivity measures) could be well suited for use in studies of neurodevelopmental changes associated with reading acquisition or intervention. NDI in particular has been associated with age-related brain maturation in several studies (Genc et al., 2017; Mah et al., 2017) and accounts for a much greater proportion of the variance in age (60%) than other measures of white matter structure: FA (27%), MD (39%), axial (14%) or radial (35%) diffusivity (Genc et al., 2017). Thus, NDI may prove to be more sensitive to experience-related changes in white matter microstructure underlying processes of reading acquisition and remediation of reading difficulties and could be used to index intervention-related changes in the brain. In contrast, ODI is not strongly associated with age, showing no correlation in children of 8-13 years old (Mah et al., 2017) and explaining only 5% of the variance in children and adolescents from 4-19 years old (Genc et al., 2017). This suggests that ODI changes very little over the course of development. Thus, while NDI may be a good marker of age- or intervention- associated plasticity, ODI is likely to be a stable and early correlate of neural efficiency. Therefore, NDI and ODI measures could be used in longitudinal research designs to index both static and dynamic brain features associated with RD.

5. Conclusion

In sum, we demonstrated that better reading and phonological processing skills are moderately associated with lower neurite density and greater tract coherence across a number of tracts in a large sample of children with a range of reading skills. Thus, we suggest that an efficient microstructural architecture with lower dendritic complexity is linked to better reading skills. These findings are consistent with extant studies for reading skills using diffusion measures but go beyond by revealing the microstructural specificity. We suggest that neurite complexity could be a useful tool for indexing intervention-related white matter tissue microstructural changes or as a biomarker for longitudinal research and may promote better understanding of relations between brain structure and behavior. This heightened specificity can inform etiological models of RD and explain sources of individual differences in reading skills.

Data and Code availability statement

All raw data (Neuroimaging) used in the study is available freely via Healthy Brain Network Biobank (https://childmind.org/center/healthy-brain-network/). The phenotypical data used could be available upon reasonable request. The toolbox used in the study (FSL) is an open access toolbox which could be downloaded from https://fsl.fmrib.ox.ac.uk/fsldownloads_registration . For specific processing protocols used in the study, please refer to method section and contact corresponding author for any further queries.

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Declaration of Competing Interest

All authors have nothing to declare.

Acknowledgments

The work was supported by Florida Learning Disabilities Research Clinic, Grant/Award Number: NIH 2P50HD052120-11 and Grant/Award Number: NSF IGERT DGE-1144399 to the University of Connecticut. We would like to express our sincere gratitude to Lindsay Alexander for her great support in acquiring the behavioral data used in the study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2021.118426.

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