Disentangling the relation between left temporoparietal white matter and reading: A Spherical Deconvolution tractography study

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Abstract

Diffusion Tensor Imaging (DTI) studies have shown that left temporoparietal white matter is related to phonological aspects of reading. However, DTI lacks the sensitivity to disentangle whether phonological processing is sustained by intra-hemispheric connections, inter-hemispheric connections or projection tracts. Spherical Deconvolution (SD) is a non-tensor model which enables a more accurate estimation of multiple fiber directions in crossing fiber regions. Hence, this study is the first to investigate whether the observed relation with reading aspects in left temporoparietal white matter is sustained by a particular pathway by applying a non-tensor model. Second, measures of degree of diffusion anisotropy, which indirectly informs about white matter organization, were compared between DTI and SD tractography.

In this study 71 children (5-6 years old) participated. Intra-hemispheric, inter-hemispheric and projection pathways were delineated using DTI and SD tractography. Anisotropy indices were extracted, i.e. fractional anisotropy (FA) in DTI, and quantitative hindrance modulated orientational anisotropy (HMOA) in SD. DTI results show that diffusion anisotropy in both the intra-hemispheric and projection tracts was positively correlated to phonological awareness; however, the effect was confounded by subjects' motion. In SD the relation was restricted to the left intra-hemispheric

connections. A model comparison suggested that FA was, relatively to HMOA, more confounded by fiber crossings; however, anisotropy indices were highly related. In sum, this study shows the potential of SD to quantify white matter microstructure in regions containing crossing fibers. More specifically, SD analyses show that phonological awareness is sustained by left intra-hemispheric connections, and not inter-hemispheric or projection tracts.

Key words: Diffusion Tensor Imaging, Spherical Deconvolution, tractography, anisotropy, phonological awareness, reading

1. Introduction

Reading activates a widespread network of distinct regions in the left hemisphere of the brain [Farris *et al.*, 2013; Hoeft *et al.*, 2006; Raschle *et al.*, 2012] consisting of inferior frontal regions, dorsal temporoparietal regions and ventral occipitotemporal regions. Those regions are connected to each other through white matter pathways. In studying neural correlates of reading it is evidently of great benefit to investigate the white matter connections involved in reading [Wandell and Yeatman, 2013]. White matter connections can be studied in the *in vivo* brain by applying Diffusion-Weighted Magnetic Resonance Imaging (DW-MRI). To quantify the study of these connections, fractional anisotropy (FA) has frequently been applied. FA is an indirect measure of white matter organization that is driven by micro-structural properties such as myelination, axon density, and macro-structural properties such as fiber crossings [Beaulieu, 2009].

Comparing studies that investigate the relation between reading and white matter organization always requires some degree of caution. Some studies only include normal readers [Beaulieu *et al.*, 2005; Nagy *et al.*, 2004; Yeatman *et al.*, 2011; Dougherty *et al.*, 2007], while other studies also include persons with dyslexia [Frye *et al.*, 2008; Niogi and McCandliss, 2006; Odegard *et al.*, 2009; Rimrodt *et al.*, 2010; Rollins *et al.*, 2009; Steinbrink *et al.*, 2008] and yet other studies compare good and poor readers [Keller and Just, 2009; Klingberg *et al.*, 2000]. Also, there can be a considerable difference between studying groups of adults and children since reading is a skill that is learned throughout childhood and for which neural reorganization is required. Finally, behavioral measures of reading and reading-related skills can be assessed by a wide range of tasks including single word reading, pseudo-word reading, letter identification and phonological awareness tasks [Boets *et al.*, 2010].

Nonetheless, despite the differences across studies, the association between white matter organization and reading and phonological skills in the left temporoparietal region, as first reported

by Klingberg and colleagues [2000], has consistently been observed [Vigneau *et al.*, 2006; Vandermosten *et al.*, 2012b]. White matter in the ventral occipitotemporal region is on the other hand suggested to sustain orthographical processing [Epelbaum *et al.*, 2008; Jobard *et al.*, 2003; Yeatman *et al.*, 2013]. The left temporoparietal region is densely connected as it hosts intra-hemispheric tracts, inter-hemispheric tracts and projection tracts. In a recent meta-analysis on studies that applied a voxel-based approach, an overlapping reading-related cluster was found in the left temporoparietal region [Vandermosten *et al.*, 2012b]. By tracking fibers through this cluster, it was shown that the region hosted the left intra-hemispheric arcuate fasciculus and the left projection tracts in all participants, and in some participants also the posterior corpus callosum. In addition to correlations of reading and phonological awareness with white matter organization in the left temporoparietal region itself [Steinbrink *et al.*, 2008; Deutsch *et al.*, 2005; Klingberg *et al.*, 2000], previous studies have also reported a correlation with (some of) these tracts (for a review see [Vandermosten *et al.,* 2012b; Wandell and Yeatman, 2013]).

The intra-hemispheric arcuate fasciculus is one of the major association pathways of the human brain [Catani and Thiebaut de Schotten, 2012]. The pathway runs in an anterior-posterior direction, sustaining a cortico-cortical connection between the frontal and temporal lobe [Kaplan *et al.*, 2010; Martino *et al.*, 2013] and is here referred to as AF_{FT} (i.e. AF in a strict sense). The AF_{FT} is one of the two subcomponents of the pathway connecting inferior frontal to broader temporoparietal regions, sometimes referred to as the superior longitudinal fasciculus (SLF) [Powell *et al.*, 2006; Deutsch *et al.*, 2005; Steinbrink *et al.*, 2008; Wakana *et al.*, 2007]. The other subcomponent connects inferior frontal to parietal regions (AF_{FP}) [Catani and Thiebaut de Schotten, 2012].

FA in the left AF_{FT} has been positively correlated to phonological awareness in pre-reading children [Saygin *et al.*, 2013] and in adults [Vandermosten *et al.*, 2012a]. Yeatman and colleagues [2012] reported a positive correlation, with individual differences in reading skills and FA development rate of the left arcuate fasciculus in children between 7 and 12 years of age. Children with good reading skills showed a positive developmental slope whereas children with poor reading skills showed a negative developmental slope. In addition, other reading processes such as multimodal grapheme-phoneme integration are also suggested to be sustained by the arcuate fasciculus [Gullick and Booth, 2014]. Finally, a lesion of this pathways resulted in a phonological skill deficit [Rolheiser *et al.*, 2011].

While structural differences in the intra-hemispheric left arcuate fasciculus are thought to distinguish between good and poor readers [Klingberg *et al.*, 2000; Thiebaut de Schotten *et al.*, 2012; Vandermosten *et al.*, 2012a], other studies suggest that differences are within the projection tracts [Beaulieu *et al.*, 2005; Niogi and McCandliss, 2006]. The projection pathway runs in a superior-inferior direction connecting the thalamus to the cerebral cortex. In children reading and decoding

skills have been positively associated with FA of the projection tracts [Beaulieu *et al.*, 2005; Niogi and McCandliss, 2006; Odegard *et al.*, 2009].

In addition to intra-hemispheric and projection pathways, inter-hemispheric tracts have also been related to reading skills. The corpus callosum (CC) pathway is the largest white matter connection in the human brain [Catani and Thiebaut de Schotten, 2008]. This pathway runs in a left-right direction connecting regions of the left and right hemisphere. The posterior CC tracts pass through the splenium of the corpus callosum and connect the left and the right angular gyrus, as already suggested in 1892 by Dejerine, and bilateral posterior superior temporal gyrus [Westerhausen *et al.*, 2009]. Phonological awareness and decoding skills in children [Odegard *et al.*, 2009; Dougherty *et al.*, 2007] and reading in adults [Frye *et al.*, 2008] have been negatively related to FA in posterior callosal tracts. Yet, in contrast to a consistent negative correlation in other studies, one study found a positive FA-relation with phonological awareness in adults [Frye *et al.*, 2008].

Although the studies described in this section suggest the involvement of intra-hemispheric, inter-hemispheric and projection white matter connections in reading-related processes, this observation might be confounded. All three white matter pathways in the left temporoparietal region run in perpendicular directions, causing multiple fiber crossings. The analyses used in previous studies are based on the diffusion tensor model. However, this model is unable to deal with crossing fibers, showing limitations to analyzing pathways running in perpendicular directions. Also, the reading-related cluster in the left temporoparietal region is based on multiple studies, lacking the ability to investigate all three white matter pathways in one group of participants.

It is essential for reading research to understand the role and organization of white matter pathways of the reading network in order to (1) improve how we teach children to read, and (2) map the deviant patterns of organization in individual's with developmental dyslexia, a learning disability that affects 5-10% of the population and is characterized by severe and persistent reading and/or spelling impairments in the absence of intellectual and sensory deficits [Shaywitz, 1998; Vellutino *et al.*, 2004]. Several studies investigating reading-related skills in children have shown that poor ability of naming letters and phonological skills in kindergarten are predictive of poor reading ability later on [Boets *et al.*, 2010; Torgesen *et al.*, 2004]. In order to define neural markers of dyslexia, it is important to determine how these cognitive skills relate to neural substrates. Therefore, we need to disentangle whether in the left temporoparietal region intra-hemispheric, inter-hemispheric and/or projection pathways drive the association with reading-related processes. This study is the first to apply a more sophisticated diffusion imaging model and to investigate all three white matter pathways in the same participants. By applying a method that can give information on white matter organization specific to the delineated pathway, we aim to disentangle which white matter connection is truly driving the relation with phonological awareness previously observed in the left

temporoparietal region of crossing fibers. Over the last decade, higher order diffusion models have been tested in simulation studies, yet we aim to evaluate its potential in addressing clinically relevant questions.

2. Diffusion Imaging models

More than two decades ago, neurological reading research consisted of *post mortem* studies. Already in the 19th century, Reil [1812] and Burdach [1822] described a group of perisylvian fibers and defined the pathway as the arcuate fasciculus. Monakow [1885] and Dejerine [1895] suggested that the frontal and temporal regions that were revealed to sustain language processes [Broca, 1861; Wernicke, 1874], are connected to each other through the arcuate fasciculus. Although there has been an undeniable added value of post mortem research, the method is confined. First, anatomical details of the white matter pathways remains unclear by post mortem investigations, especially concerning the cortical endpoint of the pathways and distinguishing different pathways [Catani *et al.*, 2008]. Second, investigations can only be performed after the patient has died. As a consequence, the cognitive profile of the patient had to be well established in advance, in order to understand post mortem findings. Also, research was mostly done on elderly individuals, rather than in young children, and the number of participants in studies was limited. Finally, developmental trajectories could not be mapped by post mortem research. Two decades ago, *in vivo* diffusion weighted MRI (DW-MRI) scans were introduced. Diffusion imaging is a structural MRI technique that is based on the knowledge that diffusion of water molecules within white matter is anisotropic whereas diffusion in grey matter and cerebrospinal fluid is isotropic (for further explanation see [Jones and Leemans, 2011; Le Bihan and van Zijl, 2002]). By applying large magnetic field gradients in distinct directions, it is possible to make the MR signal sensitive to diffusion of water molecules along these directions. By modelling this signal it is then possible to reconstruct white matter trajectories using tractography methods. Different models can be applied on this signal. The first DW-MRI model was Diffusion Tensor Imaging (DTI), introduced by Basser, Mattiello and LeBihan in 1994. Nowadays, a number of more advanced methods are available. In this section, the classic Diffusion Tensor Imaging model and the more advanced Spherical Deconvolution (SD) model will be described.

2.1 Diffusion Tensor model

Over the past two decades Diffusion Tensor Imaging (DTI) has been extensively applied in neurological research [Dubois *et al.*, 2008; Lebel and Beaulieu, 2009; Lebel *et al.*, 2008; Mohades *et al.*, 2012; Powell *et al.*, 2006; Steinbrink *et al.*, 2008; Vandermosten *et al.,* 2012a; Vernooij *et al.*,

2007]. At present, DTI is the most frequently applied model for relating the DW-MRI signal to the underlying neuroanatomy [Tournier *et al.*, 2007]. DTI is based on the classic diffusion tensor model. In each voxel a tensor is defined by estimating three eigenvectors (v1, v2, v3) and three eigenvalues (λ1, λ2, λ3). The eigenvalues represent the magnitude of the diffusion along the direction of the corresponding eigenvectors [Le Bihan and van Zijl, 2002]. Independently of the number of fibers, one major fiber direction per voxel is estimated, called the major eigenvector [Tournier *et al.*, 2007].

For quantitative analyses indirect information on white matter organization can be derived by multiple indices, defined based on the estimated eigenvalues of the tensor (e.g. mean diffusivity, radial diffusivity, axial diffusivity and fractional anisotropy). However, fractional anisotropy (FA), measuring the degree to which the diffusion of water molecules is anisotropic, is the most commonly used index [Jones and Leemans, 2011], with values ranging between 0 (completely isotropic, λ1 = λ2 = λ3) and 1 (completely anisotropic, λ1 > λ2 =/> λ3) [Basser and Pierpaoli, 1996].

One of the major advantages of DTI is that it enables us to study white matter connections in the living human brain. However, as DTI is an indirect reconstruction of the true anatomy, it comes with some limitations. First, in areas with multiple white matter fibers, only one direction per voxel can be estimated. In the majority of white matter voxels ($\approx$ 70-90%) not all the fibers are oriented along the same vector [Jeurissen *et al.*, 2010, Dell'Acqua *et al.*, 2013]. Hence, in some of these voxels, the tensor model is unable to resolve the orientation of multiple crossing fibers. In general the major eigenvector in voxels with multiple crossing fibers also does not even correspond to the orientation of any of the fibers [Assaf *et al.*, 2004; Tournier *et al.*, 2007]. As a consequence, the diffusion tensor model oversimplifies the underlying neuroanatomy, resulting in a considerable reduction in information. As shown in Figure 1C and as indicated when explaining the limitations of the DTI model, in regions with fiber crossings, DTI cannot make a precise estimation of the underlying anatomy. Second, despite the widespread use of FA and its added value to quantitatively study white matter pathways, the interpretation of the FA index is not always straightforward. FA is calculated at voxel level and is determined by a variety of microstructural properties, for example the myelination of white matter fibers, the permeability of cell walls and membranes and the size and packing density of cells [Alexander *et al.*, 2010], as well as macrostructural properties such as the number of crossing fibers. As a lot of anatomical information is reduced to one index, this implies that an increase in FA can for example be due to increasing myelination of white matter fibers, but may also be the consequence of white matter degeneration [Wheeler-Kingshott and Cercignani, 2009]. Since FA of white matter pathways is influenced by a lot of features and is dependent on its neuroanatomical location in the brain, i.e. running through regions with multiple fiber crossings, it is clear that changes in FA following development or pathology are not easy to interpret.

2.2 Spherical Deconvolution

Non-tensor models are more complex models that can characterize the orientations of more than one fiber per voxel. Examples of non-tensor models are: q-Ball imaging [Tuch, 2004], diffusion spectrum imaging (DSI) [Wedeen *et al.*, 2005], CHARMED [Assaf *et al.*, 2004], and Spherical Deconvolution (SD) [Tournier *et al.*, 2004; Dell'Acqua *et al.*, 2010]. For many non-tensor model analyses (q-ball, DSI, CHARMED), images with higher or multiple b-values must be acquired, resulting in longer acquisition times. An advantage of SD is that the acquisition time is close to that of DTI. Therefore SD methods are increasingly applied [Dell'Acqua *et al.*, 2010].

Spherical Deconvolution (SD) is a non-tensor method according to which a continuous 3D distribution of the possible fiber orientations is estimated within each voxel [Tournier *et al.*, 2004]. SD methods can provide information on white matter complexity in each voxel by estimation of the number of distinct fiber orientations. In Figure 1D the white matter fiber estimation by the SD model is presented, showing a more complex organization of the underlying neuroanatomy. The number of fiber orientation (NuFO) maps allows distinct regions to have a different degree of fiber complexity. NuFO maps have the advantage of providing additional anatomical information per voxel, but it is important to note that NuFO maps do not yet fully describe the microstructural organization of white matter tracts [Dell'Acqua *et al.*, 2013].

For quantitative SD analyses, the hindrance modulated orientational anisotropy (HMOA) index can be derived. It is defined as the absolute amplitude of each lobe of the fiber orientation distribution, (for further explanation see [Dell'Acqua *et al.*, 2013]). While FA provides a quantitative measure per voxel, HMOA provides information about the diffusion properties along each fiber orientation, in regions with multiple fiber crossings. Therefore the HMOA index might have an increased sensitivity to detecting microstructural changes in specific white matter tracts, even in regions of crossing fibers. By applying this tract-specific index, we might be able to detect fiber diffusivity changes, such as for example developmental myelination processes. The HMOA index seems to provide an advantage for the quantitative study of white matter changes over FA, as confirmed by simulation studies [Dell'Acqua *et al.*, 2013]. Nevertheless, the index has not been implemented in the study of clinical populations. To define the added value of this measure, further research of the developing and degenerating brain will be needed.

In the present study, a direct comparison between the anisotropy indices of DTI and SD models is made. FA of the DTI model and HMOA of the SD model are compared in both a region with few and with multiple fiber crossings in order to verify that SD provides unique and additive information especially in regions of crossing fibers.

3. Methods

3.1 Participants

Forty-one male and thirty female pre-reading children aged 5 to 6 years are included in this study (73.9 ± 3.3 months old). The data presented here are the first measurement of a longitudinal study on reading development and its neural correlates. In the longitudinal study a total of 87 Dutch-speaking children are included, half of whom have a family risk of dyslexia , defined by having at least one first-degree relative with dyslexia. In a subsample of 75 children, MRI scans were administered at the end of the last year of kindergarten. Due to unsuccessful DTI-acquisition, four children were excluded.

Phonological awareness, i.e. the awareness of the sound structure of language [Wagner and Torgesen, 1987], was assessed at the beginning of the last year of kindergarten, consisting of an end phoneme and end rhyme identification task [Boets *et al.*, 2010; de Jong *et al.*, 2000, adapted by van Otterloo and Regtvoort]. For the end phoneme identification task, subjects were asked to choose from four alternatives the word that had the same end sound. The task consisted of two practice items and ten test items. The maximum score was ten. For the end rhyme identification task, the children had to choose, again from four alternatives, which item had the same end rhyme as the given word. Two practice items were presented followed by twelve test items. Each item of both tasks consisted of five visually presented pictures. The first picture represented the given word, and the other four pictures were the answer alternatives. The given word was separated from the other pictures by a vertical line. All pictures were named for the child and represented high frequency monosyllabic Dutch words. To prevent guessing the distracter alternatives were systematically constructed. The phonological awareness composite score was defined as the mean score of the standardized z-scores of both tasks.

In the 71 children included in this study, 36 had a family risk of dyslexia and 35 had no family risk. The matching procedure and criteria for exclusion have been described in Vandermosten et al. [*submitted*]. For the purpose of this study both children with and without a family risk of dyslexia are included in one group since (1) both groups do not significantly differ on phonological awareness tasks assessed at the start of third grade of kindergarten (see Table I), and (2) recent evidence suggests that the family risk of dyslexia is continuous rather than discrete [Boets *et al.*, 2010]. In the group with a family risk of dyslexia, preschool children have a 30 to 50% chance of developing dyslexia [Gilger *et al.*, 1991], whereas in the group with no family risk, representing the normal

population, there is a 3 to 10% chance of developing dyslexia [Snowling, 2000]. Taking into account the variation that can be expected due to the family risk in half of the sample, this group is expected to show a wide range of reading skills as they grow up.

This study was approved by the ethics committee at the University Hospital of Leuven. The parents of all participants gave their written consent for the children to participate in the study.

< insert Table I about here >

3.2 DW-MRI acquisition

MRI data were acquired on a 3.0 T scanner (Philips, Best, The Netherlands) with a 32-channel head coil using a single shot EPI with SENSE (parallel) acquisition. DTI sagittal slices were obtained using the following parameters: repetition time 7600 ms, echo time 65 ms, flip angle 90°, voxel size 2.5 x 2.5 x 2.5 mm, 60 non-collinear directions, b-value 1300 s/mm², 6 nondiffusion-weighted images. The scan acquisition time was 10 min 32 s.

3.3 DW-MRI processing

The software ExploreDTI (version 4.8.3) [Leemans and Jones, 2009] was used to preprocess the data. Images were corrected for subject motion and eddy current-induced distortions. Next, for the DTI-analyses whole-brain tractography was conducted using the following parameters: minimum fractional anisotropy (FA-threshold) = 0.20, maximum turning angle between voxels = 40°, step length between calculations = 1 mm. For Spherical Deconvolution analysis an extra processing step was carried out by the software StarTrack [Dell'Acqua *et al.*, 2013] applying the following SD algorithm parameters: iterations = 350, n = 0.06, r = 8. Afterwards, whole-brain tractography was conducted using a modified Euler-like tractography algorithm [Dell'Acqua *et al.*, 2013] using the following parameters: absolute HMOA threshold = 0.02, relative HMOA threshold = 5%, maximum turning angle between voxels = 40° and step length between calculations = 1 mm.

The software TrackVis [Wedeen *et al.*, 2008; Wang *et al.*, 2007] was applied to perform deterministic tractography of the white matter pathways for both DTI and SD models. In each individual brain, tracts were manually delineated using a Region Of Interest (ROI) approach. ROIs are defined based on anatomical landmarks in color-coded maps. In these color-coded maps, the color defines the direction of the streamline. Red streamlines run in a left-right direction connecting both hemispheres, whereas green streamlines run in an anterior-posterior intra-hemispheric direction and blue streamlines run in a superior-inferior direction [Pajevic and Pierpaoli, 1999].

Since a lot of variation in children's brains can be expected due to growth and development or maturation, data were analyzed in native space, which does not require a conversion of the individual brain to a standard atlas.

3.4 Delineation of the ROIs

The selection of ROIs is critical, since even relatively small changes in the anatomical position of the ROI can lead to very different results [Ciccarelli *et al.*, 2005; Tournier *et al.*, 2011]. For manual delineation of white matter pathways, ROIs are drawn on areas that represent "obligatory passages" along the course of the pathway. These obligatory passages represent regions in the brain through which all fibers of one specific tract must pass [Catani *et al.*, 2002; Catani and Thiebaut de Schotten, 2008]. To be able to distinguish between the pathways of interest and other white matter pathways, the ROIs must be defined so that no other white matter pathway shares all obligatory passages. Pathways can be delineated by defining only one ROI. This can be applied when all fibers passing through one specific ROI are considered to belong to a single white matter pathway. This one-ROI approach [Catani and Thiebaut de Schotten, 2008] is used in this study to delineate the projection tracts and CC splenium pathway. For manual delineation of fibers with few and multiple crossings one ROI is defined as obligatory passage, and all fibers running through this ROI are included. When the tract of interest shares its obligatory passages with at least one other pathway, a two-ROI approach can be used. In this case a second ROI is necessary to specify the obligatory passages of the pathway so that the tract of interest can be distinguished from the other tract(s) [Catani and Thiebaut de Schotten, 2008]. In this study a two-ROI approach is used to delineate the arcuate fasciculus. Both approaches can be supplemented by ROIs to exclude undesired streamlines (NOT-ROIs). Fibers passing through these NOT-ROIs [Wakana *et al.*, 2007] are not considered to be a part of the pathway and are excluded.

The ROIs used for DTI and SD tractography are identical and include the exact same voxels. ROIs were labelled on the color-coded maps and implemented both for DTI and SD tractography. However, based on the anatomy, fibers that were no part of the pathway of interest were excluded by adding a NOT-ROI.

All white matter tracts were manually delineated by one operator. In order to test inter-rater reliability a second operator virtually dissected the arcuate fasciculus from 71 DTI-datasets. Inter-rater reliability was calculated by an intra-class correlation test. A high intra-class correlation coefficient was found for the number of streamlines for the AF_{FT} (= .97), as well as for FA measurements of the AF_{FT} (= .99). Additionally, intra-rater reliability was calculated in the 71 SD-datasets, showing a high intra-class correlation coefficient for the HMOA index for the AF_{FT} (= .98), projection tracts (= .98), and CC splenium (= .99).

3.5 Reading-related white matter pathways

With regard to the delineation of the intra-hemispheric tracts of the left temporoparietal region, i.e. the left arcuate fasciculus, the protocol of Wakana and colleagues [2007] was applied. The inferior frontal to temporal segment of the arcuate fasciculus (AF$_{FT}$) was delineated by the combination of two ROIs. The first ROI is defined in a coronal slice and the second ROI in an axial slice (Figure 2A).

The projection tracts consist of the corona radiata fibers, which inferiorly enter in the internal capsule. The corona radiata contains ascending thalamic fibers radiating out to various cortical destination, and descending motor fibers. The internal capsule can be subdivided into an anterior limb, middle genu and posterior limb. The projection tracts delineated for this pathway include the genu of the internal capsule [Catani and Thiebaut de Schotten, 2012] and include ascending and descending fibers. The projection tracts are delineated according to the protocol of Catani and Thiebaut de Schotten [2008]. To delineate this pathway, one ROI is defined at an axial slice (Figure 2B).

For the delineation of inter-hemispheric tracts running through the posterior corpus callosum (Figure 2C), one ROI is defined in the mid-sagittal slice. The ROI is placed around the posterior third of the corpus callosum containing the splenium [Aukland *et al.*, 2011].

< insert Figure 2 about here >

3.6 White matter fibers with multiple and few crossings

In order to enable a direct comparison between anisotropic indices, two ROIs containing fibers with multiple and few crossings were delineated and anisotropic indices were extracted by applying both models. The first ROI was the anterior part of the corpus callosum and was selected because it has only few fiber crossings. This anterior part, also called the genu, has been delineated at the midsagittal plane, around the anterior third of the corpus callosum. All fibers running through this ROI were included.

The second ROI was the left temporoparietal region hosting the arcuate fasciculus, projection tracts and corpus callosum and was selected for having multiple fiber crossings. A 3D-ROI of the same size (see Figure 1A and B), was in each individual defined in the area where all three white matter pathways were crossing.

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4. Results

A Shapiro-Wilk test of normality showed that all diffusion indices and behavioral measures were normally distributed. In the first part of this section, the relation between the left temporoparietal white matter pathways and phonological awareness is described. To enable comparison with the literature, analyses are first presented with Pearson correlations. For all white matter connections in DTI as well as SD tractography, there were no group differences between children with and without a family risk of dyslexia (see Table I), so correlations were not driven by group differences but represented individual variations. In a next step, a multiple regression analyses was run with phonological awareness as a dependent variable. All three white matter pathways (intra-hemispheric tracts, inter-hemispheric tracts and projections tracts) were included as independent variables. In addition, gender was included as an influence on reading related neural substrates has been proposed [Altarelli *et al.*, 2013; Sandu *et al.*, 2008] and different developmental trajectories might be expected [Lenroot *et al.*, 2007]. Eight subjects with extreme head motion, defined by more than 3 SD relative or total head motion in one of the planes [Theys *et al.*, 2014], were excluded. This exclusion procedure was based on the study of Ling and colleagues [2012] and is described for the subjects of this study in Theys *et al.* [2014]. Controlling for displacement relative to the preceding volume without excluding subjects did not change the results.

In the second part, a quantitative comparison between DTI and SD models is given, exploring the relation between FA and HMOA indices. To enable a direct comparison between the models, in addition to FA from DTI and HMOA from SD tractography, FA values were also derived from the same SD pathways.

4.1 Left temporoparietal white matter and phonological awareness

4.1.1   Diffusion Tensor Imaging

With regard to the correlation with phonological awareness, correlational analyses were first performed using traditional DTI-outcomes, represented by FA. More specifically, the three main white matter pathways that run through the left temporoparietal region (i.e. AF_{FT}, projection tracts and posterior CC) were delineated based on the diffusion tensor model, and an average FA for each of the pathways was extracted. To enable comparison with the literature, results are first presented with Pearson correlations. Results showed a positive correlation with phonological awareness for FA in the left AF_{FT} ($r = .27$, $p = .02$) and the left projection tracts ($r = .26$, $p = .03$). There was no relation with the CC splenium tracts ($r = .16$, $p = .19$). These results show that the present study replicates previous research outcomes, i.e. a positive relation with reading-related skills within the left arcuate

fasciculus [Saygin *et al.*, 2013; Vandermosten *et al.*, 2012a] and left projection tracts [Niogi and McCandliss, 2006; Odegard *et al.*, 2009].

In a next step, a multiple regression analyses was run. Eight subjects with extreme head motion were excluded (n = 63). Controlling for displacement relative to the preceding volume did not change the results. Both the arcuate fasciculus and the projection tracts no longer significantly relate to phonological awareness (AF: $t_{(4,58)}$ = 1.62, *p* = .11; projection tracts: $t_{(4,58)}$ = 1.41, *p* = .16). The relation with the corpus callosum splenium pathway remained insignificant ($t_{(4,58)}$ = -.62, *p* = .54). There was no effect of gender ($t_{(4,58)}$ = .12, *p* = .90). Applying a multiple regression model seems to attenuate the relation between DTI anisotropy measures and phonological awareness.

4.1.2   Spherical Deconvolution

In a second step, we applied a new approach by correlating phonological awareness skills with tract-based SD-outcome, as represented by HMOA. Again the arcuate fasciculus, projection tracts and posterior corpus callosum were delineated through SD tractography, which allowed for multiple directions in regions of crossing fibers. The relation with phonological awareness was again first presented with Pearson correlations. The arcuate fasciculus is positively correlated to PA (r = .28, *p* = .02), while there is no significantly relation between PA and projections tracts (r = .14, *p* = .25) and the posterior CC tracts (r = .10, *p* = .41). A multiple regression analyses after exclusion of the subjects with extreme head motion (n = 63), confirmed these results. HMOA in the left AF_{FT} significantly predicts PA ($t_{(4,58)}$ = 2.43, *p* = .02), while there was no effect of the projections tracts ($t_{(4,58)}$ = 1.07, *p* = .29) and the posterior CC tracts ($t_{(4,58)}$ = -.25, .81). No effect of gender on PA was found ($t_{(4,58)}$ = .65, *p* = .52). As in the case of the DTI analyses, controlling for displacement relative to the preceding volume did not change the results.

4.2 Quantitative model comparison

4.2.1 Anisotropy indices

In a second part of this study, the relation between the DTI and SD model was examined by investigating the relationship between the FA and HMOA indices. Anisotropy indices were derived from fibers originating from multiple and few fiber crossings. Fibers with multiple crossings were all running through the left temporoparietal region whereas fibers with few crossings were defined by running through the corpus callosum genu. For DTI tractography an FA value was obtained for each

pathway. For the pathways analyzed with SD tractography, both HMOA and FA values were derived from the same pathway. This enables a direct comparison between both models.

In Table II correlational analyses are presented. Subjects with extreme head motion were excluded. Again, controlling for displacement relative to the preceding volume without excluding subjects did not change the results. The results showed that in a region with few fiber crossings, FA of DTI tractography correlated strongly with FA (r = .88, *p* < .01) and HMOA (r = .80, *p* < .01) of the SD model. Within SD tractography, FA and HMOA values were also highly correlated (r = .76, *p* < .01).

In a region with multiple fiber crossings, DTI (FA) was significantly lower correlated to SD (FA), tested with a Fisher z test (z = 3.09, *p* < .01). However, this correlation remained relatively high (r = .67, *p* < .01). Similarly, the correlation between DTI (FA) and SD (HMOA) (r = .57, *p* < .01) was significantly lower in a region with multiple fiber crossings compared to a region with few fiber crossings (z = 2.44, *p* = .01). In contrast to this decrease in correlation between DTI and SD indices, the relation within SD tractography between FA and HMOA indices remained strong in a region with multiple fiber crossings (r = .83, *p* < .01) and did not differ significantly from the correlation in a region with few fiber crossing (z = 0.99, *p* = .32).

These results confirmed that DTI and SD tractography are different in regions with multiple fiber crossings. In particular, a decreased relation was present between DTI and SD anisotropy indices when multiple fiber crossings are present. On the contrary, comparison of FA and HMOA within the exact same voxels of the same tractography model, showed that the anisotropy indices are highly related to each other, regardless of the amount of fiber crossings.

< insert Table II about here >

4.2.2 Number of voxels

The number of included voxels was obtained for each pathway and for each model. A paired samples test showed that SD includes significantly more voxels than DTI in pathways with both few (DTI: *M* = 2483, *SD* = 313; SD: *M* = 3241, *SD* = 501, *p* < .01) and multiple fiber crossings (DTI: *M* = 3361, *SD* = 602; SD: *M* = 4782, *SD* = 697, *p* < .01). These results confirm that the SD model can track better through voxels containing fiber crossings.

5. Discussion

This is the first study that evaluates the added value of Spherical Deconvolution (SD) – over classic DTI – for finding potential relations with behavioral performance. In particular, we reconstructed and

quantified, based on both DTI and SD models, the three main pathways that cross the left temporoparietal region, i.e. left intra-hemispheric arcuate fasciculus (AF_{FT}), left projection tracts and inter-hemispheric posterior corpus callosum (CC), in 71 pre-reading children. Our results show a correlation between phonological awareness and the typical anisotropy diffusion measure, i.e. FA based on the tensor model, in both the intra-hemispheric and projection tracts. This is consistent with previous findings (for a review see [Vandermosten *et al.*, 2012b]). However, controlling for subject motion, whole-brain anisotropy and gender attenuates both relations. The novel finding of our study is that this correlational pattern is less diffuse and restricted to left intra-hemispheric connections when phonological awareness is linked to HMOA, i.e. anisotropy diffusion measures based on non-tensor SD models.

5.1 Left temporoparietal white matter and phonological awareness

The left temporoparietal region constitutes an important role in the neural reading network. The region is involved in phonological aspects of reading and in cross-modal integration [Schlaggar and McCandliss, 2007; Vigneau *et al.*, 2006]. Therefore, this region is also thought to be the neural basis of the phonological deficit in dyslexia [Hoeft *et al.*, 2006]. While a lot of research has been performed on the functional activation of the left temporoparietal region, the role and organization of white matter in this region is not clear.

White matter organization within the temporoparietal region is found to correlate with reading and reading-related processes [Vandermosten *et al.*, 2012b]. Although DTI is typically used in these studies, it is currently known that there are many regions, in particular the temporoparietal region, where the tensor model of DTI is not valid [Dell'Acqua *et al.*, 2010; Behrens *et al.*, 2003; Dell'Acqua and Catani, 2012]. This could possibly explain the heterogeneity across previous DTI-studies on the contribution of specific white matter pathways that cross in the left temporoparietal region as regards reading aspects. For example, some studies are not able to precisely allocate the observed reading-related correlation within the temporoparietal region to a specific pathway [Steinbrink *et al.*, 2008; Klingberg *et al.*, 2000; Deutsch *et al.*, 2005] whereas others vary between allocating the correlation to the intra-hemispheric connections [Vandermosten *et al.*, 2012a; Saygin *et al.*, 2013; Yeatman *et al.*, 2012], projection tracts [Niogi and McCandliss, 2006; Odegard *et al.*, 2009] or inter-hemispheric connections [Odegard *et al.*, 2009; Frye *et al.*, 2008; Dougherty *et al.*, 2007]. This is also in line with a recent meta-analysis which showed that the left temporoparietal cluster that was consistently found across previous DTI-studies hosted both the AF_{FT} and projection tracts. This cluster seemed also to host some posterior fibers of the CC, though this was not consistently found across subjects [Vandermosten *et al.*, 2012b].

When we applied the classic DTI model to our data, we observed that reading-related processes are positively correlated to diffusion anisotropy in the left intra-hemispheric connections as well as in the left projection tracts. The correlation between the posterior inter-hemispheric connections and phonological awareness was not significant. These results are in line with the literature. However, studies that previously reported a relation with the projection tracts did not control for subject motion [Beaulieu *et al.*, 2005; Niogi and McCandliss, 2006], or analyzed data in standard space [Beaulieu *et al.*, 2005; Odegard *et al.*, 2009]. Also, these studies investigate a region by performing voxel-wise analyses, and allocate this region to the projection tracts based on visualization tools. By controlling for potential confounding variables such subject motion, whole-brain anisotropy and gender in our study, the previously observed relations are attenuated, resulting in a non-significant relation with all white matter pathways.

The left temporoparietal region hosts multiple fiber crossings and since DTI is only capable of estimating one fiber direction in each voxel of the imaged brain, the application of this tensor model results in an oversimplification of the underlying neuroanatomy, which might therefore lead to faulty interpretations. Given that the FA index is only specific at the level of the voxel, and the three perpendicular pathways share a lot of temporoparietal voxels, the FA values within the different crossing pathways are not independent. This implies that a confounding effect of motion in one of the pathways might also influence the observed relation in the crossing pathways.

In order to obtain a more accurate estimation of white matter structure, we applied Spherical Deconvolution. This might alleviate the inconsistencies found in previous studies and might disentangle which white matter connections are driving the correlation with phonological awareness. Spherical Deconvolution analyses were performed on the same three white matter connections. Phonological awareness significantly correlated to HMOA in the left intra-hemispheric tracts, but not to HMOA in the projection tracts and inter-hemispheric tracts. Strong evidence was found for this relation in a regression analysis including the influence of motion, gender and whole-brain anisotropy. The observation of no significant correlation in the projection or inter-hemispheric tracts by SD-analyses, together with verification that SD provides unique information in regions with multiple fiber crossings, suggests that the left intra-hemispheric tracts are driving the correlation with phonological awareness. Hence, investigating white matter in the left temporoparietal region by applying a model that is able to estimate multiple fiber directions seems to narrow the correlations down to the left arcuate fasciculus. This observation provides support for the importance of the arcuate fasciculus in the reading circuitry, as has frequently been proposed in skilled readers and even in young children (for a review see [Vandermosten *et al.*, 2012b; Wandell and Yeatman, 2013]). Because of its anatomical connections, a crucial role of the arcuate fasciculus is not surprising. The inferior frontal endpoint of the arcuate fasciculus has been proposed to be involved in higher level

processes such as phonological processing [for a meta-analysis see Vigneau *et al.*, 2006], the construction of new multimodal representations [Hagoort *et al.*, 2009], and has been related to reading performance [Rimrodt *et al.*, 2010]. The temporal endpoint region of the AF has also been shown to be involved in phonological aspects of reading [Booth *et al.*, 2002; for a meta-analysis see Vigneau *et al.*, 2006], and in multimodal integration [Blau *et al.*, 2009, 2010; Booth *et al.*, 2002; Schlaggar and McCandliss, 2007; van Atteveldt *et al.*, 2007] and is also related to reading performance [Rimrodt *et al.*, 2010].

Based on the function of the endpoints of the arcuate fasciculus, and the suggested involvement of the pathway in reading, a relation between the intra-hemispheric arcuate fasciculus and phonological awareness seems not surprising. Nevertheless, the arcuate fasciculus is a pathway that matures later during development [Dubois *et al.*, 2008; Lebel *et al.*, 2008; Zhang *et al.*, 2007]. Interestingly, our results suggest that already prior to reading onset, the arcuate fasciculus relates to phonological awareness. This means that, although a large reorganization due to reading development still needs to take place, the relation between phonological awareness and the left AF, as reported in adults, is already present at the age of 5 to 6 years. These results also indicate that lower phonological awareness skills are related to lower anisotropy in the arcuate fasciculus. How this will further influence the development of reading and of the reading network, however, remains to be investigated. Besides the importance of these findings for reading and dyslexia research, poor phonological awareness skills have also been shown in children with Specific Language Impairment (SLI) [Vandewalle *et al.*, 2012] and white matter anomalies in the arcuate fasciculus have been reported in children with SLI [Verhoeven *et al.*, 2011]. Hence, the results of our study, narrowing the correlation between phonological awareness and white matter pathways down to the intra-hemispheric arcuate fasciculus, is presumably also relevant for the study of SLI.

Previous classic DTI-studies have indicated the involvement of the projection tracts in reading-related processes, despite their assumed role in motoric and perceptual rather than cognitive processes [Catani and Thiebaut de Schotten, 2008]. By applying DTI tractography we were able to replicate this correlation, however, this correlation seems to be driven by a confounding effect since the DTI-correlation disappears when whole-brain anisotropy and/or subject motion is controlled for as well as when SD is applied which controls for crossing fibers. The projection tracts connect the thalamus with the sensorimotor cortex [Catani and Thiebaut de Schotten, 2008], and a role in perceptual and motor functions [Schmahmann and Pandya, 2008] is therefore more straightforward than one in reading. The projection tracts also run too medially in order to connect to the temporoparietal, occipitotemporal and inferior frontal cortical areas for which fMRI studies clearly demonstrate their involvement in reading.

The posterior corpus callosum tracts inter-hemispherically connect left and right angular gyrus and superior temporal gyrus, which are involved in cross-modal integration and the processing of phonological word forms [Blau *et al.*, 2010; Booth *et al.*, 2002]. Therefore, a role of these pathway in reading, as has been proposed in children [Dougherty *et al.*, 2007; Odegard *et al.*, 2009] and adults [Frye *et al.*, 2008], is not unexpected. In the pre-reading brain, however, we did not find such a relation with phonological awareness skills. Inter-hemispheric connections might play a role during more advanced stages of reading or be involved in other reading related mechanisms. Vandermosten and Poelmans *et al.* [2013] suggested a compensatory role of CC splenium in adults with reading problems. Higher engagement of right posterior areas in individuals with dyslexia has also been suggested [Shaywitz *et al.*, 2002], although it should be noted that this finding has not consistently been replicated [Richlan *et al.*, 2009].

5.2 Quantitative model comparison

The diffusion anisotropy index of the Spherical Deconvolution model, hindrance modulated orientational anisotropy (HMOA), was shown to vary within one voxel, depending on the white matter tract passing through the voxel [Dell'Acqua et al., 2013], therefore increasing specificity to the level of the tract rather than the voxel, as is the case for FA. A simulation study suggests that HMOA is sensitive to fiber diffusivity changes (e.g. myelination processes or axonal loss) and differences in structural organization of white matter (e.g. axonal diameter and fiber dispersion) [Dell'Acqua *et al.*, 2013]. Also, HMOA would be able to detect degeneration in one white matter tract while another crossing tract remains intact. As part of our study, we verified that Spherical Deconvolution provides unique and additive information over DTI, especially in regions with multiple fiber crossing. Anisotropy indices of DTI and SD were compared. The FA index is defined by different micro- (myelination, axon density) and macro- (fiber crossings) structural properties. Since the SD model is better able to solve fiber crossings, the question arises whether the HMOA index is therefore less influenced by these crossings. The results within SD tractography, showing no influence of the amount of fiber crossings on the relation between FA and HMOA indices, together with the results on the relation between FA of the DTI model and HMOA of SD model, showing a lower correlation in a region with multiple fiber crossings, indicates an influence of fiber crossings at the level of the model. This is however not unexpected, since the SD model is better able to solve fiber crossings. To summarize, there seems not to be a direct influence of crossing fibers on the indices, but there is a confounding effect of crossing fibers on DTI tractography.

HMOA is already a valuable attempt to disentangle white matter organization in one voxel, as it provides a different anisotropy value for different crossing fibers in a single voxel. However,

additional neuroimaging measurements might provide more information about the micro-structural properties of the independent crossing fibers. Tractometry is a recent approach [Bells *et al.*, 2011; Dell'Acqua and Catani, 2012] combining tractography with microscopic quantitative measurements of the individual tracts based on, for example, myelinated water fraction [Deoni *et al.*, 2008] and might lead to a better insight into microscopic white matter structure. Applying the Spherical Deconvolution model as well, Apparent Fibre Density (AFD) uses similar methods to present a quantitative measure of fiber orientation distributions [Raffelt *et al.*, 2012]. In addition to Spherical Deconvolution, there are a number of other non-tensor models providing a better estimation of white matter organization than tensor models. Diffusion spectrum imaging (DSI), and the generalized fractional anisotropy (GFA) measure have been applied to study patients with obsessive-compulsive disorder (OCD) [Chiu *et al.*, 2011]. A recent study used high angular resolution diffusion imaging (HARDI) to investigate neurodegeneration in patients with amyotrophic lateral sclerosis (ALS) [Trojsi *et al.*, 2013]. The added value of diffusion kurtosis imaging (DKI) in comparison to classic DTI has been investigated by Gooijers et al. [2013] and Kamagata et al. [2013] in patients with Parkinson's disease. Although these studies seem to suggest an added value of applying higher order imaging models to study clinical populations, the potential added value of these non-tensor models for quantitatively studying white matter largely still needs to be explored. Also the potential added value of Spherical Deconvolution in other clinical populations remains to be explored.

In summary, the main results of this study suggest that the relation between left temporoparietal white matter and phonological awareness is sustained by left intra-hemispheric connections, and not by inter-hemispheric connections or projection tracts. In addition, SD tractography seems to have an increased sensitivity for finding a phonological correlation within left temporoparietal white matter, as results are less confounded by fiber crossings. These results have significant implications for reading research, suggesting the use of more advanced diffusion imaging models to study complex white matter regions. However, as this is to the best of our knowledge the first study to investigate the relation between a quantitative Spherical Deconvolution index and a behavioral measure which has been previously related to fractional anisotropy, further research is indicated. This research should include the relation between this index and behavioral measures that have been linked to white matter organization in the brain as well as the developmental and pathological trajectory of the brain. Further advances in the development of higher order diffusion models as well as of techniques that can target specific microscopic properties could help to further increase the specificity and sensitivity of white matter relations with behavior.

Acknowledgements

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Figure 1. Left temporal-parietal white matter, DTI and SD. The three white matter connections running through the left temporoparietal region in a left sagittal view (A) and posterior coronal view (B). Green = AF, red = posterior CC, blue = projection tracts, temporoparietal ROI = orange. Zooming in on the cluster where all white matter tracts cross shows a significant difference between the Diffusion Tensor model (C) and Spherical Deconvolution model (D), whereby in panel D a lot more callosal (red) fibers are visible.

Figure 2. The three main white matter tracts of the left temporoparietal region. Sagittal view of the left hemisphere showing the three main tracts and their corresponding ROIs for manual delineation: the left frontotemporal arcuate fasciculus (A), left projection tracts (B), and left corpus callosum splenium (C).

Figure 3. Scatterplots of the relation between phonological awareness and HMOA (SD tractography) of the intra-hemispheric, inter-hemispheric and projections pathways.

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Table I. Description of participants' gender and phonological awareness assessment and the investigated white matter pathways. Group means are compared using independent samples t-test, except for the variable gender, which was analyzed by Fisher's exact test.

> FRD^{+} = children with a family risk of dyslexia, FRD^{-} = children with no family risk of dyslexia, WM = white matter, FA = fractional anisotropy, HMOA = hindrance modulated orientational anisotropy, AF_{FT} = fronto-temporal arcuate fasciculus, CC = corpus callosum
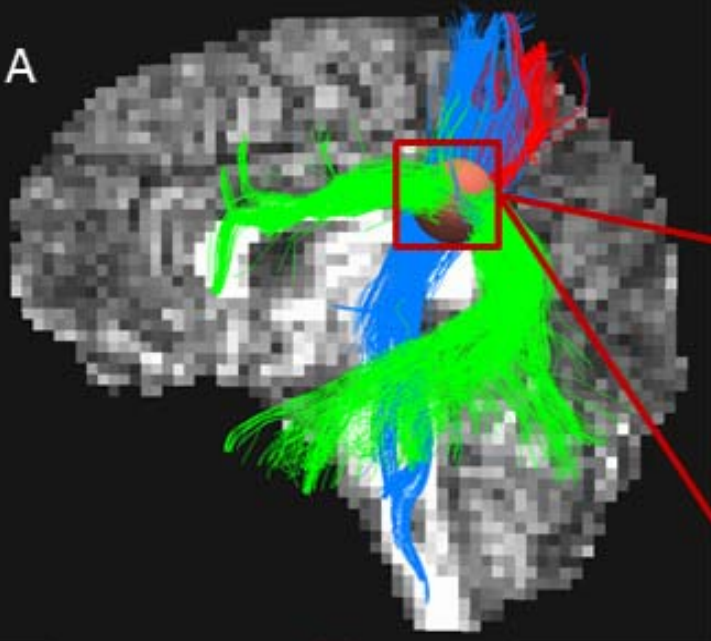> [a] To assist in the interpretation of the results, the composite score of phonological awareness was transferred to effect sizes relative to the mean and standard deviation of the FRD^{-} group

Table II. Pearson correlation between FA (DTI and SD) and HMOA (SD) indices derived from a region hosting few and a region hosting multiple fiber crossings. (**$p \leq .01$; *$p < .05$)

Tables

Table I. Description of participants' characteristics and the investigated white matter pathways. Group means are compared using independent samples t-test, except for the variable gender, which was analyzed by Fisher's exact test.

	FRD$^+$ (n = 36)	FRD$^-$ (n = 35)	Test statistics
Participant characteristics			
Gender (boy/girl)	23/13	18/17	*p* = .34
Phonological awareness			
End phoneme (items correct)	4.39 (2.18)	3.74 (2.34)	$t_{(69)}$ = 1.20; *p* = .23
End rhyme (items correct)	8.31 (2.73)	9.17 (2.12)	$t_{(69)}$ = -1.49; *p* = .14
Composite score^a	-0.06 (1.28)	0 (1)	$t_{(69)}$ = -.17; *p* = .86
White matter pathways			
DTI (FA)			
AF$_{FT}$	.48 (.03)	.49 (.03)	$t_{(69)}$ = -.66; *p* = .51
Projection tracts	.49 (.02)	.50 (.02)	$t_{(69)}$ = -1.39; *p* = .17
CC splenium	.55 (.02)	.56 (.02)	$t_{(69)}$ = -.97; *p* = .34
SD (HMOA)			
AF$_{FT}$	.10 (.01)	.10 (.01)	$t_{(69)}$ = -.41; *p* = .69
Projection tracts	.10 (.01)	.11 (.01)	$t_{(69)}$ = -1.29; *p* = .20
CC splenium	.17 (.02)	.17 (.02)	$t_{(69)}$ = -1.08; *p* = .29

FRD$^+$ = children with a family risk of dyslexia, FRD$^-$ = children with no family risk of dyslexia, WM = white matter, FA = fractional anisotropy, HMOA = hindrance modulated orientational anisotropy, AF$_{FT}$ = fronto-temporal arcuate fasciculus, CC = corpus callosum
^{a} To assist in the interpretation of the results, the composite score of phonological awareness was transferred to effect sizes relative to the mean and standard deviation of the FRD$^-$ group

Table II. Pearson correlations between FA values of Diffusion Tensor Imaging [DTI (FA)], FA values of Spherical Deconvolution [SD (FA)] and the HMOA index of Spherical Deconvolution [SD (HMOA)], derived from a region hosting few and a region hosting multiple fiber crossings.
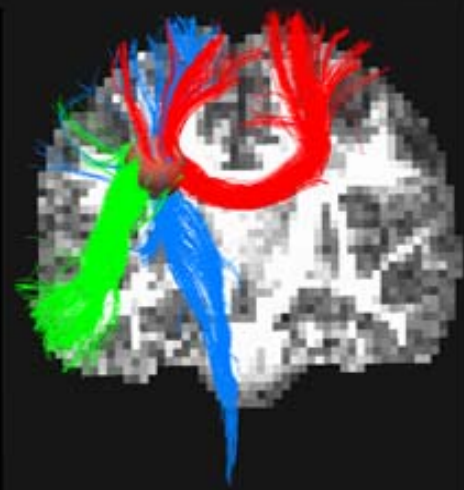
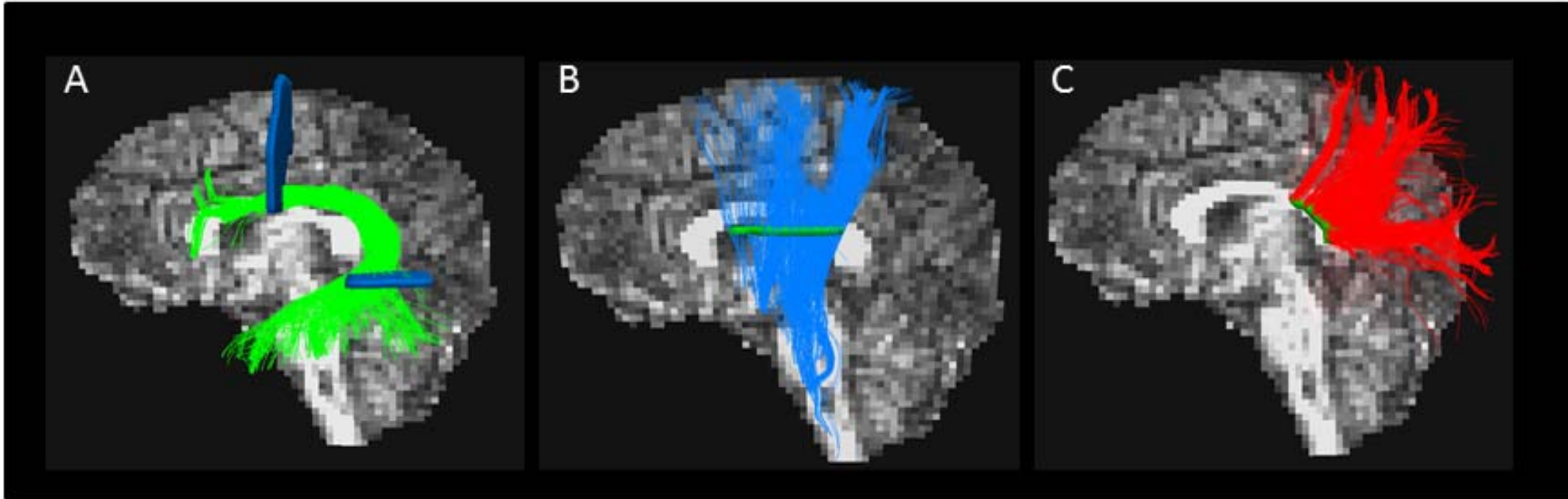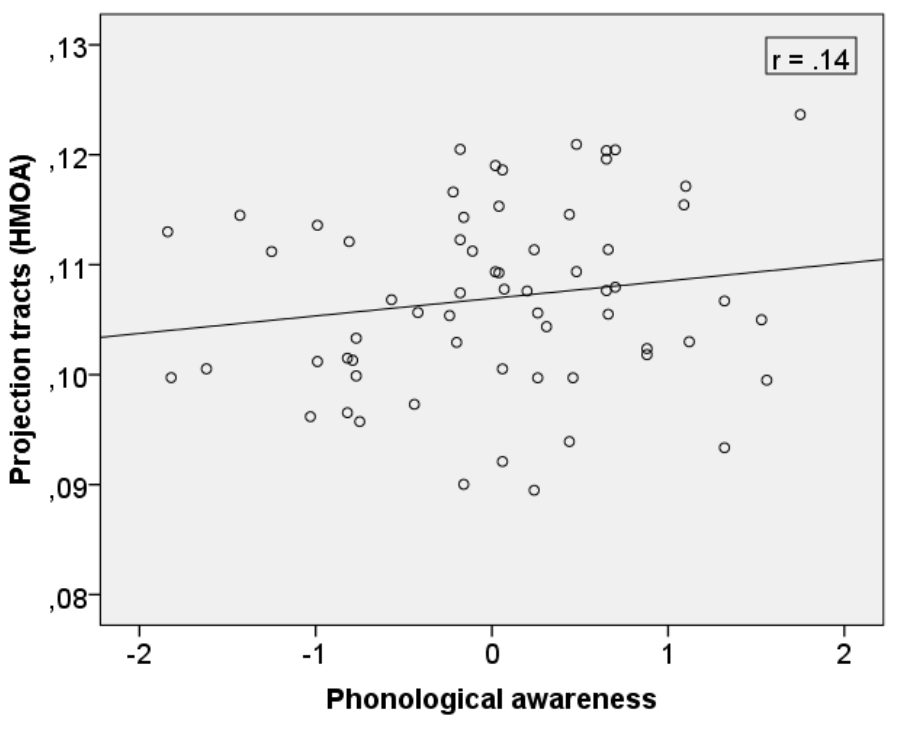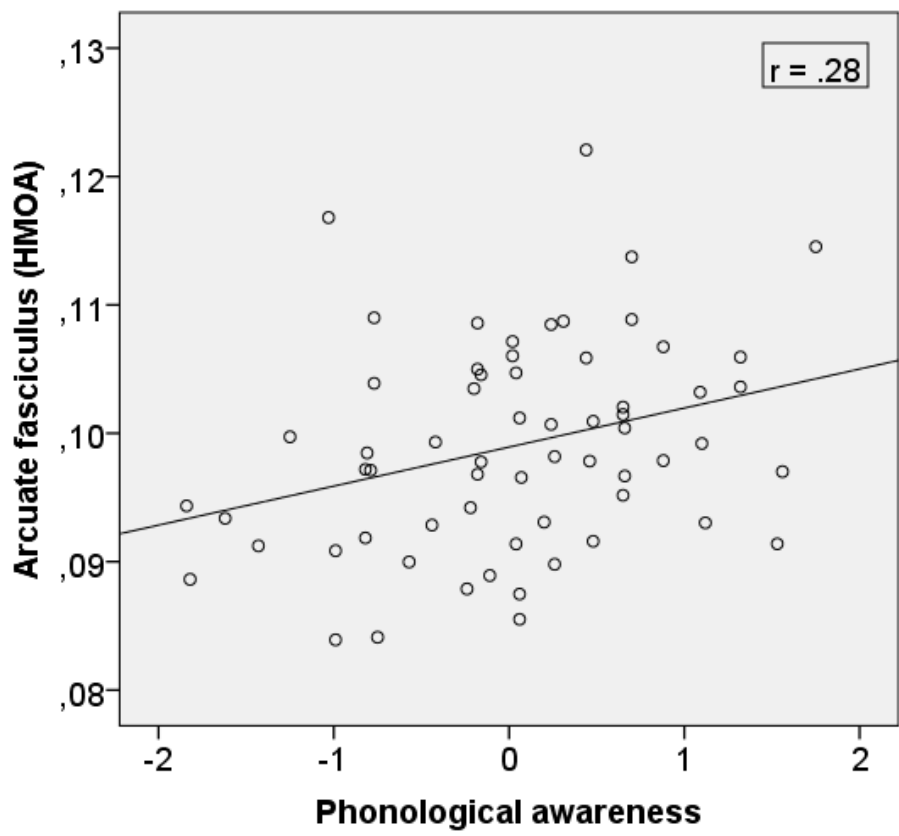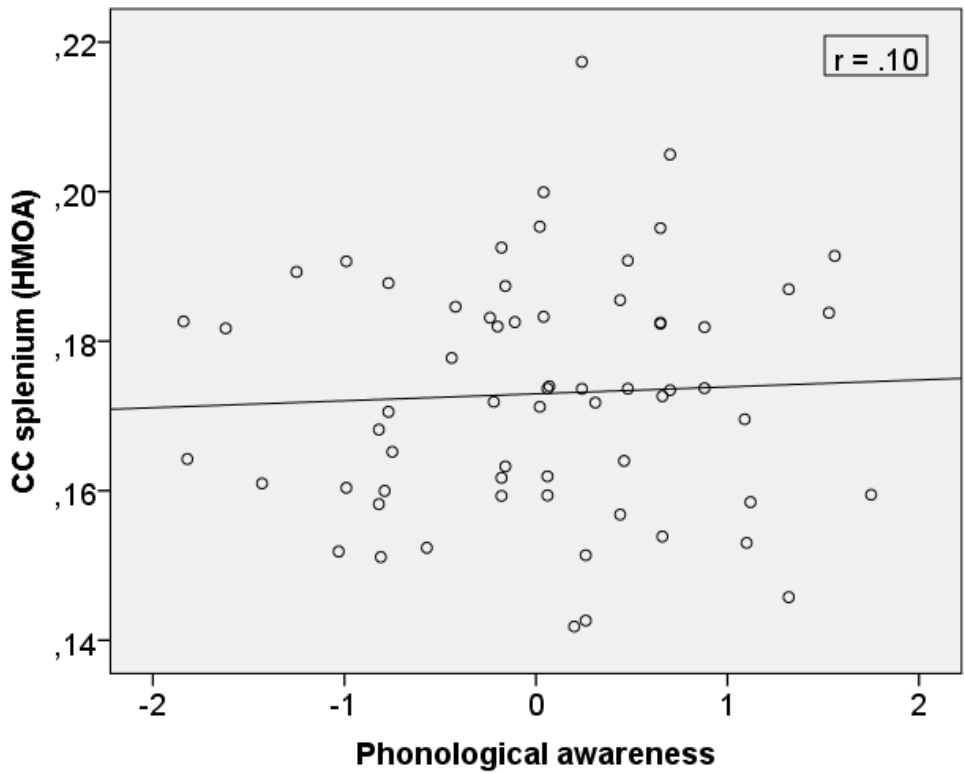|	ROI with few crossings	ROI with multiple crossings	Fisher z test
DTI (FA) * SD (FA)	.88**	.67**	z = 3.09; *p* < .01
DTI (FA) * SD (HMOA)	.80**	.57**	z = 2.44; *p* = .01
SD (FA) * SD (HMOA)	.76**	.83**	z = 0.99; *p* = .32

**p ≤ .01; *p < .05

Figure 3. Scatterplots of the relation between phonological awareness and HMOA (SD tractography) of the intra-hemispheric, inter-hemispheric and projections pathways.