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White Matter Abnormalities and Impaired Attention Abilities in Children Born Very Preterm

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Abstract

While attention impairments are commonly observed in very preterm (<32 weeks' gestational age) children, neuroanatomical correlates of these difficulties are unclear. We aimed to determine whether the microstructural organization of key white matter tracts thought to be involved in attention (cingulum bundle, superior longitudinal fasciculi, reticular activating system, and corpus callosum) were altered in very preterm children compared with term-born controls. We also aimed to determine whether alterations in microstructural organization of these tracts were associated with attention functioning in very preterm children. One hundred and forty-nine very preterm children and 36 term-born controls underwent neuroimaging and assessment of their attention abilities at 7 years. Constrained spherical deconvolution and probabilistic tractography was used to identify the key white matter tracts. Altered microstructural organization and reduced tract volume within reticular activating system and corpus callosum were found in the very preterm group compared with the control group. Diffusion and volume changes in the cingulum bundle, superior longitudinal fasciculi, reticular activating system, and corpus callosum were related to variations in attention functioning in the very preterm children. These findings emphasize that white matter tract integrity is associated with later attentional abilities in very preterm children.

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Keywords

Very preterm; attention; magnetic resonance imaging; diffusion-weighted imaging; white matter injury

1.1 Introduction

While children born very preterm (VPT) are at increased risk of a spectrum of medical, neurological, cognitive, and behavioral disorders (Bhutta *et al.*, 2002, Arpino *et al.*, 2005, Aylward, 2005), attention problems are arguably the most commonly reported concern of both caregivers and teachers (Anderson *et al.*, 2011). As attention is an elementary ability from which other more complex cognitive abilities develop (Anderson *et al.*, 2001, Rose *et al.*, 2011), it is imperative that children who are at risk of developing attention difficulties are identified to enable early intervention that may reduce the impact of attention dysfunction on the other cognitive systems.

VPT children exhibit impaired basic attentional skills, such as orienting (i.e., focusing attention to relevant stimuli) and alerting (i.e., acquiring and maintaining an alert state), compared with term-born controls (van de Weijer-Bergsma *et al.*, 2008, Mulder *et al.*, 2009). They also demonstrate difficulties with more complex attentional processes, such as shifting (i.e. attentional flexibility) (Bayless and Stevenson, 2007, Aarnoudse-Moens *et al.*, 2009, Mulder *et al.*, 2011, Murray *et al.*, 2014) and divided attention (i.e. multi-tasking ability) (Murray *et al.*, 2014). The increased prevalence of attention problems in the VPT population may occur as a consequence of early structural damage to the brain. Between 20 to 40 weeks of gestation the CNS undergoes substantial formative change (Volpe, 2008), thus rendering infants born preterm vulnerable to brain injury. The immature vascular system of the preterm neonate makes their brains highly susceptible to injuries such as hemorrhage, hypoxia/ischemia, excitotoxicity, oxidative stress, and inflammation (Leviton *et al.*, 2013, Raybaud *et al.*, 2013).

White matter injury is the most common neuropathology associated with preterm birth (Volpe, 2009). In addition to the approximately 10% of infants with focal cystic and punctate lesions, MRI studies show evidence of diffuse white matter injury in approximately 50% of VPT infants (Inder *et al.*, 2003, Miller *et al.*, 2005, Cheong *et al.*, 2009). Such injury leads to a reduction in mature myelin producing cells leading to impairment in myelination and axonal development (Boardman and Dyet, 2007, Volpe, 2009). As a consequence, white matter development can be atypical in the preterm brain, with abnormalities most commonly occurring within bilateral frontal, parietal and temporal regions (Ment *et al.*, 2009). Our group and others have reported that white matter abnormality on neonatal MRI is predictive of later cognitive functioning (Woodward *et al.*, 2006, Woodward *et al.*, 2012, Omizzolo *et al.*, 2014), including attention (Murray *et al.*, 2014).

Considering the high prevalence of both white matter injury on neonatal neuroimaging and attentional difficulties in the VPT population, an exploration of white matter tracts thought to be related to attention is worthy of investigation. White matter can be examined using diffusion-weighted MRI (dMRI), a technique which models water diffusion properties and

provides several key parameters that offer information regarding white matter microstructural organization. Fractional anisotropy (FA) is the metric used to determine the proportion of directional diffusion existing within a voxel (Pierpaoli and Basser, 1996). Mean diffusivity (MD) reflects the magnitude of overall diffusion within each voxel. In order to obtain additional microstructural information, the axial diffusivity (diffusion along the prominent diffusion orientation; AD) and radial diffusivity (diffusion perpendicular to the prominent diffusion orientation; RD) parameters can also be investigated.

While the literature on dMRI and prematurity is limited, some studies have found reduced fractional anisotropy (Anjari *et al.*, 2007) and increased axial, radial, and mean diffusivity in the white matter of VPT infants, children and adolescents compared with term-born controls (Bonifacio *et al.*, 2010, Feldman *et al.*, 2012, Thompson *et al.*, 2014). Studies also show abnormal microstructural organization in a number of white matter pathways in the preterm brain, including the internal capsule, external capsule, inferior fronto-occipital fasciculus, uncinate fasciculus, superior longitudinal fasciculus, inferior longitudinal fasciculus, centrum semiovale (Nagy *et al.*, 2003, Skranes *et al.*, 2007, Constable *et al.*, 2008, Mullen *et al.*, 2011, Jo *et al.*, 2012, Lee *et al.*, 2013, Groeschel *et al.*, 2014), and corpus callosum (Thompson *et al.*, 2014), which has previously been reported for the current cohort. dMRI studies exploring structure-function associations in preterm cohorts have found that alterations in white matter microstructure are related to motor deficits (Skranes *et al.*, 2007, Counsell *et al.*, 2008, Rose *et al.*, 2009, Thompson *et al.*, 2012, van Kooij *et al.*, 2012, Northam *et al.*, 2012), neurosensory impairments (Bassi *et al.*, 2008, Berman *et al.*, 2009, Reiman *et al.*, 2009, Glass *et al.*, 2010, Groppo *et al.*, 2014), and behavioral dysfunction (Nagy *et al.*, 2003, Skranes *et al.*, 2007, Rogers *et al.*, 2012). Altered microstructural organization has also been associated with general cognitive ability (Skranes *et al.*, 2007, Counsell *et al.*, 2008, Allin *et al.*, 2011, van Kooij *et al.*, 2012), language (Northam et al., 2012), memory (Allin et al., 2011), and executive functioning (Skranes et al., 2009).

While the *functional networks* of attention are well-established (Petersen and Posner, 2012), few studies have investigated the *structural networks* (i.e., white matter tracts) involved in attention, and most of the published studies have reported on neurotypical or adult populations. Such studies have demonstrated a link between orienting performance and the superior longitudinal fasciculus and corpus callosum (Niogi *et al.*, 2010, de Schotten *et al.*, 2011, Bennett *et al.*, 2012), and alerting performance and the right superior longitudinal fasciculus and corpus callosum (Mabbott *et al.*, 2006, Takahashi *et al.*, 2010, Klarborg *et al.*, 2013). Complex attention processes (i.e., shifting and divided attention) have been associated with the cingulum bundle, superior longitudinal fasciculus and corpus callosum (Schulte *et al.*, 2008, Kubicki *et al.*, 2009, Salo *et al.*, 2009, Takei *et al.*, 2009, Schulte *et al.*, 2012, Lebel *et al.*, 2013, Peters *et al.*, 2014).

A fiber pathway known as the reticular activating system is also believed to play a key role in attention. The reticular activating system is made up of various source nuclei in the brainstem responsible for arousal, such as the serotoninergic raphe nuclei (Azmitia and Gannon, 1986), the noradrenergic locus coeruleus (Aston-Jones and Cohen, 2005), and the cholinergic pedunculo-pontine nucleus and laterodorsal tegmental nucleus (Jones, 2004). While the reticular activating system has been identified many times in the animal brain

(Moruzzi and Magoun, 1949, Glenn and Steriade, 1982, Steriade and Glenn, 1982, Steriade *et al.*, 1982), it is difficult to identify in the human brain due to a number of methodological barriers, such as insufficient resolution on conventional MRI to identify the source nuclei, and lack of angular resolution on diffusion tensor MRI to identify its prominent crossing fibers. To date, only one study has detailed the this tract using high angular resolution diffusion imaging, and images were obtained using a high field 4.7 Tesla MRI scanner (Edlow *et al.*, 2012).

In summary, the attention dysfunction typically observed in preterm populations may be explained, at least in part, by alterations in the white matter microstructure of the cingulum bundle, superior longitudinal fasciculus, reticular activating system and corpus callosum, and examination of these tracts in VPT children is needed. Thus, we have studied the relationship between the microstructural organization of these tracts and four aspects of attention functioning in VPT 7 year-olds. We hypothesized that VPT children would display less mature microstructural organization of attention tracts compared with controls, and among VPT children, microstructural organization of these tracts would relate to attention performance.

1.2 Materials and methods

1.2.1 Participants

Participants were prospectively recruited from the Victorian Infant Brain Studies (VIBeS) cohort, which is a group of 224 VPT infants who were born at the Royal Women's Hospital, Melbourne, Australia, between July 2001 and December 2003 with a gestational age of <30 weeks' or a birth weight of <1250 g. Infants with genetic or congenital abnormalities were excluded from the cohort. A group of 46 term (37 to 42 weeks' gestational age) and normal birth weight (≥2500 g) infants were recruited from the Royal Women's Hospital at birth. Previous follow-up assessments have been performed at ages 2 and 5 years, corrected for prematurity (Thompson *et al.*, 2005, Roberts *et al.*, 2011, Treyvaud *et al.*, 2012). For this study, neuroimaging and neuropsychological data from 149 VPT children (67% of the original 224 VPT infants) and 36 term-born children (78% of the 46 term controls at term-equivalent age) were obtained at age 7 years, corrected for prematurity. Reasons for exclusion from this study included failure of the mock MRI training session, non-consent to the MRI only, study withdrawal, time restrictions, refusal, too impaired, contraindications to MRI, as well as loss to follow-up. The study was approved by the Human Research Ethics Committees of the Royal Women's Hospital and the Royal Children's Hospital, Melbourne, Australia, and parents provided written informed consent for their child to participate.

1.2.2 Neuropsychological assessment

At the 7-year time point a detailed neuropsychological assessment was administered. To assess attention functioning the four core subtests from the Test of Everyday Attention for Children (TEA-Ch) were administered (Sky Search, Score!, Creature Counting, and Sky Search Dual Task [DT]). The TEA-Ch is an age-sex standardized test battery with good psychometric properties, which is used extensively in clinical and research setting to assess different attention domains (Manly *et al.*, 2001). Orienting performance, as measured using

Sky Search, was determined by the number of correctly identified targets (maximum = 20). Alerting and shifting abilities, measured using the Score! and Creature Counting subtests respectively, were determined by the number of correct trials (maximum = 10 and maximum = 7 respectively). Divided attention performance, as measured by Sky Search DT, was scored using the following calculation previously described by Anderson et al. (2011): [(number of counting games correct/number of counting games attempted)/2 + (number of correct targets found/maximum targets)/2] × 100 (maximum = 100).

Social risk was assessed using a composite scale (Roberts *et al.*, 2008) that assesses 6 factors (family structure, education of primary caregiver, occupation and employment status of primary income earner, language spoken at home, and maternal age when the child was born). Each factor is scored on a three-point scale where 0 represented lowest risk and 2 represented highest risk, summed to produce a score ranging from 0 to 12.

1.2.3 Magnetic resonance imaging acquisition

Neuroimaging data were obtained using a 3 Tesla MRI scanner (Siemens Magnetom Trio Tim system) at the Royal Children's Hospital. Structural sequences were obtained. Sagittal three-dimensional rapid gradient-echo T_1-weighted imaging parameters were as follows: T_R = 1900 ms, T_E = 2.27 ms, matrix = 256 × 256, field of view = 210 × 210 mm, isotropic voxels = 0.8 mm^3, and bandwidth = 200 Hz/Px. Parameters for sagittal three-dimensional turbo spin-echo T_2-weighted images were as follows: T_R = 3200 ms, T_E = 447 ms, matrix = 256 × 230, field of view = 240 × 215 mm, isotropic voxels = 0.9 mm^3, and bandwidth = 610 Hz/Px. Two echo planar diffusion-weighted sequences were also obtained, one with a *b*-value of 1200 s/mm^2 and the other with a *b*-value of 3000 s/mm^2. The first diffusion protocol parameters were as follow: T_R = 12000 ms, T_E = 96 ms, matrix = 144 × 144, field of view = 250 × 250 mm, isotropic voxels = 1.7 mm^3, one image with *b*-value = 0 s/mm^2, and 25 gradient directions with *b*-values up to 1200 s/mm^2. The second diffusion protocol parameters were as follows: axial slices, T_R = 7600 ms, T_E = 110 ms, matrix = 104 × 104, field of view = 240 × 240 mm, isotropic voxels = 2.3 mm^3, six images with *b*-value = 0 s/mm^2, and 45 gradient directions with *b*-value = 3000 s/mm^2.

1.2.4 Diffusion weighted imaging tractography

Fiber tracking was performed using MRtrix version 0.2.10 (Tournier, 2010). This software uses constrained spherical deconvolution (CSD) and probabilistic tractography to estimate white matter tracts in a manner that is robust to crossing fibers (Tournier *et al.*, 2007). The data with a *b*-value of 3000s/mm^2 were utilized for tractography, as recommended due to its better ability to resolve fiber orientation distributions than lower *b*-value data (Tournier *et al.*, 2004, Tournier *et al.*, 2007). Brain masks were first created to remove non-brain matter. To perform the CSD, the response function coefficient was estimated from voxels with fractional anisotropy over 0.6, assumed to have single-fiber orientations. A maximum harmonic order of 6 was used for the CSD (Tournier *et al.*, 2004). In order to reconstruct the white matter tracts, regions of interest (ROI) were manually defined on each subjects' image in native space, in relation to anatomical landmarks which were used to determine where the tracking was initialized and which regions it passed through. Structural maps registered to

the diffusion images were used in conjunction with the color-coded eigenvector maps to assist in identifying and defining the ROIs.

To identify the left and right cingulum bundle, anterior and posterior ROIs were drawn on the coronal slices passing through the mid-genu and mid-splenium of the corpus callosum (Wahl *et al.*, 2010, Lin *et al.*, 2011) (Fig. 1).

To identify the left and right superior longitudinal fasciculus, anterior ROIs were selected in each hemisphere on a coronal slice just lateral to the superior-inferior fibers of the corona radiata (Shinoura *et al.*, 2009, Barre *et al.*, 2011, Galantucci *et al.*, 2011, Wilson *et al.*, 2011). Posterior ROIs, also drawn on the coronal slice, included the entire parietal lobe of each hemisphere at the point where the posterior commissure is visible on the structural T1-weighted scan (de Schotten *et al.*, 2011) (Fig. 2).

Identification of the reticular activating system was largely experimental and involved multiple inclusion and exclusion ROIs. An inferior ROI was placed at the most inferior point of the midbrain tegmentum on the axial plane of the structural T1 scan (see Fig. 3 left panel). A superior ROI was traced over the thalamic nuclei on the coronal plane. While the reticular nucleus, the central lateral nucleus and the centromedian/parafascicular nuclear complex are all involved in attention, only the latter nuclear complex could be visualized on our scans thus the superior ROI only encompasses this thalamic nuclear complex (see Fig. 3 middle panel). A third ROI was placed at the most inferior point of the pons on the axial plane to standardize the length of the tract across all participants (see Fig. 3 right panel). Exclusion ROIs were placed over the superior cerebellar peduncles, cerebral peduncles, and ventral nuclei of the thalamus (i.e., ventroposterior medial and lateral nuclei and ventroanterior nuclei) to exclude all fibers running within close neuroanatomical proximity to the reticular activating system. The exclusion ROIs removed the following fiber bundles: superior cerebellar, middle cerebellar, corticospinal, medial/spinal lemnisci, and ventral trigeminothalamic fibers (Edlow *et al.*, 2012). The medial longitudinal fasciculus could not be excluded because of insufficient resolution (Sakaie *et al.*, 2011). It is important to note that the reticular activating system is a complex and diffuse structure and only those fibers travelling through the thalamic nuclei visible on the scans were included in this tract.

Finally, to identify the corpus callosum a single ROI was traced on the mid-sagittal slice of the structural T1 scan and overlaid on the diffusion image as previously reported (Thompson *et al.*, 2014) (Fig. 4).

Probabilistic tractography using the CSD map was conducted, identifying 1000 streamlines per tract (see Fig. 5). A threshold of 0.005 was then applied to the tracts to eliminate any streamlines that were unlikely to be part of the tract (i.e. voxels containing fewer than 5/1000 streamlines were removed).

1.2.5 Fiber tract diffusion tensor measures

Diffusion tensor measures were obtained from the *b*=1200 diffusion data, processed using the Explore DTI software (http://www.ExploreDTI.com). Residual maps were created to check that no images or slices had any major outlier voxels. Motion and eddy current

correction was conducted using the *b*=0 diffusion image as a reference (Leemans and Jones, 2009). The diffusion tensor model was fitted using weighted linear least squares, generating diffusion maps (Veraart *et al.*, 2013).

To obtain the diffusion values for each tract, the b=1200 diffusion images were co-registered to the b=3000 diffusion images using FSL's linear registration tool (Jenkinson and Smith, 2001), to account for any movement between acquisitions. The co-registered diffusion maps were then multiplied by the binary thresholded tract volume to obtain a single measure of fractional anisotropy, axial, radial, and mean diffusivity for each tract. Measures of tract volume were also obtained by multiplying the number of voxels in the binary thresholded tract by the voxel size. All tracts were examined qualitatively via visual inspection, and 4 participants were excluded due to artifacts interfering with successful tracking (e.g., significant movement and/or signal dropout). Tracking was redone in a blinded manner using 20 participants to check intra-rater reliability. Intraclass correlations were above .90 for all diffusion parameters and above .80 for volumes.

1.2.6 Statistical analysis

Data were analyzed using Stata 12.0 (StataCorp, 2011). Differences between the VPT and term groups on demographic and perinatal characteristics were analyzed using simple linear regressions or Mann-Whitney U tests for continuous variables, and χ^2 analyses or Fisher exact tests for categorical variables. To determine whether the microstructural organization of the attention tracts differed between the VPT and term-born children, independent multivariate linear regressions were run for each MRI parameter each tract. Results are presented as mean differences with 95% confidence intervals (CIs), adjusted for age at scan, and additionally intracranial volume (ICV) for analyses involving tract volume. To determine whether alterations in the microstructural organization of the attention tracts was related to attention functioning in the VPT children, associations between the 7-year MRI parameters and attention outcomes were assessed using independent multivariable regression models for each outcome-predictor (attention variable-MRI variable) combination. Results are presented in terms of the estimate of regression coefficient (i.e., the slope of the change in the dependent variable as a function of a one-unit increase in the independent variable) with 95% CIs, adjusted for age at scan, and additionally ICV for analyses involving tract volume. The Huber/White/Sandwich method was used to account for the large proportion of twins and triplets in the VPT sample (48%) (Carlin *et al.*, 2005). The issue of multiple comparisons was considered given the large number of regressions run. Bonferroni corrections were not applied, however, as the comparisons are not independent: the attention outcomes are dependent on one another as are the MRI parameters (Tabachnick and Fidell, 2007). Regression results were instead interpreted with caution, identifying overall patterns and magnitudes of differences, rather than focusing on individual p-values, according to modern statistical practice (Kirkwood and Sterne, 2003).

1.3 Results

1.3.1 Sample characteristics

The characteristics of the VPT and term groups at birth and 7 years are presented in Table 1. As expected, the VPT group differed from the term group on a number of perinatal medical variables, such as longer hospital stays, lower Apgar scores, greater episodes of sepsis, and greater percentages of patent ductus arteriosus, bronchopulmonary dysplasia, and exposure to antenatal corticosteroids. While very few of the VPT group had cystic periventricular leukomalacia or Grade III/IV intraventricular hemorrhage, a large proportion had white matter abnormalities on neonatal MRI compared with the term group. Overall, the VPT group also had a lower proportion of singletons, and worse cognitive development at 2 years of age compared with the term group. At 7 years, the VPT group had lower IQ, smaller overall ICVs, and greater social risk compared with term controls. Importantly, the VPT group performed more poorly than term-born controls across all measures of attention, and significantly so for orienting, shifting and divided attention (Murray *et al.*, 2014). The group differences ranged from 0.4 to 1.1 SD, indicating group differences of clinical relevance.

1.3.2 Group differences on diffusion parameters and volumes at 7 years

Mean differences between the VPT and term-born children in diffusion parameters and volumes for each tract are presented in Fig. 6. For diffusion values, axial, radial, and mean diffusivity of the reticular activating system and radial diffusivity of the corpus callosum were significantly greater in the VPT children compared with the term controls. Fractional anisotropy values of the corpus callosum were significantly reduced in the VPT group compared with the term group. Significant volume reductions were also found in the reticular activating system of the VPT children compared with the term children. No clear group differences were observed for the other tracts.

1.3.3 Structure-function relationships in VPT children

There was evidence for associations between poorer orienting performance (i.e., Sky Search) and reduced fractional anisotropy and increased radial diffusivity in the left cingulum. Poorer performance on the orienting task was also associated with decreased fractional anisotropy in the corpus callosum and reduced volume in the reticular activating system (Fig. 7A). For alerting (i.e., Score!), poorer performance was associated with reduced fractional anisotropy and increased radial diffusivity in the left cingulum. There was also evidence that impaired alerting performance was associated with reduced fractional anisotropy in the right superior longitudinal fasciculus (Fig. 7B). There were no clear associations between shifting performance (i.e., Creature Counting) and tract measures (Fig. 7C). Poorer divided attention performance (i.e., Sky Search DT) was associated with reduced fractional anisotropy and increased radial diffusivity in the left cingulum and reduced fractional anisotropy in the left superior longitudinal fasciculus (Fig. 7D). There were no associations between any of the attention outcomes and either axial or mean diffusivity (data not shown).

1.4 Discussion

This study aimed to assess the integrity of attention tracts in VPT children compared with term-born children at 7 years, and the association between the microstructural organization of these tracts and attention functioning in VPT children. Compared to term children, our VPT group had reduced volumes and increased diffusivity in the reticular activating system, together with reduced fractional anisotropy and increased radial diffusivity in the corpus callosum. In the VPT group, attention performance was mostly associated with microstructural organization of the left cingulum bundle. These findings help us to understand vulnerable white matter pathways in VPT children, and infer that the cingulum bundle is important for attention functioning in VPT children.

In the typically developing brain, white matter volume and fractional anisotropy increase over development (Brouwer *et al.*, 2012), while axial, radial, and mean diffusivity decrease with time (Mukherjee and McKinstry, 2006). In our VPT sample we observed greater diffusion and reduced volume, indicating there may be either impairment or delayed development in the white matter tracts of the VPT brain. These findings are consistent with other studies of preterm cohorts that have reported altered microstructural organization in numerous white matter tracts, compared with term-born controls (Nagy *et al.*, 2003, Skranes *et al.*, 2007, Constable *et al.*, 2008, Mullen *et al.*, 2011, Jo *et al.*, 2012, Lee *et al.*, 2013).

In relation to attention functioning, orienting attention was associated with the left cingulum bundle, reticular activating system, and weakly associated with the corpus callosum; alerting performance was associated with the left cingulum bundle and right superior longitudinal fasciculus; and divided attention performance was associated with the left cingulum bundle and weakly associated with the left superior longitudinal fasciculus. The cingulum bundle, superior longitudinal fasciculus, and corpus callosum have previously been found to be associated with attention in a number of populations, including typically developing children (Klarborg *et al.*, 2013), adolescents (Mabbott *et al.*, 2006), and adults (Bennett *et al.*, 2012, Peters *et al.*, 2014); however, no previous study has identified an association between the reticular activating system and attention functioning in a human sample. This study used a novel segmentation protocol to identify the reticular activating system, which has not been validated, thus this relationship should be interpreted with some caution.

The specific structure-function associations found in this study were slightly different to those previously reported in the literature. These differences are likely to exist for a number of reasons. The first is that each attention test relies on a slightly different set of abilities and consequently recruits a unique set of brain regions (Mulder *et al.*, 2009). The structure-function association found in any particular study will thus be largely dependent on the task used to measure attention. The second reason for the differences may be that many structure-function associations have been defined in healthy and/or adult brains, not in developing, injured brains. In the younger brain, connectivity is undergoing substantial structural change. After initial establishment of white matter connections, a dynamic process of pruning allows the developing brain to reconfigure and ultimately resemble the mature brain (Supekar *et al.*, 2009). In the injured brain, functions are likely to recruit alternative pathways if damage or structural anomalies prevent the use of more typically engaged

networks. Finally, due to the relatively small magnitude of the effect for our structure-function relationships and the issue of multiple comparisons, we consider our results to be exploratory, requiring replication by other studies.

An interesting and novel finding was that the left cingulum bundle was associated with reduced performance across multiple domains of attention in the VPT children. Previous studies have also shown that the default mode network (DMN), the functional network underlying the cingulum (Greicius *et al.*, 2009, Teipel *et al.*, 2010), plays a key role in attention functioning, particularly in the 'tuning' of our attentional focus (Leech and Sharp, 2013). A number of recent studies have also found that the DMN is particularly susceptible to preterm birth, with studies showing reduced functional connectivity in preterm children compared with controls at 3 years (Damaraju *et al.*, 2010) and in later childhood (Wisnowski *et al.*, 2013). Regions of the brain housing the functional DMN and structural cingulum bundles should be the focus for future research attempting to explain attention difficulties in the preterm population.

While diffusion tensor imaging is an ideal technique when scanning pediatric cohorts due to its relatively short acquisition time, there is still much uncertainty about the relationship between diffusion parameters and underlying microstructural properties (Vos *et al.*, 2011, Vos *et al.*, 2012). The extent to which diffusion is impeded in any one direction is dependent on biological properties of the axons (e.g., axonal density, axon diameter, myelin, membrane permeability) as well as the geometric configuration of the axons (e.g., curvature, coherence and crossing fiber tracts) (Winston, 2012, Jones *et al.*, 2013). Diffusion parameters are sensitive to all of these tissue properties, thus it is largely unknown what diffusion findings mean in terms of white matter microstructure. While other diffusion weighted imaging acquisition techniques exist (e.g., multi tensor models, ball and stick model, composite hindered and restricted model of diffusion, diffusion kurtosis imaging, q-space methods, and diffusion spectrum imaging) (Jones, 2010), each technique is associated with its own advantages and disadvantages. The diffusion tensor imaging technique was chosen in this study because of its relatively short scanning time, which is better tolerated by children.

In this study, the microstructural organization of each attention tract was characterized using single diffusion estimates averaged over the entire tract, which may have obscured our ability to detect additional group differences between the tracts. Future studies should attempt to provide more detailed characterization of the microstructural organization of the tracts associated with attention by looking at localized differences along the pathways, especially the cingulum bundle. Newly available tractography software, such as Automatic Fiber Quantification (AFQ), can be used for this purpose (Yeatman *et al.*, 2012).

In summary, we found that the microstructural organization of tracts associated with attention was altered in VPT children compared with term-born children. We also found that, among VPT children, variations in the microstructural organization of some of these tracts were associated with attention outcomes, particularly within the left cingulum bundle. These findings may indicate that a delay and/or impairment in the development of these tracts may, at least in part, be responsible for the attention dysfunction observed in VPT children.

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Abbreviations

CSD	constrained spherical deconvolution
dMRI	diffusion-weighted MRI
DMN	default mode network
ICV	intracranial volume
ROI	regions of interest
VPT	very preterm

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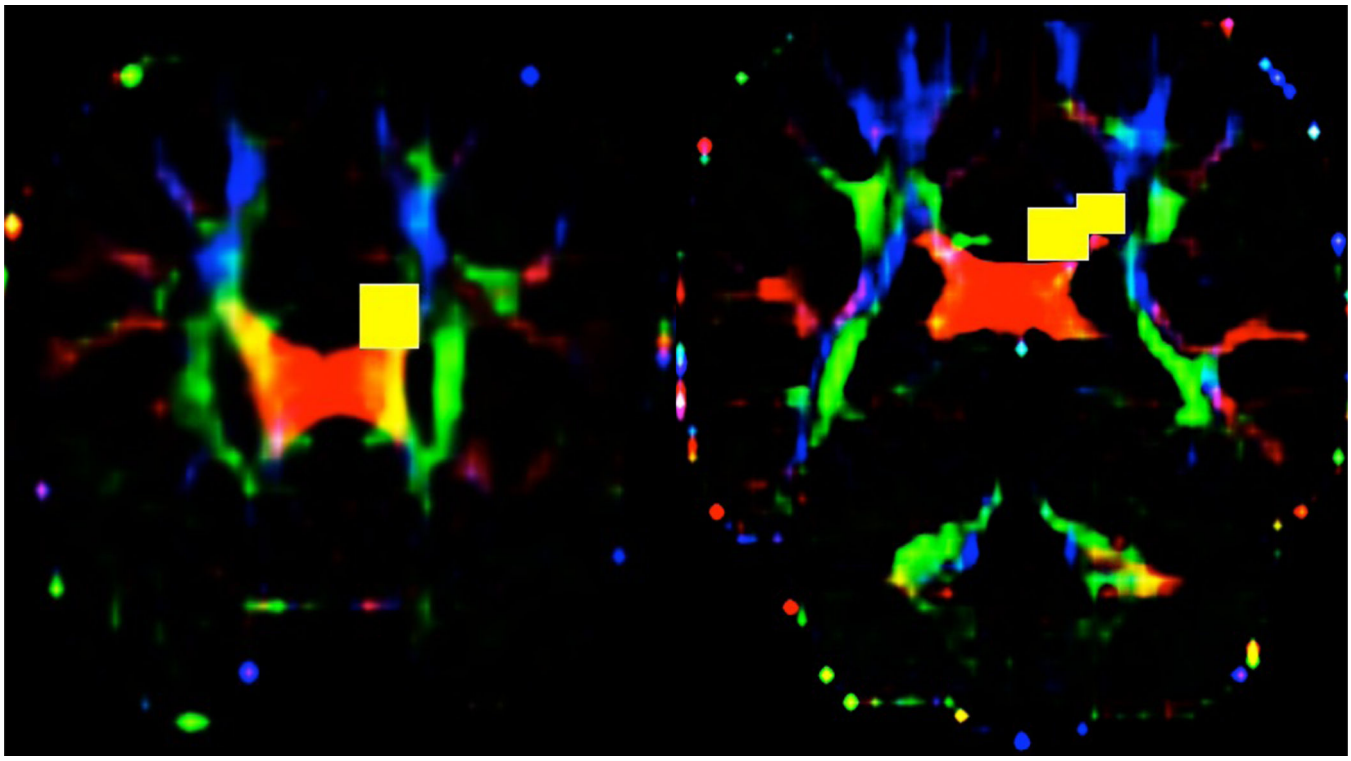

Fig. 1.

Anterior (left) and posterior (right) regions of interest (ROIs) drawn on the coronal plane were used to identify the left and right cingulum bundles. ROIs are presented on color-coded fibre orientation maps: red indicates directions in the X axis (left to right), green indicates directions in the Y axis (anterior to posterior), and blue indicates directions in the Z axis (superior to inferior).

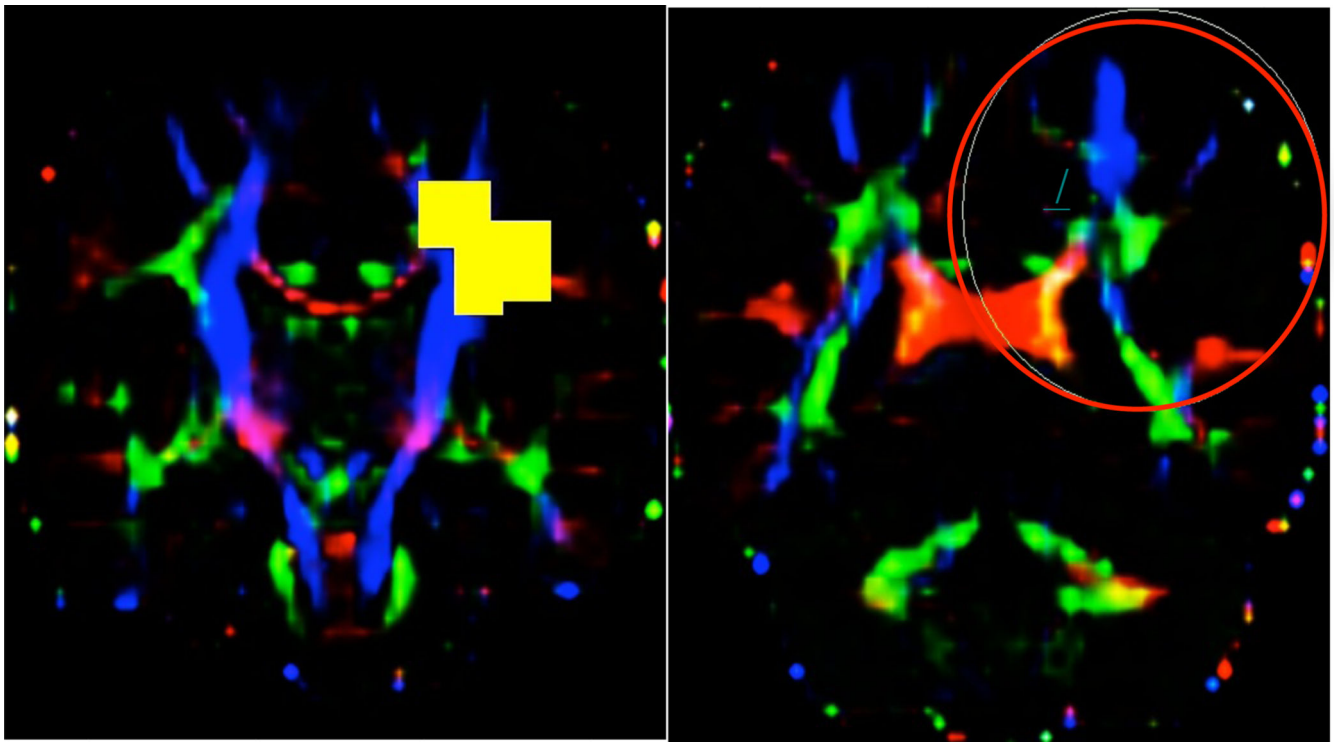

Fig. 2.

Anterior (left) and posterior (right) ROIs drawn on the coronal plane were used to identify the left and right superior longitudinal fasciculus.

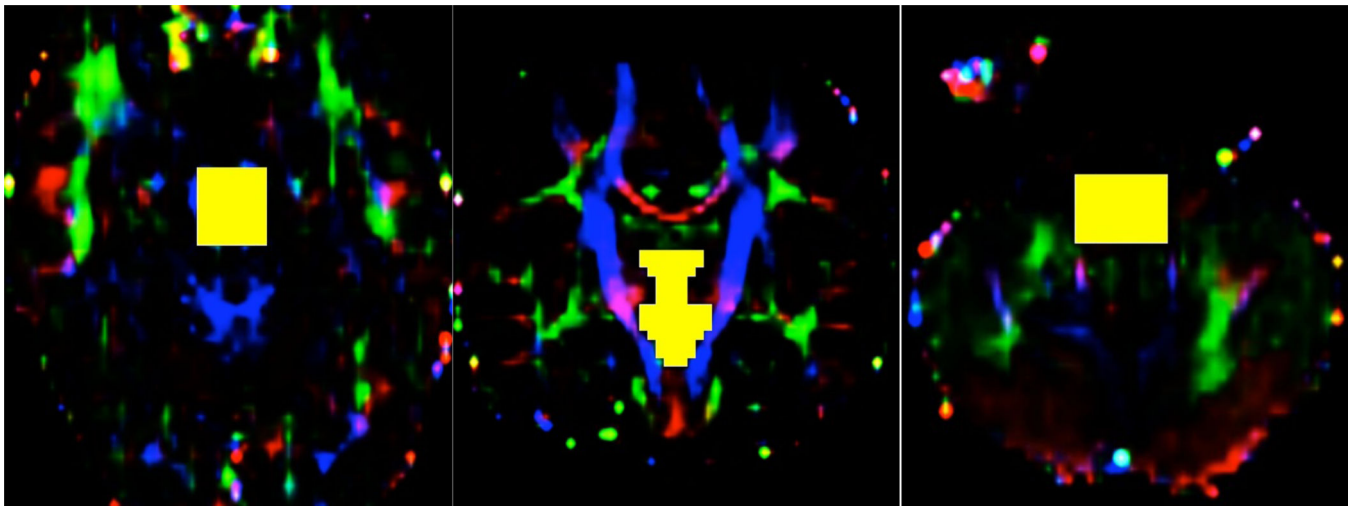

Fig. 3.

An inferior ROI drawn on the axial plane (left), a superior ROI drawn on the coronal plane (middle), and a stop ROI drawn on the axial plane (right) were used to identify the reticular activating system.

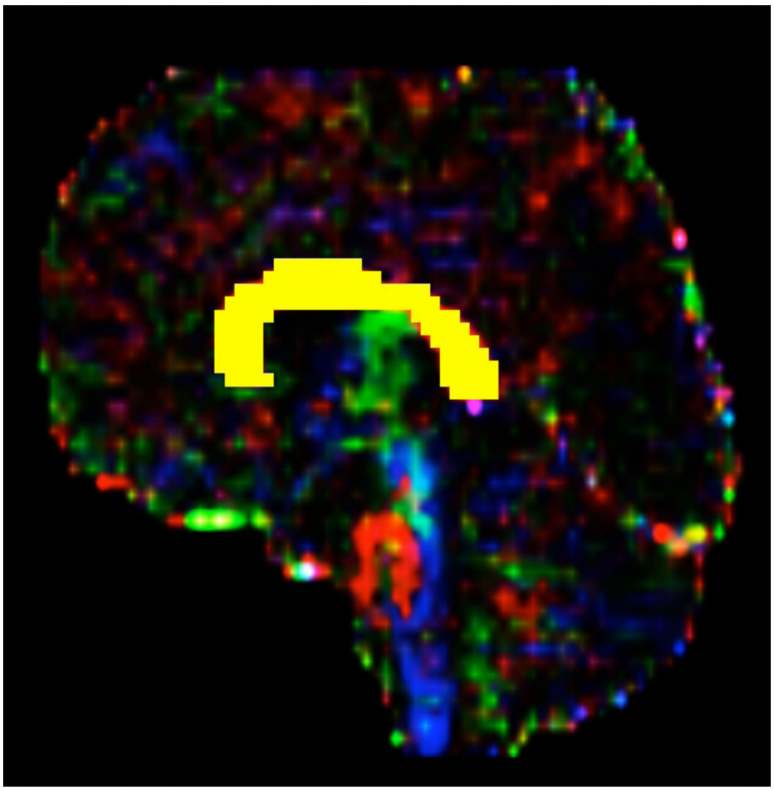

Fig. 4.
A single ROI drawn in the sagittal plane was used to identify the corpus callosum.

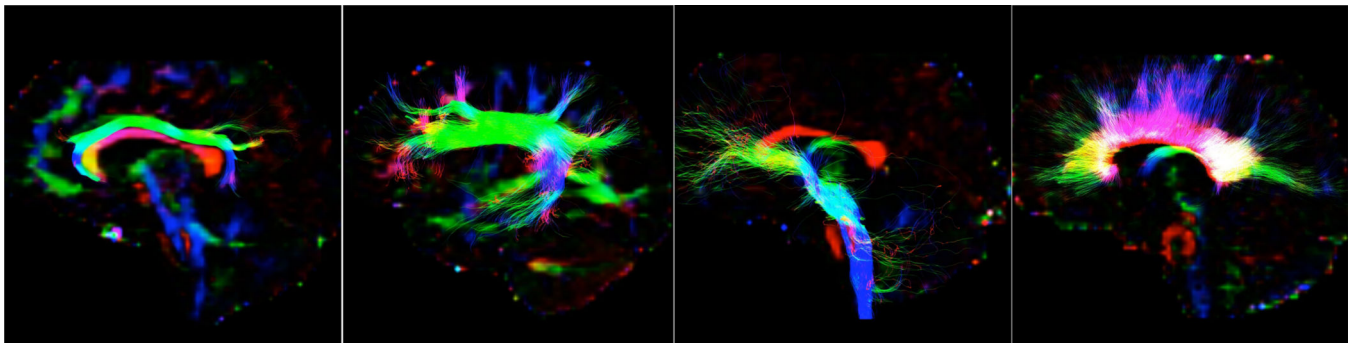

Fig. 5.

Examples of tracts derived by probabilistic tractography using constrained spherical deconvolution (CSD) for the cingulum bundle, superior longitudinal fasciculus, reticular activating system, and corpus callosum (from left to right).

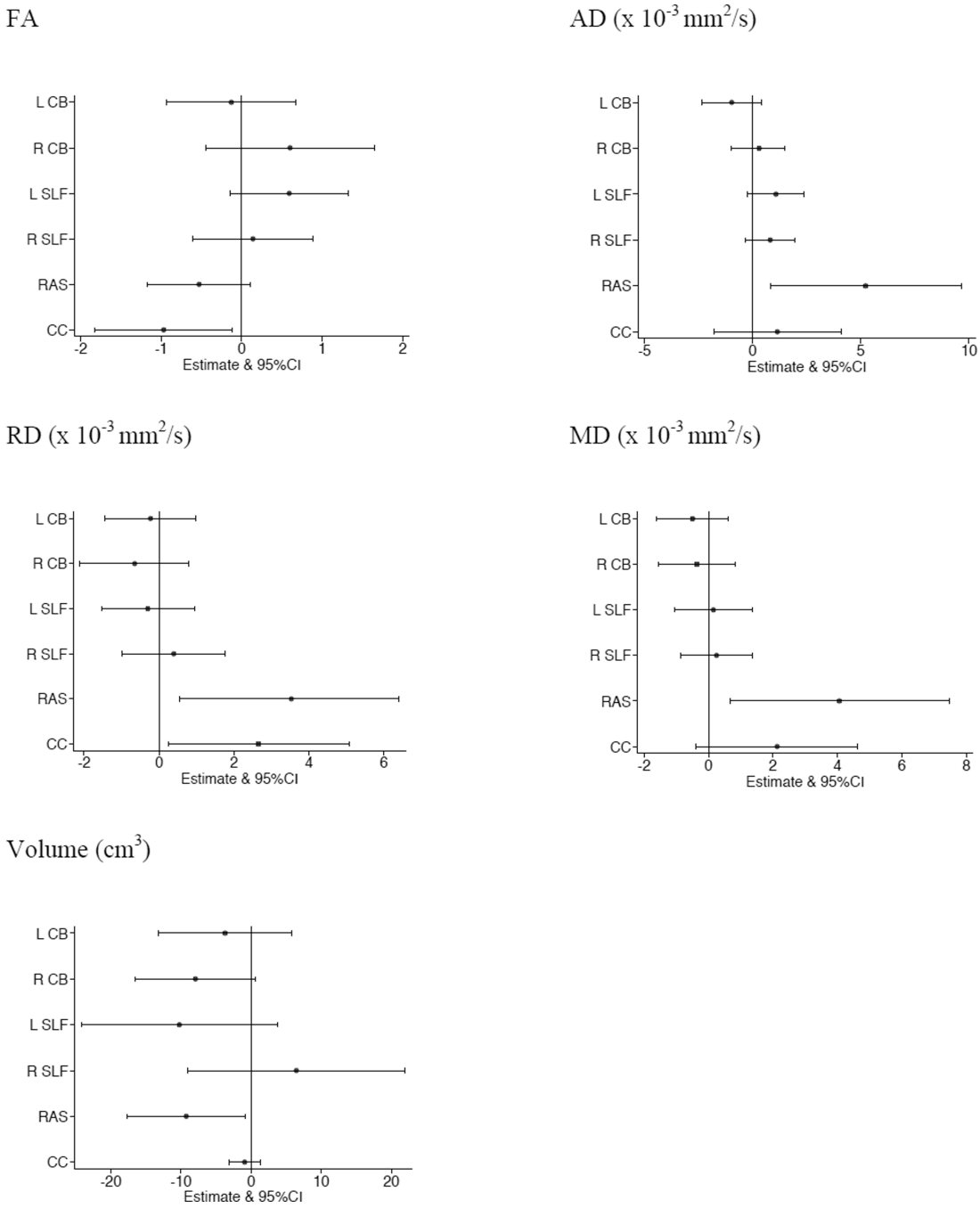

Fig. 6. Group differences between VPT and term children in diffusion parameters and volumes at 7 years

Estimate, estimate of regression coefficient from the linear regression models; CI, confidence intervals; FA, fractional anisotropy; AD, axial diffusivity; RD, radial diffusivity; MD, mean diffusivity; CB, cingulum bundle; SLF, superior longitudinal fasciculus; RAS, reticular activating system; CC, corpus callosum.

Mean differences between diffusion values are age adjusted. Mean differences between tract volumes are age and ICV adjusted.

NB: If the mean difference is statistically significant ($p<.05$), the 95% CI will not cross 0. For FA and volume, if the 95% CI is to the left of 0, the mean is lower in the VPT group than the term group. For AD, RD, and MD, if the 95% CI is to the right of 0, the mean is higher in the VPT group than the term group.

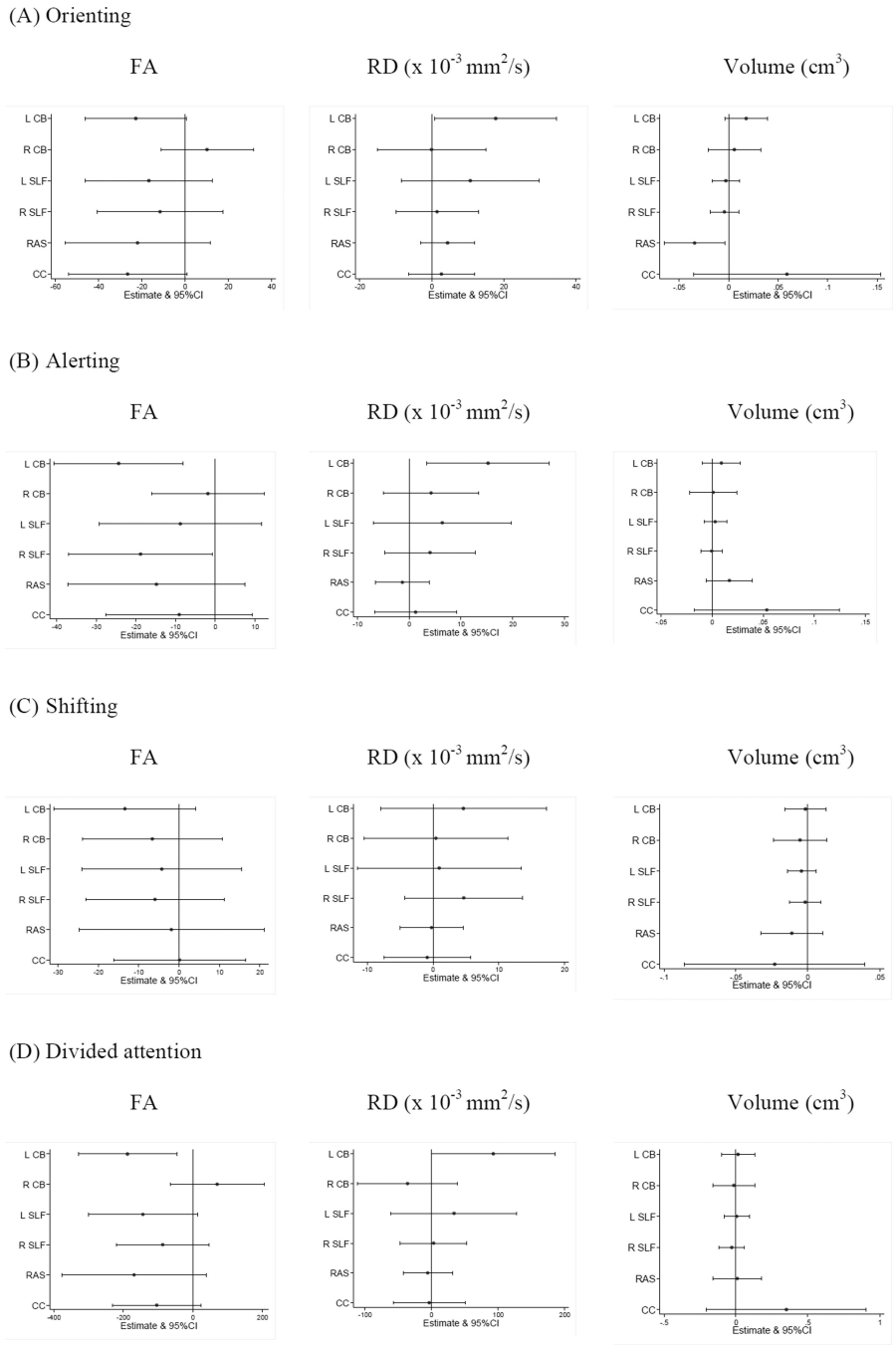

Fig. 7. Associations between tract parameters and attention outcomes at 7 years of age in very preterm (VPT) children- (A) Orienting, (B) Alerting, (C) Shifting, (D) Divided attention

Estimate, estimate of regression coefficient from the linear regression models; CI, confidence intervals; FA, fractional anisotropy; RD, radial diffusivity; CB, cingulum bundle; SLF, superior longitudinal fasciculus; RAS, reticular activating system; CC, corpus callosum.

Association between diffusion values and attention variables are age adjusted. Associations between tract volumes and attention variable are age and ICV adjusted.

NB. If the regression is statistically significant ($p<.05$), the 95% CI will not cross 0. For FA and volume, if the 95% CI is to the left of 0, decreased FA or volume is associated with decreased performance. For RD, if the 95% CI is to the right of 0, increased RD is associated with decreased performance.

Table 1

Characteristics of the VPT and Term groups at birth and 7 years corrected age.

	VPT group n* = 149	**Term group n* = 36**	***p***
Gestational age (weeks), mean (SD)	27.5 (1.9)	38.7 (1.4)	**<.001**
Birth weight (grams), mean (SD)	974 (229)	3250 (480)	**<.001**
Male sex, n (%)	74 (49.7)	18 (50.0)	0.97
Singleton, n (%)	77 (51.7)	34 (94.4)	**<.001**
Small for gestational age**, n (%)	12 (8.0)	1 (2.8)	0.27
Apgar score at 5 mins, median (25^{th}–75^{th} percentile)	9 (8–9)	9 (9–10)	**<.001**
Proven episodes of sepsis, n (%)	61 (40.9)	2 (5.56)	**<.001**
Patent ductus arteriosus, n (%)	71 (47.7)	0	**<.001**
Necrotising enterocolitis (proven), n (%)	6 (4.0)	0	0.47
Bronchopulmonary dysplasia, n (%)	47 (31.5)	0	**<.001**
Length of stay (days), median (25^{th}–75^{th} percentile)	79 (66–96)	5 (4–6)	**<.001**
Antenatal corticosteroids, n (%)	129 (86.6)	0	**<.001**
Postnatal corticosteroids, n (%)	8 (5.4)	0	0.15
Cystic periventricular leukomalacia, n (%)	6 (4.0)	0	0.22
Intraventricular haemorrhage, grade 3/4, n (%)	5 (3.4)	0	0.27
WMA, n (%)	78 (53.4)	2 (6.1)	**<.001**
Maternal age at birth (years), mean (SD)	30.4 (5.8)	31.9 (4.5)	0.14
Social risk at 7 years, median (25^{th}–75^{th} percentile)	2 (1–3)	1 (0–2)	**<.01**
MDI at 2 years, mean (SD)	87.6 (16.6)	102.7 (15.5)	**<.001**
Age at 7 years (years), mean (SD)	7.51 (0.2)	7.57 (0.2)	0.07
FSIQ at 7 years, mean (SD)	99.2 (13.1)	109.3 (11.2)	**<.001**
ICV at 7 years (cm^3), mean (SD)	1333.8 (121. 2)	1420.6 (100.3)	**<.001**
Orienting at 7 years, mean (SD)	16.0 (3.7)	18.1 (1.9)	**<0.01**
Alerting at 7 years, mean (SD)	6.4 (2.5)	7.2 (1.9)	0.11
Shifting at 7 years, mean (SD)	3.6 (2.3)	4.7 (1.9)	**<0.01**
Divided attention at 7 years, mean (SD)	73.3 (19.2)	81.9 (13.3)	**<0.05**
ADHD diagnosis, n (%)	13 (9.4)	2 (6.1)	0.54

VPT, very preterm; SD, standard deviation; WMA, white matter abnormality (mild, moderate, or severe); MDI, Bayley Scales of Infant Development Mental Developmental Index; FSIQ, Wechsler Abbreviated Scale of Intelligence Full Scale Intelligence Quotient; ICV, intracranial volume.

* Some group sizes are less than the total sample because of missing data

** >2SD below expected weight for gestational age

NB. Bold text indicates statistically significant values.