Chapter 7

White matter alterations underpinning interference control problems of very preterm children

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Abstract

Attention problems are among the most prominent behavioral deficits reported in very preterm (<32 weeks of gestation) children at school age. In this study, we aimed to elucidate the brain abnormalities underlying attention problems in very preterm children by investigating the role of abnormalities in white and grey brain matter during interference control, using functional magnetic resonance imaging guided probabilistic diffusion tensor tractography. Twenty-nine very preterm children at the mean age of 8.6 (0.3) years, and 47 term controls at the mean age of 8.7 (0.5) years, performed an functional magnetic resonance imaging version of the Eriksen Flanker task measuring interference control. Very preterm children showed slower reaction times than term controls when interfering stimuli were presented (*d*=0.67, p=.005), indicating poorer interference control. Very preterm children and term controls did not differ in mean activation of the cortical regions involved in interference control. However, impaired white matter integrity was found in very preterm children, indicated by lower mean fractional anisotropy of specifically those fiber tracts that innervate the cortical regions involved in interference control (*d*=0.61, p=.01). Lower white matter tract integrity was related to poorer interference control, only in very preterm children. Results indicate a crucial role of white matter alterations in the interference control problems of very preterm children.

Introduction

Improved perinatal care has increased survival rates of very preterm (<32 weeks of gestation) infants. However, surviving very preterm children appear to have pervasive behavioral problems more frequently than term peers, which may persist into adulthood.[1;2] At school age, attention problems are among the most prominent behavioral deficits in very preterm children,[3;4] having a detrimental impact on school performance and social functioning. Attention problems in very preterm children are crucially mediated by differences in neurocognitive functioning and underpinned by abnormalities in white and grey brain matter development.[5] In very preterm children, impairments of white matter integrity in major white matter tracts[6;7] as well as differences in cortical development[8] have been described using methods of Diffusion Tensor Imaging (DTI) and structural Magnetic Resonance Imaging (sMRI), respectively. However, the exact relationship between these brain alterations and the observed attention problems in very preterm children is poorly understood.

One core aspect of attention is interference control; the ability to successfully inhibit irrelevant information.[9] The brain attention network involved in interference control has been well-established, encompassing both the dorsal anterior cingulate cortex (dACC) and inferior parietal cortices, which can be reliably identified using functional MRI (fMRI) tasks such as the Color-Word Stroop and the Eriksen Flanker task.[9-11]

This study aims to elucidate brain abnormalities underpinning attention problems in very preterm children, by investigating the role of impairments in white and grey brain matter in interference control in very preterm children and term controls. First, we examined interference control problems and potential differences in cortical activation between very preterm children and term controls using the Eriksen Flanker task adapted for fMRI. Second, by using fMRI-guided probabilistic Diffusion Tensor Tractography (DTT), we studied potential differences between very preterm children and term controls in white matter integrity of specifically those fiber tracts that innervate cortical regions activated in interference control. Finally, the functional relations between cortical activation, white matter integrity, and interference control were explored in very preterm children and term controls.

Methods

Sample

All very preterm children (<32 weeks of gestation) admitted to the level III neonatal intensive care unit (NICU) of the VU University Medical Center Amsterdam between September 2001 and July 2003 were eligible for inclusion in a randomized controlled trial on the effects of glutamine supplementation.[12] As we found some evidence that glutamine supplementation may have influenced brain development (see chapter 10), only very preterm children of the control group of this trial were included in the current study. At 7-8 years of age, (parents of) 30 of the 39 children (77%) of the control group agreed to participate in the follow-up study, and 29 (97%) successfully finished MRI follow-up at the mean (SD) age of 8.6 (0.3) years. MRI data for one child were not collected due to restrictions in scanning time availability. For each child, birth weight in grams, gestational age in weeks, and other clinical data were extracted from the original dataset.

Age-matched, term born peers (>37 weeks of gestation) from the same classrooms as attended by the very preterm children, or recruited from other schools located in the same area, were invited to participate in the study. Controls had to be born without any perinatal complications as reported by their parents, to attend regular classes, and to be free of behavioral and emotional problems and academic difficulties as reported by their teacher. A total of 51 term born peers agreed to participate in the scanning session. Data for one child were not collected due to restrictions in scanning time availability, and data of three children had to be excluded due to too much head movement (>3 mm) during the fMRI scanning blocks. A total of 47 term born peers successfully finished MRI at the mean (SD) age of 8.7 (0.5) years.

Socio economic status (SES) was determined by classifying the highest level of education in a household with a number ranging from one to four.[13] A higher number indicated a higher level of education and a corresponding higher SES.

Procedure

All parents completed written informed consent prior to the study, which was approved by the medical ethical committee of the VU University Medical Center. MRI took place at the VU Medical Center. A simulation scanner was used for subjects to get comfortable with the scanner environment and procedures.[14]

Acquisition MRI, fMRI, and DTI

MRI was performed with a 1.5T MRI scanner, equipped with an 8-channel phased-array head coil (Siemens Sonata, Erlangen, Germany). Structural 3D T1-weighted images were obtained in the sagittal plane with an MP-RAGE (Magnetization-Prepared Rapid Acquisition Gradient Echo) sequence (TR=2730 ms, TE=3.7 ms, TI=1000 ms, flip angle=7˚, with a 1x1 mm in-plane resolution and slice thickness of 1 mm). Functional MRI images were acquired using an EPI sequence (TR=2400 ms, TE=40 ms, flip angle=90°, 36 slices, slice gap=17%, with a 3.1x3.1 mm in-plane resolution and slice thickness of 3.1 mm). DTI images were collected during one acquisition with single shot EPI consisting of four volumes without directional weighting, and 24 volumes with 24 non-collinear gradient directions (b-value=750 s/mm2, TR=7500 ms, TE=85 ms, with a 2.5x2.5 mm in-plane resolution and 54 contiguous slices with slice thickness of 2.5 mm).

Eriksen Flanker task

During fMRI scanning, performance on an adapted version of the Eriksen Flanker task[15] was measured. In this task, children had to respond as fast as possible to a centrally presented arrow pointing towards the left or the right, by pressing a button with their left or right index finger, respectively. Two flanker arrows were presented on both sides of the central arrow, which were either congruent (four arrows pointing in the same direction as the central arrow), incongruent (four arrows pointing in the opposite direction as the central arrow), or neutral (four dashes) with the central arrow, yielding three different conditions. Incongruent flanker arrows interfere with the response to the central arrow, and therefore need to be inhibited. This inhibition leads to an interference-effect,[15] a well-documented increase in reaction time (RT) as compared to the neutral or congruent condition, providing a measure of interference control with larger increases in RT indicating worse interference control. A total of 90 trials were administered, divided over two scanning blocks of 45 trials each. There were 30 trials for each condition, presented in a fixed random order, completely balanced across left and right pointing central arrows. The percentage of errors and the average RT difference between the incongruent condition and the neutral and congruent condition were included in the analyses as dependent measures of the interference effect.

fMRI data processing

Processing of fMRI data was performed using BrainVoyager QX software (Brain Innovation, Maastricht, The Netherlands). Series of 113 volumes were acquired for each of the two scanning blocks of 45 trials of the Eriksen Flanker task. The first two volumes were discarded in order to avoid differences in T1 saturation. Voxel time-series of the remaining 111 volumes were slice-time and motion corrected, high-pass filtered (0.02 Hz), temporally (3.0 s FWHM Gaussian kernel), and 3D spatially (6 mm FWHM Gaussian kernel) smoothed. A block of trials was excluded from further analyses when head motion during the block exceeded 3 mm in either the x, y, or z direction. As indicated, this was the case for three term controls for both blocks of trials. For 19 children (nine very preterm children, 10 term controls), data of one block of trials was removed due to too much head motion. For each child the individual 3D T1 scan was registered to standard Talairach space. The individual EPI volumes were first co-registered with the individual 3D T1 scan, followed by the corresponding transformation into Talairach space.[16] Voxel time series were corrected for serial correlations. Regions of interest (ROIs) were defined on the basis of the whole-brain activation obtained in response to the incongruent condition as opposed to all other trials (congruent and neutral trials) for the whole sample of very preterm children and term controls. Next to the regressor for the interference effect, we included a separate regressor for errors, as the activation during these trials should not be confounded with the activation involved in suppressing the interference effect. Both regressors were convolved with a standard hemodynamic response function, and ROIs were determined using a Bonferroni corrected statistical threshold, and a minimum cluster-size of 0.3 ml. The resulting beta weights for each ROI and participant during the interference effect were included as dependent variables of cortical activation in the statistical analyses.

DTI data processing

DTI data processing was performed using the FMRIB's Diffusion Toolbox (FDT) as implemented in the FSL software package version 4.1.9 (FMRIB Analysis group Oxford, UK[17]). After eddy current and motion correction, all volumes for each child were screened for the presence of artifacts. If an artifact was present within a volume, this volume was removed for this child. For all included children, on average 96.6% (range 71.4% - 100%) of all volumes were found to be suitable for DTI analyses. After that, analyses were conducted using default settings of bedpostx from FDT. Probabilistic fiber tracking was performed using the ROIs as derived from the fMRI outcomes as seeding regions. First, coordinates of each voxel of a ROI were transposed from Talairach space into MNI space by the Lancaster method[18] using the GingerALE software package,[19] and imported in FSL. Second, the ROI in MNI space was dilated 1 mm in every direction to make sure that the area of contact between neuronal grey matter and their innervating white matter fiber tracts was included in the seeding region. The ROIs were transformed from MNI space into subject DTI space using the inverse non-linear transformation needed to register individual FA maps to MNI space. Third, the regions of the left and right thalamus were determined using the 3D T1 series of each child using the FIRST tool provided by FSL. These thalamus ROIs were also transformed into subject DTI space. Finally, path tracing was performed, using a total of 5000 permutations for each voxel, from the seeding regions towards the left and right thalamus, and vice versa. For analyses, a threshold was set for each voxel to include at least 15% of the total number of fibers in the tract, in order to limit the possibility that fiber tract connections between the seeding region and the thalamus were erroneously included by chance. For each participant, mean volume, mean FA value, and the mean of the eigenvalues L1 (measure of axial diffusivity) and L23 (the mean of L2 and L3, measure of radial diffusivity) were derived from all tracts between the left and right thalamus and seeding regions.

Statistical analyses

Statistical analyses were performed using PASW Statistics 20.0 (SPSS Inc, Chicago, IL, USA). Independent t-test (for normally distributed continuous data), Mann–Whitney U-test (for not normally distributed continuous data), and chi-square test (for dichotomous data) were performed to investigate whether there were differences between very preterm children and term controls in terms of age, SES, and gender, respectively. Group differences in RT during the congruent, neutral, and incongruent condition of the Flanker task were investigated using ANOVA, with group and condition as between and within subject factors, respectively. To examine the potential role of abnormal cortical grey matter development on differences in interference control, group differences in beta weights of mean activation of each ROI during the interference condition were investigated using ANOVA. In addition, to examine the potential role of white matter alterations on differences in interference control, group differences in volume, FA, L1, and L23 values of fiber tracts innervating the cortical regions involved in interference control were investigated using ANOVA. Finally, Pearson correlations were determined between beta weights of mean activation, mean FA, and the interference effect, to signify the functional relations between cortical activation, white matter integrity, and interference control separately for very preterm children and term controls. Group differences were analyzed using an α of .05, and quantified in terms of effect-sizes (Cohen's *d*) with values of 0.20, 0.50 and 0.80 referring to small, medium and large effects, respectively.[20]

Table 1. Demographic variables and interference control performance

	Very preterm (N = 29)		Controls (N = 47)			
	M	SD	M	SD	p	Effect size
Sample characteristics						
Gender (male/female)	12 / 17		21 / 26		.78	0.07
Age at MRI scan in years	8.6	0.3	8.7	0.5	.28	0.23
Socio economic status	3.1	0.7	3.3	0.8	.42	0.26
Birth weight in grams	1187	342		NA		
Gestational age in weeks	28.9	1.7		NA		
Prenatal corticosteroids, n (%)	26 (90)					
BPD, n (%)	9 (31)					
IVH grade I/II, n (%)	4 (14)					
PVL, n (%)	1 (3)					
≥1 serious neonatal infections, n (%)	23 (79)					
Flanker task performance						
Incongruent condition RT in ms	858	241	721	180	**.01**	0.64
Congruent condition RT in ms	687	153	620	146	.06	0.45
Neutral condition RT in ms	708	157	629	138	**.03**	0.53
Interference effect in ms	160	116	97	77	**.005**	0.67
Incongruent condition errors in %	10.0	14.2	6.4	7.5	.21	0.32
Congruent condition errors in %	6.9	13.1	3.1	5.4	.15	0.38
Neutral condition errors in %	7.0	12.2	3.1	4.3	.11	0.43
Error increase by interference effect in %	3.0	6.4	3.3	5.7	.21	0.05

Note. BPD = Bronchopulmonar dysplasia; IVH = Intraventricular haemorrhage; NA = Not available; PVL = Periventricular leukomalacia. Intraventricular haemorrhage grading was performed according to Papile et al. M and SD pertain to mean and standard deviation, respectively. Bold numbers pertain to a significant p-value (p<.05). Effect sizes are depicted as Cohen's *d*.

Results

Demographic variables

Sample characteristics are shown in Table 1. Age at MRI scan (p=.28), SES (p=.42), and gender (p=.75), were not different between the 29 very preterm children and the 47 term controls.

Eriksen Flanker task

There was a significant effect of group (F(1,74)=6.15, p=.02) and condition (F(2,73)=73.40, p<.001), on Flanker task RT performance (Table 1). In post-hoc analyses, RT was significantly slower in the incongruent trials compared to the neutral trials (*d*=0.70, p<.001) and congruent trials (*d*=0.79, p<.001), whereas RT was not different between the neutral trials and the congruent trials (*d*=0.09, p=.61). In addition, there was a significant larger interference effect in very preterm children (*d*=0.67, p=.005), substantiating the presence of poorer interference control in very preterm children as compared to term controls. No significant differences between very preterm children and term controls were found in error percentage for each of the three conditions.

fMRI

The whole-brain analysis of cluster activation showed three ROIs with significantly increased activation during incongruent trials as compared to neutral and congruent trials in the left parietal cortex, right parietal cortex, and dACC (Table 2 for details). There were no differences in activated areas between very preterm children and term controls, and there were no areas with significantly lower activation. Furthermore, during the incongruent condition of the Flanker task, the increase in activation of the left parietal cortex (p=.14), right parietal cortex (p=.70), and the dACC (p=.50) were not different between very preterm

Table 2. fMRI results: beta values, group differences, and characteristics of activated cortical regions in interference control

	Preterms (N=29)		Controls (N=47)			Peak activation[1]			Center of gravity[1]						Clustersize[2]
						X	Y	Z	X		Y		Z		
	M	SD	M	SD	p				M	SD	M	SD	M	SD	
Left parietal	0.60	0.52	0.40	0.57	.14	-40	-41	42	-38.2	4.6	-41.9	4.1	40.6	2.2	1.348
Right parietal	0.61	0.71	0.55	0.71	.70	32	-44	36	26.6	6.0	-57.9	10.7	42.6	4.4	3.141
dACC	0.50	0.67	0.40	0.61	.50	-1	7	45	1.6	2.2	5.8	4.2	47.4	2.5	0.315

Note. [1]Coordinates are in Talairach space. [2]clustersize in ml. ACC = Anterior cingulate cortex. M and SD pertain to mean and standard deviation, respectively.

children and term controls. To ensure that there were no group differences in the mean activation of the cortical area directly surrounding the three ROIs, we additionally tested differences in mean activation of the three ROIs as determined using less stringent p-value (false discovery rate). This approach also did not show any group differences in increase in activation of the left parietal cortex (p=.08), right parietal cortex (p=.47), and the dACC (p=.21). There were no differences between children from which data of two blocks were included and children from which data of one block was removed due to too much head motion.

DTI

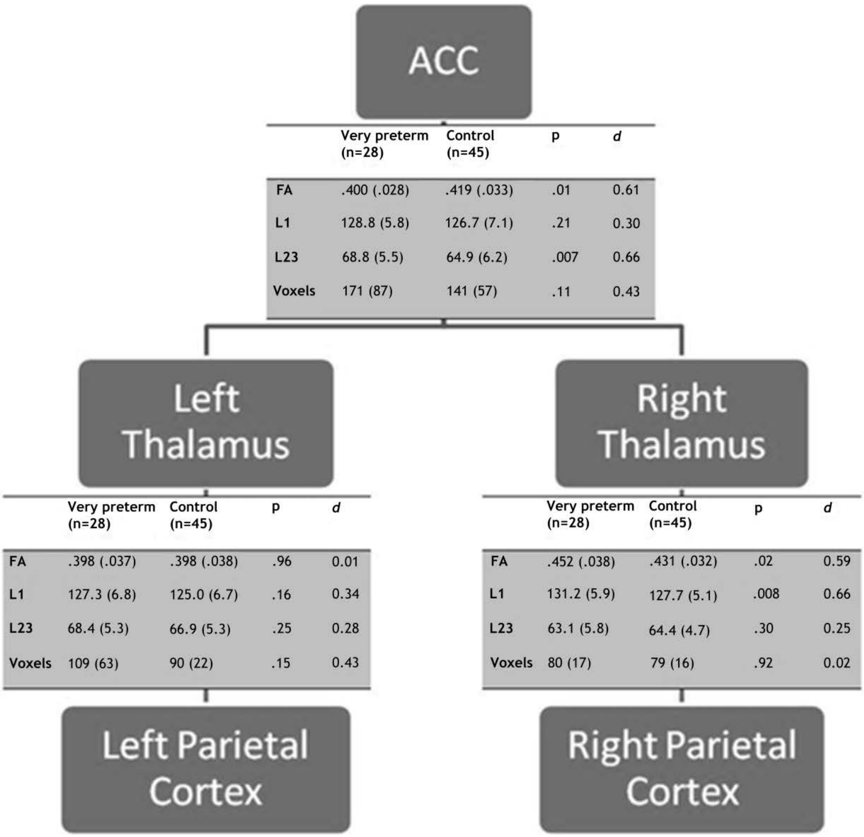
The three ROIs showing increased activation during the incongruent condition (left parietal cortex, right parietal cortex, dACC) were used as seeds in tracking analyses. In order to determine the fiber tract connections between the left and right parietal regions and the ACC, we subdivided the tract in parts, with the thalamus as 'relay station'. First, connections between the left parietal cortex and the left thalamus, and between the right parietal cortex and the right thalamus, were tracked. Second, connections between the dACC and the bilateral thalami were tracked. In this latter analysis the left and right thalami were combined, as many fibers from both the left and the right thalamus cross the corpus callosum to the contralateral part of the dACC, creating the risk that (parts of) tracts are erroneously included twice. Data of three children (one very preterm, two term controls) were excluded, as the implemented tracking algorithm was not successful in finding any connections between the left and right thalamus and the dACC. For these three children, more than 10% of the volumes had to be removed due to the presence of artifacts, leading to lower DTI data quality and consequently the inability to track any connections.

The volumes of the three tracts were not different between very preterm children and term controls (see Figure 1). Mean FA value was significantly higher in very preterm children as compared to term controls in the fiber tract connecting the right parietal cortex and the right thalamus (*d*=0.59, p=.02, Figure 1), underpinned by higher L1 values in very preterm children (*d*=0.66, p=.008). In addition, mean FA value was significantly lower in the fiber tracts connecting the left and right thalamus with the dACC (*d*=0.61, p=.01), which was underpinned by higher L23 values in very preterm children as compared to term controls (*d*=0.66, p=.007).

Functional relations

A higher interference effect with respect to RT in the Eriksen Flanker task was significantly associated with an increase in activation of the dACC in the whole group (*r*=.34, p=.002), as well as for very preterm children separately (*r*=.40, p=.03). For term controls, the

Figure 1. DTI results: FA values, radial diffusivity, axial diffusivity, and tract volume in voxels in very preterm children and term controls



ACC

	Very preterm (n=28)	Control (n=45)	p	*d*
FA	.400 (.028)	.419 (.033)	.01	0.61
L1	128.8 (5.8)	126.7 (7.1)	.21	0.30
L23	68.8 (5.5)	64.9 (6.2)	.007	0.66
Voxels	171 (87)	141 (57)	.11	0.43

Left Thalamus – Left Parietal Cortex

	Very preterm (n=28)	Control (n=45)	p	*d*
FA	.398 (.037)	.398 (.038)	.96	0.01
L1	127.3 (6.8)	125.0 (6.7)	.16	0.34
L23	68.4 (5.3)	66.9 (5.3)	.25	0.28
Voxels	109 (63)	90 (22)	.15	0.43

Right Thalamus – Right Parietal Cortex

	Very preterm (n=28)	Control (n=45)	p	*d*
FA	.452 (.038)	.431 (.032)	.02	0.59
L1	131.2 (5.9)	127.7 (5.1)	.008	0.66
L23	63.1 (5.8)	64.4 (4.7)	.30	0.25
Voxels	80 (17)	79 (16)	.92	0.02

association between a higher interference effect and an increase in dACC activation showed a clear trend (*r*=.29, p=.053). Furthermore, a higher interference effect was also associated with lower FA values of the tract connecting the left and right thalamus with the dACC in the whole group (*r*=-.26, p=.03). Interestingly, this association was only significant in very preterm children (*r*=-.46, p=.02), and non-existent for term controls (*r*=.03, p=.83). Using a

Fisher r-to-z transformation test, this difference in the association between lower FA values of the tract connecting the left and right thalamus with the dACC and a higher interference effect between very preterm children and term controls was significant (z=2.09, p=.04).

Discussion

This study investigated the nature of attention deficits in very preterm children by studying the role of white and grey brain matter abnormalities in interference control, as measured using the Eriksen Flanker task. We found significantly larger behavioral interference in very preterm children compared to term controls (*d*=0.67, p=.005), indicating that very preterm children have more difficulty with interference control than term peers. By using fMRI-guided probabilistic DTT, we demonstrated differences between very preterm children and term controls in white matter integrity of specifically those fiber tracts that innervate the activated cortical regions involved in interference control. Besides a lower mean FA value in the tract connecting the left and right thalamus with the dACC (*d*=0.61, p=.001), signaling lower white matter integrity, we found an increase in white matter integrity in the tract connecting the right parietal cortex with the right thalamus (*d*=0.59, p=.02) in very preterm children. Interestingly, we found no evidence for differences in the mean activation of the cortical regions involved in interference control between very preterm children and term controls. In both very preterm children and term controls, there was a relation between poorer interference control and activation of cortical regions involved in interference control. In contrast, a relation between lower white matter integrity of the tract connecting the thalamus with the dACC and poorer interference control was only present in very preterm children. This finding suggests a crucial role of white matter abnormalities in the interference control problems of very preterm children.

Our findings confirm the increase in mean activation of the dACC as well as the left and right parietal cortex during interference control.[10;11] A previous study has shown that the left and right parietal cortex are involved in 'activating' all possible responses, whereas the dACC is involved in the selection of the appropriate response during interference control.[11] Interestingly, an increase in mean activation of the dACC was directly related to poorer interference control in very preterm children, suggesting the presence of a compensatory increase in cortical activation during interference control. Some other studies have described differences in cortical activation patterns between very preterm children and term controls, investigating the brain systems underlying language functions, motor response inhibition, and visual memory.[21-24] However, we did not find differences in the mean activation of cortical regions underlying interference control between very preterm children and term controls at school age. Given the differences in interference control performance between very preterm children and term controls, the absence of any compensatory increase in cortical activation may demonstrate an upper limit in the possibility for very preterm children to utilize additional cortical activation to further improve interference control.

Widespread impairment of white matter integrity of major white matter tracts has been frequently described in very preterm children throughout childhood and adolescence.[6;7;25;26] In general, white matter development comprises a cascade of events including the development of pre-oligodendrocytes, axons, and subplate neurons, which may be negatively affected in preterm children by multiple factors with accompanying excitotoxicity and ischemic events.[27] Measures of radial and axial diffusivity may elucidate the origin of differences in white matter integrity between very preterm children and term controls, although interpretation(s) in terms of the underlying pathology might need further validation.[28] Our findings illustrate that lower white matter integrity of the tract connecting the left and right thalami with the dACC in very preterm children was characterized by an increase in radial diffusivity, suggesting that alterations may be caused by impaired tract myelination in very preterm children. The increase in white matter integrity of the tract connecting the right parietal cortex with the right thalamus was characterized by an increase in axial diffusivity, potentially indicating a compensatory increase in axonal density and axonal caliber of this tract to counterbalance the negative effects of reduced white matter integrity in the tract connecting the right and left thalami with the dACC in very preterm children. The presence of adaptive compensation, in terms of an increase in white matter integrity, has been described in children with cerebral paresis in the motor tracts of the unaffected hemisphere.[29] This adaptive compensation may be the result of a complex process of activity-dependent ‘pruning’ that normally takes places during childhood,[29] however, other factors may also explain the observed increase in white matter integrity in very preterm children. For instance, given the impact of very preterm birth on white matter development, it is not unlikely that less fibers crossed the white matter tracts in very preterm children as compared to term controls, which may have resulted in the relatively higher FA value for very preterm children. Interestingly, other studies also described increases in white matter integrity of similar tracts in very preterm children at term, in childhood, or at adolescent age.[30-32] Future studies are warranted to further clarify the potential presence of adaptive compensation in white matter tracts underlying interference control in very preterm children.

Widespread reductions in white matter integrity in very preterm children at school age are associated with a broad range of neurocognitive deficits, in particular motor and cognition functions, as compared to term controls.[6;7] Given the crucial role of white matter alterations in neurocognitive and behavioral deficits of very preterm children, including interference control problems, future research directed at improving long term development of very preterm children might in particular benefit from prevention and treatment of white matter impairment in very preterm children. Interestingly, some promising results of training for improving white matter integrity of the tracts innervating the dACC have been demonstrated in young adults,[33] although future investigation using a sample of children is warranted.

This study has some limitations which need to be taken into account. First, some studies showed differences in FA values between males and females,[6] or illustrated an effect of gender regarding relations between white matter integrity and functional outcomes.[34] However, we did not find any evidence for differences between males and females on our measures of cortical activation, white matter integrity, or functional outcomes. Second, although crucially involved in attentional performance, interference control is only one of multiple aspects underlying attention in children. Other aspects, including the abilities to orient to, to maintain focus, or to shift attention between events[9] may also play an important role in attention deficits of very preterm children,[4] indicating that future studies should further explore the underlying pathology of attention deficits in very preterm children.

In summary, by using fMRI guided DTT, this study presents evidence that differences in white matter integrity underpin interference control problems of very preterm children. The important role of abnormal white matter development in interference control problems of very preterm children suggests a window of opportunity to help improve attention problems in very preterm children.

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