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Attention and Regional Gray Matter Development in Very Preterm Children at Age 12 Years

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Abstract

Objectives: This study examines the selective, sustained, and executive attention abilities of very preterm (VPT) born children in relation to concurrent structural magnetic resonance imaging (MRI) measures of regional gray matter development at age 12 years. **Methods:** A regional cohort of 110 VPT (≤32 weeks gestation) and 113 full term (FT) born children were assessed at corrected age 12 years on the Test of Everyday Attention-Children. They also had a structural MRI scan that was subsequently analyzed using voxel-based morphometry to quantify regional between-group differences in cerebral gray matter development, which were then related to attention measures using multivariate methods. **Results:** VPT children obtained similar selective ($p = .85$), but poorer sustained ($p = .02$) and executive attention ($p = .01$) scores than FT children. VPT children were also characterized by reduced gray matter in the bilateral parietal, temporal, prefrontal and posterior cingulate cortices, bilateral thalami, and left hippocampus; and increased gray matter in the occipital and anterior cingulate cortices (family-wise error–corrected $p < .05$). Poorer sustained auditory attention was associated with increased gray matter in the anterior cingulate cortex ($p = .04$). Poor executive shifting attention was associated with reduced gray matter in the right superior temporal cortex ($p = .04$) and bilateral thalami ($p = .05$). Poorer executive divided attention was associated with reduced gray matter in the occipital ($p = .001$), posterior cingulate ($p = .02$), and left temporal ($p = .01$) cortices; and increased gray matter in the anterior cingulate cortex ($p = .001$). **Conclusions:** Disturbances in regional gray matter development appear to contribute, at least in part, to the poorer attentional performance of VPT children at school age. (*JINS*, 2017, *23*, 1–12)

Keywords: Very preterm, Outcome, MRI, Attention, Gray matter, Brain

INTRODUCTION

Children born very preterm (VPT; ≤32 weeks gestation) are at increased risk of attention problems and are twice as likely as full term (FT) children to receive a diagnosis of attention deficit hyperactivity disorder (ADHD) (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever & Oosterlaan, 2009; Bhutta, Cleves, Casey, Cradock & Ananad, 2002). Despite higher risks of inattentive ADHD (Jaekel, Wolke & Bartmann, 2013), few follow-up studies have included neuropsychological measures that differentially assess key components of attention. Thus, the nature and extent of attention problems in VPT children are not well understood.

Attention is comprised of functionally related, yet distinct, cognitive and neural processes (Dosenbach, Fair, Cohen, Schlagger, & Petersen, 2008; Petersen & Posner, 2012). Three key domains of attention include selective, sustained, and executive attention. Selective attention is the capacity to orient to, prioritize, and select task-relevant information (Cohen, 2014). The dorsal and ventral attention networks underlie selective attention, and include the intraparietal sulcus and superior parietal cortex, and the temporal–parietal junction and ventral frontal cortex, respectively (Fan, McCandliss, Sommer, Raz, & Posner, 2002; Petersen & Posner, 2012). Supported by frontal and parietal cortices, sustained attention is the maintenance of a vigilant state to

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detect incoming/changing task-based information, (Sarter, Givens, & Bruno, 2001; Fan et al., 2002).

Finally, executive attention is maintained by two networks that use top–down processes to control, shift, and divide attention across competing information/tasks (Cohen, 2014; Dosenbach et al., 2008). The fronto-parietal network includes the dorsolateral prefrontal and inferior parietal cortices and the intraparietal sulcus, and modulates task/response selection (Dosenbach et al., 2008; Posner & Petersen, 1990). The cingulo-opercular network, characterized by the anterior prefrontal and medial frontal cortices, the dorsal anterior cingulate cortex and the thalamus, detects task conflict and monitors performance (De Pisapia & Braver, 2006; Posner & Petersen, 1990; Power et al., 2011). In children, the right superior temporal gyrus and the bilateral occipital cortex are also involved in executive attention (Konrad et al., 2005).

Findings from existing follow-up studies suggest that school age children born VPT are at increased risk of poorer sustained and executive attention compared to FT children, while findings relating to selective attention are mixed. In terms of sustained attention, VPT children are less accurate and take longer to complete continuous performance tasks than FT children (de Kieviet, van Elburg, Lafeber, & Oosterlaan, 2012; Shum, Neulinger, O'Callaghn, & Mohay, 2008). They are also more likely to lapse into absent-minded responding on behavioral measures of inhibitory control (Anderson et al., 2011; Bayless & Stevenson, 2007; Mulder, Pitchford, & Marlow, 2011).

In contrast to sustained attention, links between prematurity and visual selective attention are less clear. For example, Anderson et al. (2011) found that 43% of extremely preterm (<28 weeks gestation) children had impaired selective attention compared to 17% of FT children at age 7. Conversely, other studies have not found a significant difference between VPT and FT children in selective attention (Bayless & Stevenson, 2007; Mulder et al., 2011; Shum et al., 2008). However, these latter studies were characterized by smaller samples, low participant response rates, and/or differences in attention measure used, which may potentially explain differences in study findings.

Compared to sustained attention, stronger links between VPT birth and executive attention have been found at school age. For shifting attention, several studies report that VPT children obtain raw or standardized shifting attention scores at least half a standard deviation below FT children (Bayless & Stevenson 2007; Mulder et al., 2011; Shum et al., 2008). Extremely preterm children struggle even more on shifting attention tasks, having odds of impairment that are 3.6 times higher than FT children (Anderson et al., 2011). To date, executive divided attention remains understudied. Although findings from two school age Australian cohorts suggest that 62% of extremely and 41% of VPT born children have impairments in executive divided attention compared to 20–26% of FT children (Anderson et al., 2011; Murray et al., 2014).

Follow-up studies have examined the extent to which neonatal clinical factors predict attention impairments, with relatively modest results (Anderson et al., 2011; Wilson-Ching et al., 2013). Although diffuse white matter abnormalities on neonatal magnetic resonance imaging (MRI) significantly predict cognition and executive function in VPT children (Iwata et al., 2012; Woodward, Anderson, Austin, Howard, & Inder, 2006; Woodward, Clark, Bora, & Inder, 2012), cerebral growth and maturation appear to be more strongly associated with attention (Bora, Pritchard, Chen, Inder, & Woodward, 2014). Specifically, Bora et al. (2014) found that reduced cerebral tissue volumes in dorsal prefrontal, orbitofrontal, sensorimotor, and parieto-occipital regions at term were associated with attention/hyperactivity problems in VPT children from age 4 to 9 years.

Further elucidating the role of early brain development, gray matter abnormalities assessed on neonatal MRI have been related to inattention in the Victorian Infant Brain Studies (VIBeS) cohort of children born <30 weeks gestation. Murray et al. (2014) used an abnormality scoring system comprised of qualitative ratings and brain metrics and found that gray matter abnormalities in the caudate heads, lentiform nuclei, and thalami were strong predictors of shifting and divided attention at age 7. Although Murray et al. (2014) highlighted subcortical gray matter, concurrent relations between attention and diffusion tensor imaging findings were also found (Murray et al., 2016). Specifically, reduced fractional anisotropy (FA) and increased radial diffusivity in the left cingulum bundle was associated with impairments in selective, sustained, and divided attention amongst VPT children. Reduced FA in the corpus callosum was associated with poorer selective attention, while reduced FA in the superior longitudinal fasciculus related to poorer sustained and divided attention. Altered maturation of the corpus callosum between term and age 7 years in the same cohort has also been linked with poorer sustained attention (Thompson et al., 2015).

Together, these studies suggest that early alterations in cerebral maturation and gray matter development place the VPT infant at risk of inattention. Part of the mechanism also appears to reflect ongoing abnormalities in white matter fiber tracts underlying the networks of attention (Leech, Kamourieh, Beckmann, & Sharp, 2011; Murray et al., 2016; Thompson et al., 2015). However, a remaining issue concerns the extent to which regional gray matter development relates to inattention in VPT children at school age. Thus, the aims of this study were to examine in VPT and FT children at age 12 years: (1) birth-group differences in selective, sustained, and executive attention functioning; (2) birth-group differences in regional gray matter volumes; and (3) the extent to which regional gray matter volumes explain relations between VPT birth and attention functioning in childhood. We hypothesized that VPT birth would be associated with poorer selective, sustained, and executive attention functioning at age 12 years. We also hypothesized that volumetric alterations in key anatomical gray matter regions implicated in the networks of attention, including the prefrontal, temporal, parietal, anterior and posterior cingulate cortices, and deep nuclear gray matter would help to explain links between VPT birth and inattention at age 12 years.

METHOD

Sample

Two groups of children, born 1998–2000, were studied prospectively to age 12 years. The first group consisted of a non-selective regional cohort of 110 VPT infants (≤32 weeks gestation) who were admitted consecutively to the Level-III Neonatal Intensive Care Unit at Christchurch Women's Hospital, New Zealand (92% recruitment). Excluding deaths ($n = 3$), 97% of VPT children were assessed at corrected age 12 years. The second group included 113 FT infants (38–41 weeks gestation). These infants were identified from hospital records ($N = 7200$ live births) by selecting for each VPT infant, the second-previous or the second-next, same-sex FT born infant in the birth register (62% recruitment) to match infants on date of birth and to enhance random selection of the FT group.

At age 12 years, 96% (109/113) of FT children were assessed. Exclusion criteria for both groups included congenital anomalies, fetal alcohol syndrome, and/or non-English speaking parents. Comparison with regional census data showed that families of FT infants were highly representative of the Canterbury region from which they were recruited (Statistics New Zealand, 2001). Recruited and non-recruited infants did not differ in gestational age, birth weight, sex, family type, ethnicity, or socioeconomic status ($p > .05$). Sample characteristics are provided in Table 1.

Procedures

At age 12, children completed a two-phase evaluation that consisted of a half-day neurodevelopmental assessment at the University of Canterbury and a 60-min MRI scan at the New Zealand Brain Research Institute. Testers and MRI technicians were blind to children's birth group. There was no significant difference in the age of children at the time of their neurodevelopmental assessment (VPT: 12.1 ± 0.1 years; FT: 12.2 ± 0.1 years; $p = .45$). However, there was a small tendency for FT children to be 3 weeks older than the corrected age of VPT children at the time of their MRI assessment ($p = .02$) due to a short-term closure of the MRI facility and scheduling conflicts. All study procedures were approved by the Upper South Regional Ethics Committee (URA/10/05/040). Written and informed consent was obtained from all parents/guardians and assent from all children.

Table 1. Clinical and social background characteristics of FT and VPI ($n = 206$)

	FT ($n = 106$)	VPT ($n = 100$)	p-Value
Clinical factors			
Gestation (weeks), *M* (*SD*)	39.5 (1.2)	27.9 (2.4)	<.001
Birth weight (grams), *M* (*SD*)	3601.1 (405.2)	1063.5 (314.2)	<.001
Small for gestational age, %	0.9	11.0	.002
Male, %	53.8	50.0	.68
Twin birth, %	2.8	34.0	<.001
Retinopathy of prematurity, %[a]	—	37.4	
Confirmed sepsis, %	—	29.3	
Necrotizing enterocolitis, %	—	4.0	
Antenatal corticosteroid, %	—	84.0	
Dexamethasone, %	—	6.0	
Oxygen at 36 weeks, %	—	34.0	
Right handedness at age 12 years, %[b]	89.1	78.0	.08
Early brain injury			
Hydrocephalus/shunt placement, %	—	1.0	
Cystic periventricular leukomalacia, %	—	7.0	
Intraventricular hemorrhage grade 3/4, %	—	5.0	
Hemorrhagic infarction, %	—	1.0	
Moderate/severe white matter abnormality, %	—	17.2	
Social background			
Young mother (<21 years), %	1.9	4.0	.43
No high-school qualification, %	18.9	40.0	.001
Single mother, %	12.3	19.0	.25
Ethnic minority, %	12.3	14.0	.84
Low socio-economic household, %	10.4	30.0	<.001
Social Risk Index, *M* (*SD*)	0.56 (0.81)	1.07 (1.03)	<.001

[a]Retinopathy of prematurity data available for 99 preterm infants from hospital records.
[b]Handedness collected from neurological exam at age 9 years for 201/206 children seen at age 12 years (98%).

Measures

Attention

Five subtests from the Test of Everyday Attention-Children (TEA-Ch; Manly et al., 2001) were used to assess children's selective, sustained, and executive attention at age 12 years. These included Sky Search (visual selective attention), Score! (sustained auditory attention), Walk Don't Walk (sustained response inhibition), Creature Counting (executive shifting attention), and Sky Search Dual Task (DT, executive divided attention). Sky Search requires a child to visually scan and select target spaceships as quickly as possible. The Sky Search Attention Score is reported, which reflects children's time and accuracy while taking motor control into account. The Score! subtest consists of 10 trials in which a child is required to count laser sounds that are presented at varying intervals without using counting aids. Walk Don't Walk requires children to maintain a state of awareness and inhibit drawing on a paper trail when directed by an auditory cue. Creature Counting requires the flexible transfer of attention as children count creatures along a trail, changing counting direction when prompted by arrows positioned along the trail. The total number of correct trials is reported for Score! (max = 10), Creature Counting (max = 7), and Walk Don't Walk (max = 20).

Finally, the Sky Search DT involves a child simultaneously having to complete the Sky Search and Score! task at the same time. The Sky Search DT Decrement Score is reported and represents the extent to which performance is compromised relative to the Sky Search single task condition. The TEA-Ch is psychometrically reliable and has good convergent validity with existing attention tasks (Manly et al., 2001). Raw scores are reported due to narrow and equivalent age range between-groups, selection of a single test battery, and to compare VPT children against a regionally-representative FT comparison group. Attention data were collected for 96% (100/104) of VPT and 97% (106/109) of FT children. Reasons for data loss included global developmental delay (n = 2), severe cerebral palsy (n = 1), blindness (n = 1), overseas relocation (n = 1), task refusal (n = 1), and file misplaced (n = 1).

MRI

Structural images were acquired on a 3 Tesla GE HDxt scanner, with an eight channel head coil and a T1-weighted, three-dimensional inversion recovery-prepared spoiled gradient recalled echo acquisition (250 mm field-of-view, 256 × 256 acquisition matrix, sagittal acquisition, 186 1-mm-thick slices, ~1 mm^3 isotropic voxels, echo time/repetition time = 4.8/10.7 ms, flip angle = 15°, inversion time = 400 ms). MRI scans were obtained for 93% (97/104) of VPT and 89% (97/109) of FT children. Scans were not obtained for 19 children due to orthodontic braces (n = 4), anxiety (n = 4), relocation (n = 2), and declined MRI (n = 9). All acquired scans were visually inspected by two blinded reviewers for image quality. Based on this review, eight scans were excluded (motion = 6, hydrocephalus/parieto-occipital shunt = 1, nifti failure = 1) leaving 186 usable scans (VPT = 90; FT = 96).

T1-weighted images were pre-processed using VBM8 and TOM8 (http://dbm.neuro.uni-jena.de/vbm/) toolboxes for SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) in Matlab (Matlab R2013a). Images were manually realigned to the anterior commissure. A study-specific DARTEL template was created by performing an initial segmentation of the structural images into gray and white matter segments. Using an affine transformation, segments were normalized to tissue probability maps created in TOM8 using NIH age- and sex-matched priors to provide *a-priori* knowledge of the spatial distribution of tissue types and improve image registration (Mechelli, Price, Friston, & Ashburner, 2005; Waber et al., 2007). Visual inspection of gray matter segments saw four subjects excluded due to poor segmentation (VPT = 89; FT = 93).

Structural images were then intensity bias corrected, tissue classified again, and spatially normalized to the study-specific DARTEL template. Next, gray matter segments were modulated by non-linear components of the spatial normalization only (i.e., multiplying warped tissue segments by the Jacobian determinant of the warp) to preserve actual tissue values locally and account for individual brain size globally during spatial normalization. Modulation allows gray matter values to be interpreted as a measure of the regional difference in the absolute volume of gray matter at the voxel-level rather than gray matter concentration (Ashburner, 2007, 2009).

The modulated, normalized gray matter segments were smoothed using an 8 mm FWHM Gaussian kernel to improve the signal-to-noise ratio, to ensure that the assumptions underlying Gaussian random fields theory were met, and to account for any spatial normalization imperfections (Ashburner & Friston, 2000). To restrict analysis to gray matter voxels, a mask was created from the mean gray matter image of all 89 VPT and the first consecutive 89 FT modulated, normalized gray matter segments (threshold ≥ 0.15). An equal number of VPT and FT gray matter segments were selected for the mask so that the isolation of gray matter voxels would not be biased toward the larger FT group.

Social risk

To assess the socio-familial characteristics of the sample, a social risk index score was created based on five key indicators of children's family social background assessed over the first 2 years of life (score range: 0–5). These factors were all dichotomized into present (1) or absent (0) and summed. They included: (1) mother <21 years old, (2) child born into single parent family, (3) ethnic minority, (4) mother had no formal high-school qualification, and (5) birth family a low socioeconomic household. The Elly-Irving Socio-economic Index measured family socioeconomic status (SES; Elly & Irving, 2003), with ratings based on the profession of the highest earning parent. Low SES included semiskilled, unskilled, and unemployed primary breadwinner.

Data Analysis

Data analysis was performed with the largest data set available for attention (VPT = 100; FT = 106) and gray matter (VPT = 89; FT = 93) outcomes to enhance detection of small-to-medium effect sizes, rather than limiting analysis to a smaller subset of children who had complete attention and gray matter data (VPT = 87; FT = 91). Subject numbers, therefore, vary accordingly.

First, birth-group differences in attention were examined using multivariate analysis of variance (MANOVA) which takes into account several dependent variables in combination, thus reducing the probability of Type 1 error. If a significant effect of group is found on the multivariate *F* statistic, ANOVA describes the pattern of group differences on the individual TEA-Ch subtests. ANOVA results were not corrected for multiple comparisons as this study focuses on the patterns and magnitudes of group differences rather than *p*-values (see Anderson & Doyle, 2004; Murray et al., 2016; Thompson et al., 2016). Cohen's *d* provided an estimate of effect size. Chi-squared analysis compared rates of attention impairment between-groups, defined as a TEA-Ch score greater than 1SD below the mean of the FT group (see Anderson et al., 2011; Nosarti et al., 2008). Odds ratios (ORs; 95% confidence intervals) provided an estimate of effect size for rates of impairment. TEA-Ch results were re-run adjusting for social risk index.

As MANOVA is highly sensitive to statistical outliers, TEA-Ch outliers (>3*SD*) were reassigned the next poorest non-outlier value in their respective birth group to retain children in the analysis. Outlier scores were reassigned for four children on Sky Search, seven children on Sky Search DT, and one child on Walk Don't Walk. Reassigning outlier scores did not alter the pattern of significant findings. Furthermore, independent *t* tests performed without statistical outliers (>3 *SD*) did not change study findings (please see Table 5 of Online Supplement 1).

Second, whole-brain voxel-based morphometry (VBM) was used to quantify regional gray matter development between VPT and FT children. In SPM8, independent sample *t* tests were performed on smoothed, modulated, normalized gray matter segments and tested two Contrasts: (1) regional reductions in gray matter volume in VPT relative to FT children, and (2) regional increases in gray matter volume in VPT relative to FT children. Analysis was family-wise error (FWE) rate corrected for multiple comparisons (uncorrected $p < .001$ followed by voxel-wise FWE-corrected, $p < .05$). Clusters $k > 10$ voxels are reported. Birth-group differences in regional gray matter volumes were re-examined in SPM8 adjusting for covariates: age at MRI scan, sex, puberty, and social risk index (Table 6 of Online Supplement 1). Puberty was assessed with The Tanner Scale (Marshall & Tanner, 1969, 1970).

Third, modulated, normalized gray matter volume values were extracted from the VBM clusters surviving FWE-correction in Contrasts 1 and 2, and related to attention measures for all children ($n = 178$) using multivariate linear regression in SPSS (Version 23, IBM New York). Inspection of regional gray matter volume values did not identify any significant (>3 *SD*) outliers. Regression models were developed in a stepwise manner for each domain of attention. In Step 1, birth group (VPT = 1; FT = 2), alongside the following four covariates (age at MRI scan, sex [M = 1; F = 2], puberty, and social risk index), was entered to examine the proportion of variance in attention scores attributed to birth group.

In Step 2, regional gray matter volumes that were significantly associated with prematurity from the VBM results were added to this base model in a stepwise manner to determine which gray matter regions explained birth-group differences in attention outcomes. All gray matter regions associated with prematurity were included as previous developmental research has shown that the neural correlates of attention in children includes regions outside *a-priori* defined regions-of-interest (Konrad et al., 2005). Stepwise criteria for variable inclusion was set at Probability of *F* Entry $p = .05$, and Removal $p = .10$. Final models were examined for violations in nonlinearity, distribution of errors, homoscedasticity, and multicollinearity. The total proportion of variance accounted for, regression coefficients, standard errors, and significance levels are reported. A supplementary analysis was conducted including gestational age as a covariate with sex, puberty and age at MRI scan (Tables 7 and 8 of Online Supplement 1).

RESULTS

Attention at Age 12

As shown in Table 2, the effect of birth group on the multivariate *F* statistic representing the linear combination of the five TEA-Ch subtests was highly significant ($F(5,198) = 5.12$; $p = .001$). Results for each of the individual subtests are as follows.

Selective attention

VPT children did not differ significantly from FT children in their mean selective attention scores ($p = .85$; $d = .03$) or their rates of impairment ($p = .41$; OR = 0.71) on the Sky Search task.

Sustained attention

In terms of sustained auditory attention, VPT children obtained fewer correct items than FT children on the Score! subtest ($p = .02$; $d = .33$), indicating that they were less vigilant across the task. They also achieved fewer correct trials than FT children on the Walk Don't Walk subtest which assessed sustained response inhibition ($p = .02$; $d = .32$). Examination of rates of impairment across these two sustained attention tasks showed that the performance of VPT children was more often impaired when inhibiting a response

Table 2. Mean TEA-Ch scores and rates of impairment for FT and VPT children at age 12 years ($n = 206$)

	FT ($n = 106$)	VPT ($n = 100$)	Unadjusted p	Cohen's d/ OR (95% CI)	Adjusted for social risk p
Multivariate $\lambda = 0.89$			<.001		.002
Selective attention					
Sky Search Attention Score,[a] M (SD)	3.49 (1.01)	3.46 (1.17)	.85	.03	.62
Impairment, %	16.0	12.0	.41	0.71 (0.32–1.59)	.34
Sustained auditory attention					
Score! total correct, M (SD)	8.75 (1.49)	8.18 (1.93)	.02	.33	.12
Impairment, %	22.6	28.0	.38	1.33 (0.71–2.50)	.92
Sustained response inhibition					
Walk Don't Walk total correct, M (SD)[b]	15.91 (2.47)	14.91 (3.66)	.02	.32	.10
Impairment, %	16.0	29.0	.03	2.09 (1.06–4.11)	.04
Executive shifting attention					
Creature Counting total correct, M (SD)	5.86 (1.47)	5.28 (1.70)	.01	.36	.02
Impairment, %	14.2	30.0	.006	2.60 (1.30–5.20)	.02
Executive divided attention					
Sky Search DT Decrement Score,[a] M (SD)	1.29 (1.87)	2.88 (3.06)	<.001	.63	<.001
Impairment, %	9.5	24.0	.005	3.03 (1.37–6.73)	.02

Note. Raw TEA-Ch scores are reported. λ: Wilks' Lambda.
[a]Higher scores indicate poorer performance.
[b]FT $n = 104$ as MANOVA excluded two cases with partial data.
CI = confidence interval.

(29% *vs*. 16%; $p = .03$; OR = 2.09) than when simply being asked to sustain their attention ($p = .38$; OR = 1.33).

Executive attention

VPT children were less accurate than FT children on the Creature Counting subtest, which assesses the ability to shift attention ($p = .01$; $d = .36$). They were also twice as likely to have a total correct score in the impaired range (30% *vs*. 14%; $p = .006$, OR = 2.60). In terms of executive divided attention, both groups showed the expected decrement in performance under dual task conditions, but the impact on performance was greater for VPT children. Specifically, VPT children had higher mean Sky Search DT Decrement Scores compared to FT children ($p = .001$; $d = .63$), suggesting greater difficulty dividing their attentional resources. Approximately one quarter of the VPT group (24%) had a Sky Search DT Decrement Score in the impairment range, compared to only 10% of FT children ($p = .005$; OR = 3.03).

To assess the extent to which group differences in attention might be explained by differences in social background, TEA-Ch analyses were re-run adjusting for social risk index. As shown in the last column of Table 2, results remained largely unchanged with the exception of mean scores on Score! ($p = .12$) and Walk Don't Walk ($p = .10$), which were attenuated to marginal non-significance, although the risks of sustained attentional impairment were not.

Regional Gray Matter Volume at Age 12

Contrast 1: VPT < FT

Table 3 and Figure 1 show the VBM results for Contrast 1, showing regions where VPT children had reduced gray matter compared to FT children. These regions included the bilateral parietal cortex (medial juxtapositional lobule, extending from the paracentral lobule to the pre/post-central lobule), right inferior post-central gyrus, right superior temporal sulcus, left superior temporal sulcus, left prefrontal cortex, posterior cingulate gyrus, bilateral thalami, left parahippocampus, and right inferior cerebellum (FWE-corrected $p < .05$).

Contrast 2: VPT > FT

Also shown in Table 3 and Figure 1 are the VBM results for Contrast 2 which identified regions where VPT children had increased gray matter relative to FT children. These regions included the medial occipital cortex (supra-calcarine, cuneal, intra-calcarine) and the medial anterior cingulate gyrus (FWE-corrected $p < .05$). Additional slices from the VBM statistical parametric maps are included in Online Supplement 2.

To account for alternative explanations of VBM findings, group differences in regional gray matter volumes were re-run in SPM8, adjusting for children's age at MRI scan, sex, puberty, and social risk index. As shown in the last column of Table 3, the results of Contrasts 1 and 2 remained unchanged. Adjusted results are reported in full in Table 6 of Online Supplement 1.

Regional Gray Matter Volume and Attention at Age 12

Whole-brain VBM findings identified regions in which VPT children showed altered cerebral gray matter development compared to FT children at age 12. The final aim of the study

Table 3. MNI coordinates for voxels with peak t- and *Z*-scores from VBM analysis comparing regional differences in gray matter volume between FT (n = 93) and VPT (n = 89) children at age 12 years

	MNI coordinates								
Region	X	Y	Z	Cluster-extent	*t*-Score	*Z*-Score	Uncorrected *p*	FWE-corrected *p*	Adjusted *p*[a]
Contrast 1 (VPT < FT)									
Bilateral parietal cortex (medial juxtapositional lobule)	1.5	0.0	73.5	128	5.32	5.12	$1.51x10^{-7}$	.004	.03
Right inferior post-central gyrus	57.0	–10.5	–10.5	2765	10.01	Inf.	$4.44x10^{-16}$	<.001	<.001
Right superior temporal sulcus	46.5	–43.5	–15.0	246	5.86	5.60	$1.09x10^{-8}$	.001	.02
Left superior temporal sulcus	–54.0	–10.5	–10.5	2612	10.95	Inf.	$4.44x10^{-16}$	<.001	<.001
Left prefrontal cortex	–7.5	67.5	–12.0	42	4.86	4.70	$1.29x10^{-6}$	.01	.02
Posterior cingulate gyrus	6.0	–39.0	19.5	258	6.55	6.20	$2.89x10^{-10}$	.001	.004
Bilateral thalami	13.5	–28.5	18.0	6178	9.28	Inf.	$4.44x10^{-16}$	<.001	<.001
Left parahippocampus	–27.0	–31.5	–16.5	506	5.77	5.52	$1.73x10^{-8}$	<.001	.006
Right inferior cerebellum	13.5	–48.0	–63.0	173	5.36	5.16	$1.23x10^{-7}$	.002	.02
Contrast 2 (VPT > FT)									
Medial occipital cortex (supra-calcarine, cuneal, intra-calcarine)	6.0	–79.5	16.5	2107	8.05	7.43	$5.47x10^{-14}$	<.001	<.001
Medial anterior cingulate gyrus	–9.0	22.5	49.5	123	5.23	5.03	$2.39x10^{-7}$	.004	.04

Note. Cluster-extent threshold $k > 10$.
[a]*P*-value adjusted in SPM8 for: age at MRI scan, sex, puberty, and social risk index.
MNI = Montreal Neurological Institute; Inf = infinity.

was to examine the extent to which regional gray matter volume explains, at least in part, associations between VPT birth status and poor attentional performance at age 12. Normalized gray matter volume values were extracted from the VBM clusters that survived FWE-correction and related to attention measures using multivariate stepwise linear regression. Based upon the non-significant finding for selective attention, Sky Search was excluded from this analysis. Table 4 shows the extent to which regional gray matter volumes explain the sustained and executive attention problems associated with VPT birth. For each model, Step 1 shows the proportion of variance in attention scores accounted for by birth group and any significant covariates ($p \leq .05$). Step 2 shows the gray matter regions that were significantly associated with attention ($p \leq .05$). Regression analysis preformed with VPT and FT groups separately yielded a similar set of gray matter regions associated with attention at age 12 (Tables 7 and 8 of Online Supplement 1).

Sustained attention

As shown in Table 4, increased gray matter in the anterior cingulate gyrus was associated with poorer sustained auditory attention on the Score! task (β = –.16; p = .04) and helped to, at least partially, explain between-group differences in very preterm and FT children's performance (p = .02). In contrast, no significant associations were found

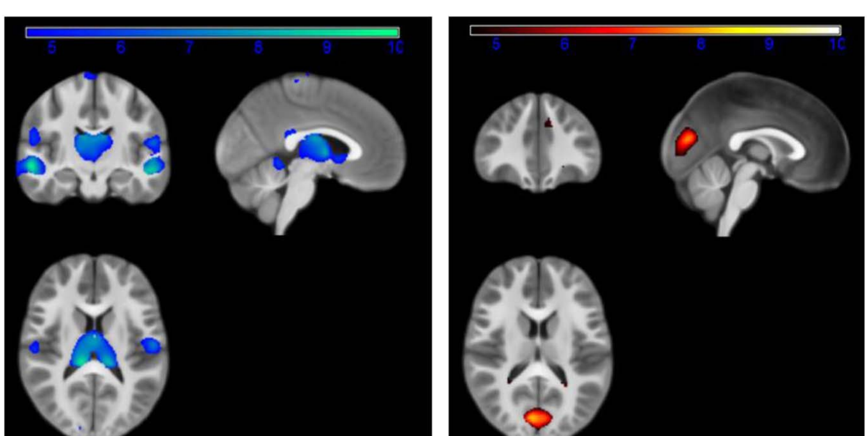

Fig. 1. Statistical parametric maps showing regional gray matter volume differences between VPT (n = 89) and FT (n = 93) children at age 12 years (voxel-wise FWE-corrected, $p < .05$). Blue indicates areas of reduced gray matter volume in VPT relative to FT. Red indicates increased gray matter volume in VPT relative to FT. Color shade indicates t-value, displayed on the colorbar.

Table 4. Summary of regression models for the prediction of attention outcomes in all children (FT = 91, VPT = 87) at age 12 years

	Step 1			Step 2		
	B (*SE*)	β	*p*-Value	B (*SE*)	β	*p*-Value
Sustained auditory attention (Score!)						
Model summary		$R^2 = .11, p < .001$			$R^2 = .13, p < .001$	
Group	.61 (.26)	.18	.02	.39 (.27)	.11	.15
Sex	.71 (.25)	.21	.004	.66 (.25)	.19	.01
Social risk index	−.27 (.13)	−.15	.04	−.24 (.13)	−.14	.07
Anterior cingulate gyrus				−2.44 (1.18)	−.16	.04
Executive shifting attention (Creature Counting)						
Model summary		$R^2 = .03, p = .03$			$R^2 = .08, p = .003$	
Group	.50 (.23)	.16	.03	−.12 (.30)	−.04	.70
Right superior temporal sulcus				3.08 (1.50)	.19	.04
Bilateral thalami				2.55 (1.27)	.17	.05
Executive divided attention (Sky Search DT)						
Model summary		$R^2 = .10, p < .001$			$R^2 = .26, p < .001$	
Group	−1.71 (.38)	−.32	<.001	−.61 (.56)	−.12	.28
Occipital cortex				−6.34 (1.83)	−.27	.001
Anterior cingulate gyrus				5.72 (1.72)	.25	.001
Posterior cingulate gyrus				−4.35 (1.78)	−.19	.02
Left superior temporal sulcus				−6.53 (2.48)	−.24	.01

between any gray matter regions and sustained response inhibition at age 12.

Executive attention

Shown in Table 4, reduced gray matter in the right superior temporal sulcus ($\beta = .19$; $p = .04$) and bilateral thalami ($\beta = .17$; $p = .05$) were significantly related to poorer Creature Counting scores which provided a measure of executive shifting attention. These associations were in the expected direction based on the results of Aims 1 and 2. Inclusion of these variables in the model attenuated between-group differences to non-significance, suggesting that thalamic and right temporal regions may explain associations between preterm birth and poor executive shifting attention outcomes (Step 1 $p = .03$; Step 2 $p = .70$).

In terms of executive divided attention, results show that between-group differences in children's Sky Search DT performance ($\beta = -.32$; $p = .001$) were explained by altered gray matter development in four regions ($p = .28$). Specifically, poorer performance on this subtest (i.e., higher scores) was associated with reduced gray matter in the posterior cingulate gyrus ($\beta = -.19$; $p = .02$), left superior temporal sulcus ($\beta = -.24$; $p = .01$), and occipital cortex ($\beta = -.27$; $p = .001$). Poor performance on this task was also associated with increased gray matter in the anterior cingulate gyrus ($\beta = .25$; $p = .001$).

DISCUSSION

This study examines the selective, sustained and executive attention outcomes of a regional cohort of VPT children at school age. Of particular interest was the extent to which children's attention skills were explained by concurrent volumetric MRI measures of regional gray matter development. The key findings of this study are discussed below.

VPT children showed difficulties in sustained and executive attention compared to FT children, while abilities in selective attention were similar between the two birth groups. Importantly, group differences on measures of sustained attention and all measures of executive attention persisted after accounting for family social risk. Specifically, poorer scores and higher rates of impairment persisted for VPT children compared to FT in executive shifting attention and executive divided attention after adjusting for social risk index. For sustained attention, adjusted rates of impairment in sustained response inhibition remained higher in VPT children relative to FT children, although findings suggested that social risk may, at least in part, be contributing to between group differences in test scores on these measures.

Our finding with respect to visual selective attention is consistent with existing reports of similar selective attention abilities between VPT and FT children at school age. Specifically, two studies, Mulder et al. (2011) and Bayless and Stevenson (2007), found that VPT and FT children were either similarly accurate on Sky Search or obtained equivalent Sky Search Attention Scores. In contrast, two larger Australian studies found that VPT children identified significantly fewer Sky Search targets than FT children at age 7 (Murray et al., 2014, 2016). It is, therefore, possible that effects in selective attention are small and larger samples are needed to detect group differences. Additionally, selective attention impairments may be more prominent in children born at earlier gestational ages (Anderson et al., 2011).

Regarding sustained attention, the small to medium effect size found on the Score! subtest ($d = .33$) was similar to Anderson et al. (2011) on this task ($d = .34$). However, it was smaller than that observed by de Kieviet et al. (2012) and Shum et al. (2008) on the Attention Network ($d = .55$) and Trail Making ($d = .50$) tasks. These effect size variations may reflect differences in the clinical characteristics of the samples and/or differences in measurement sensitivity or task demands. Attention tasks may emphasize accurate and/or speeded responding, or draw upon information processing or motor control skills, making direct comparisons across studies difficult (Mulder, Pitchford, Hagger, & Marlow, 2009).

Finally, our results for executive attention were highly consistent with previous research (Anderson et al., 2011; Bayless & Stevenson, 2007). We found that VPT children had odds of impaired attentional shifting that were 2.6 times higher and divided attention 3 times higher than FT children. Murray et al. (2014) reported similar odds of impairment for executive attention, although odds for shifting impairments (OR = 3.3) were slightly higher than for divided attention (OR = 2.9). These findings suggest that VPT children may particularly struggle with the effortful control of attention.

At age 12, VPT children had reduced gray matter in the bilateral parietal and temporal cortices, right inferior post-central sulcus, posterior cingulate gyrus, left prefrontal cortex, left parahippocampus, right inferior cerebellum, and bilateral thalami compared to FT children. Decreased gray matter volume has also been reported in similar regions across several preterm studies (Kesler et al., 2008; Nagy et al., 2009; Nosarti et al., 2008; Soria-Pastor et al., 2009). In contrast, Kesler et al. (2004) found that parietal gray matter was 4–5% larger in VPT compared to FT children at age 7–11 years. The discrepancy in findings may reflect differences in approach used to analyze structural MRI measures. Kesler et al. (2004) used a large region-of-interest scheme whereas we used VBM to investigate highly localized regions of gray matter. Even so, decreased regional gray matter volume in preterm infants is thought to be an ongoing consequence of injury to pre-oligodendrocytes, poor axonal myelination, and/or trophic anomalies in developing gray matter (Boardman et al., 2006; Leviton & Gressens, 2007; Volpe, 2009a). Further research is, however, needed to delineate whether gray matter alterations are due to abnormalities in the underlying regional white matter and/or postnatal experiences during the neonatal period (Norsarti et al., 2011; Volpe, 2009b).

In addition to reduced gray matter, study findings also identified increased gray matter volume in the medial anterior cingulate gyrus and occipital cortex in VPT relative to FT children at age 12 (see Nosarti et al., 2008, 2011; Peterson et al., 2000). Increased gray matter in the anterior portion of the cingulate cortex, coupled with reductions in the posterior area, suggest regional vulnerability in the development of the cingulum (see Zhang et al., 2015). Increased gray matter volume in VPT children may indicate impaired or delayed synaptic pruning that should occur during typical recessive maturational processes (Giedd et al., 1999; Murner-Lavanchy et al., 2014; Nosarti et al., 2008).

Current study findings indicate that volumetric alterations in the gray matter of key brain regions helped to explain the attention outcomes of VPT children at age 12. First, gray matter in the cingulum was associated with sustained auditory attention. Overall, the cingulum of VPT children was characterized by increased gray matter in the anterior region and decreased gray matter in the posterior region. Our findings suggest that increased gray matter in the anterior region of the cingulum is more strongly related to poorer sustained attention than the posterior region. The anterior cingulate cortex is thought to play a role in regulating attention and monitoring task performance (Cohen 2014; Sadaghiani & D'Esposito, 2014; Shenhav, Botvinick, & Cohen, 2013). Of interest, Murray et al. (2016) also linked white matter aberrations in the cingulum bundle to sustained attention, which when taken with current study findings, highlights the vulnerability of the cingulum for sustained attention in VPT children.

Second, reduced gray matter in the right superior temporal sulcus and the bilateral thalami appeared to explain the relationship between VPT birth and poorer executive shifting attention. Thalamic and temporal regions are theoretically linked to executive attention. For example, the thalamus is implicated in the cingulo-opercular network and plays a role in the covert shifting of visual selective attention (Kastner, Saalmann, & Schneider, 2012; Posner & Petersen, 1990) and modulation of arousal during task performance (Kinomura, Larsson, Gulyás, & Roland, 1996; Petersen & Posner, 2012). The superior temporal cortex more generally forms part of the ventral information processing system and may support the top–town control of executive attention in children (Konrad et al., 2005; Shapiro, Hillstrom, & Husain, 2002; Vossel, Gegg, & Fink, 2014).

Third, and last, reduced gray matter in the occipital, left temporal, and posterior cingulate regions; and increased gray matter in the anterior cingulate gyrus was associated with poorer executive divided attention. The occipital cortex is an early and higher-order visual cortical area that processes high-priority information in the visual field during selective attention tasks (Davidesco et al., 2013, Heinze et al., 1994; Woldorff et al., 2002). Although VPT birth was associated with increased gray matter in the occipital region relative to controls, increased gray matter was associated with lower (i.e., better) Sky Search DT scores. We interpret this finding with caution but speculate that alterations in the neural architecture of gray matter in the cerebral visual processing region of the VPT brain may be a marker for impaired visual selective attention when tested under dual task conditions (*cf.* Shah et al., 2006).

Although the precise neurobiological mechanism remains unclear, this finding could also indicate neural compensation in such that increased gray matter supports visual attention when neural abnormalities are present in the wider networks of attention. Nonetheless, both the posterior and anterior regions of the cingulate were associated with performance on

Sky Search DT. The posterior and anterior cingulate regions are strongly implicated in the default mode and cingulo-opercular networks which are modulated by task demands/ conflict (Berg, Alaburda, & Hounsgaard, 2007; Greicius, Krasnow, Reiss, & Menon, 2003; Power et al., 2011). The anterior cingulate cortex detects and resolves task conflict (Cohen, 2014; De Pisapia & Braver, 2006; Petersen & Posner, 2012) and the posterior cingulate cortex acts as a hub region in the executive network integrating information that has been processed by other connected brain regions (Leech, Braga, & Sharp, 2012). Therefore, gray matter alterations/ abnormalities in regions implicated in the functional networks of attention suggest a neural basis for the sustained and executive attention difficulties experienced by VPT children.

Strengths of this study include the prospective longitudinal design, large non-selective samples and high rates of retention, follow-up into school age, the standardized assessment of attention, and adjustment for several covariates. However, limitations should also be noted. First, TEA-Ch data are not reported for children who failed practice items ($n = 2$), were cognitively delayed ($n = 2$), or who had behavioral difficulties ($n = 1$). Thus, attention impairments may be slightly under-reported (cf. Murray et al., 2014). Second, selective attention was assessed with one subtest whereas sustained and executive attention was assessed with two subtests each. Third, VBM may be less sensitive to the detection of structural alterations than other methods when neuroanatomical variability is high across subjects (Good et al., 2001). This factor may explain why the prefrontal cortex was not related to attention measures (cf. Urben et al., 2015). Fourth, the inclusion of movement parameters specifically acquired during structural MRI scans may help minimize the effects of very subtle motion artifacts (Reuter et al., 2015). While movement parameters were collected for the resting state and diffusion scans in the larger study, these data were not collected for structural scans.

Nonetheless, the novel contribution of this study is the reported link between regional gray matter volumes and sustained and executive attention functioning in VPT children. Future directions include the replication of study findings using a sophisticated cross-validation multi-modal approach on an independent data set with analysis extended to examine functional and structural connectivity between brain regions associated with attention (see Kesler et al., 2008; Thompson et al., 2016).

In conclusion, school age VPT born children experience lapses in attention, are less flexible when shifting attention, and struggle with multitasking. VPT children also show regionally specific disturbances in gray matter development with volumetric alterations in the parietal, temporal, occipital, cingulate, prefrontal and thalamic regions at age 12. Importantly, reduced gray matter in the temporal, occipital, posterior cingulate, and thalamic regions; and increased gray matter in the anterior cingulate cortex helped to explain attention problems associated with prematurity. Thus, results highlight the importance of altered gray matter development in the pathogenesis of attention problems common among children born VPT.

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Supplementary material

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