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NEONATAL CEREBRAL MORPHOMETRY AND LATER RISK OF PERSISTENT INATTENTION/HYPERACTIVITY IN CHILDREN BORN VERY PRETERM

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Abstract

Background—Attention problems are among the most prevalent neurobehavioral morbidities affecting very preterm (VPT) born children. The first study aim was to document rates of persistent attention/hyperactivity problems from ages 4 to 9 years in a regional cohort of VPT born children. The second aim was to examine the extent to which persistent problems were related to cerebral white matter abnormality and structural development on neonatal MRI.

Methods—Data were drawn from a prospective longitudinal study of 110 VPT (< 32 weeks' gestation) and 113 full-term (FT) children born from 1998 to 2000. At term equivalent, all VPT and 10 FT children underwent cerebral structural MRI, with scans analyzed qualitatively for white matter abnormalities and quantitatively for cortical and subcortical gray matter, myelinated and unmyelinated white matter, and cerebrospinal fluid volumes. At ages 4, 6, and 9 years, each child's parent and teacher completed the Inattention/Hyperactivity subscale of the Strengths and Difficulties Questionnaire.

Results—VPT born children had a 5-fold increased risk of persistent attention/hyperactivity problems compared to FT children (13.1% vs. 2.8%; $p=.002$). No association was found between neonatal white matter abnormalities and later persistent inattention/hyperactivity risk ($p=.24$). In contrast, measures of cerebral structural development including volumetric estimates of total cerebral tissue and cerebrospinal fluid relative to intracranial volume were associated with an increased risk of persistent attention/hyperactivity problems in VPT born children ($p=.001$). The dorsal prefrontal region showed the largest volumetric reduction ($\downarrow 3.2$ – 8.2 ml). These brain-behavior associations persisted and in some cases, strengthened after covariate adjustment for postmenstrual age at MRI, sex, and family socioeconomic status.

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Conclusions—Just over one in 10 VPT born children are subject to early onset and persistent attention/hyperactivity problems during childhood. These problems appear to reflect, at least in part, neonatal disturbances in cerebral growth and development rather than the effects of white matter injury.

Keywords

attention; brain development; low birth weight; magnetic resonance imaging; very preterm; white matter injury

Introduction

Attention problems are one of the most common neurobehavioral morbidities associated with very preterm (VPT) birth, with around 10%–50% of children affected (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009; Bhutta, Cleves, Casey, Craddock, & Anand, 2002). A meta-analysis of 7 case-control studies published from 1980 to 2001 reported that VPT born children were 2.6 times more likely to be diagnosed with Attention-Deficit/Hyperactivity Disorder (ADHD) than full-term (FT) born children at school age (Bhutta, et al., 2002). A more recent meta-analysis of 9 case-control studies published from 1998 to 2008 found that VPT born children obtained parent and teacher rated attention problems scores that were on average 0.4 to 0.6 standard deviations higher than their FT peers (Aarnoudse-Moens, et al., 2009).

Almost all studies concerned with the risks of attention problems and ADHD following VPT birth have been cross-sectional with many relying on data from a single report source or measure (Aarnoudse-Moens, et al., 2009; Bhutta, et al., 2002). As a result, little is known about the development of symptoms over time or the extent to which those with attention problems represent a stable group. Identifying VPT born children with persistent attention/hyperactivity problems and/or ADHD symptomatology is important given their likely elevated risks of academic underachievement and social difficulties (Biederman, et al., 2009; Biederman, Petty, Evans, Small, & Faraone, 2010). Thus, the first aim of this study was to examine rates of inattention/hyperactivity across multiple time-points during early/middle childhood and determine the extent of persistent problems in children born VPT.

The second major, related, focus was to examine the neonatal neurological factors that may place VPT born children at an increased risk of persistent attention/hyperactivity problems. Existing studies suggest two potential factors. These include perinatal cerebral injury and altered cerebral structural development (Nosarti, Allin, Frangou, Rifkin, & Murray, 2005; Whitaker, et al., 2011). While perinatal cerebral injuries such as germinal matrix hemorrhage-intraventricular hemorrhage with ventriculomegaly or periventricular hemorrhagic infarction have been linked with ADHD/attention problems (Whitaker, et al., 2011; Whitaker, et al., 1997), they are now relatively rare. In contrast, noncystic, diffuse white matter injuries/abnormalities remain common and have been shown to be strongly predictive of neuromotor and cognitive risk (Spittle, et al., 2011; Woodward, Anderson, Austin, Howard, & Inder, 2006; Woodward, Clark, Bora, & Inder, 2012). The extent to

which these cerebral white matter abnormalities (WMAs) are also predictive of later risk of inattention/hyperactivity is not known.

Another factor that may also contribute to attention/hyperactivity problems in VPT born children is altered cerebral structural development characterized by delayed maturation or impaired growth as a result of perinatal cerebral injury or the clinical complications of VPT birth (Inder, et al., 1999; Thompson, et al., 2007). Many neuroanatomical areas affected by VPT birth overlap with brain regions implicated in the pathogenesis of attention problems and ADHD in the general population. For example, ADHD has been linked with structural alterations of the corpus callosum, caudate nucleus, amygdala, hippocampus, and lateral ventricles in the general population (Seidman, Valera, & Makris, 2005). Similarly, poor postnatal growth and thinning of the corpus callosum has been documented in younger and older children born VPT (Inder, Wells, Mogridge, Spencer, & Volpe, 2003; Skranes, et al., 2007). Significant reductions of hippocampal and caudate nuclei volumes have also been reported at both term equivalent and adolescence (Abernethy, Palaniappan, & Cooke, 2002; Thompson, et al., 2008).

Global and regional neuroanatomical alterations at term equivalent in VPT born children have been associated with a range of adverse neurodevelopmental outcomes, particularly oculomotor function, working memory, cognitive and psychomotor development (Peterson, et al., 2003; Shah, et al., 2006; Thompson, et al., 2008; Woodward, Edgin, Thompson, & Inder, 2005). However, the relationship between neonatal cerebral growth and maturation and later risk of attention problems remains unclear. Nonetheless, studies have shown associations between ADHD symptoms and altered cerebral morphometry, and in particular the hippocampus, corpus callosum, and caudate nucleus, in VPT born adolescents (Abernethy, et al., 2002; Indredavik, et al., 2005; Nosarti, et al., 2005). Neuroanatomical alterations in regions involved in the frontostriatal circuitry have also been found, with these potentially contributing to later inattention/hyperactivity risk (Thompson, et al., 2007; Woodward, et al., 2005).

Accordingly, the specific study aims were to:

1. Document rates of inattention/hyperactivity at ages 4, 6, and 9 years, and to assess the extent of persistent problems across assessment time-points in VPT and FT born children.
2. Examine within the VPT born group, associations between a) qualitatively defined cerebral WMAs, b) volumetric estimates of global and regional cerebral tissues, as identified on magnetic resonance imaging (MRI) at term equivalent and later persistent inattention/hyperactivity.

METHODS

Sample

The sample included two groups of children. A descriptive profile of the neonatal clinical and social background characteristics of the sample is provided in Table 1. The first group consisted of a regional cohort of 110 VPT born infants (32 weeks' gestation) admitted

consecutively to the level III Neonatal Intensive Care Unit of Christchurch Women's Hospital (New Zealand) from 1998 to 2000 (92% recruitment). Infants with congenital anomalies, fetal alcohol syndrome, and/or non-English speaking parents were excluded. There were no significant differences in the perinatal characteristics of recruited and non-recruited infants. Excluding deaths ($n=3$), 92% ($n=99$) of VPT born infants were assessed at ages 4, 6, and 9 years.

The second group included 113 FT born infants (38–41 weeks' gestation). These infants were identified from hospital records ($N=7,200$ live births) by selecting for each VPT infant, the second previous or the second next same sex term born infant in the birth-register (62% recruitment). Infants with congenital anomalies, fetal alcohol syndrome, and/or non-English speaking parents were excluded. Recruited and non-recruited infants did not differ on measures of infant gestational age, birth weight, sex, family type, ethnicity, or socioeconomic status. Comparison with regional census data showed that families of FT born infants were highly representative of the population from which they were recruited (Statistics New Zealand, 2001). Overall, 94% ($n=106$) of FT born infants were assessed at ages 4, 6, and 9 years. Study protocols were approved by the Regional Health and Disability Ethics Committee and written informed consent obtained from all parents/guardians.

Measures

MRI Acquisition and Analysis (Term Equivalent Age)—At term equivalent, all VPT born infants underwent a cerebral structural MRI scan without sedation. In addition, a subsample of 10 FT infants without cerebral injury was also scanned on the week of their due date. Prior to imaging, infants were fed, wrapped, swaddled, and placed in a vacuum-fixation bean bag (Vac-Fix; S & S X-ray Products, Brooklyn, NY) to minimize motion artifacts. Images were acquired using a 1.5-Tesla General Electric Signa System (GE-Medical Systems). Imaging protocols included 1) a three-dimensional T1 spoiled gradient recalled sequence (1.5mm coronal slices, flip angle 45°, repetition time 35ms, echo time 5ms, field of view 18cm, matrix 256×256) and 2) a T2 double-echo (interleaved acquisition) spin echo sequence (3mm axial slices, repetition time 3000ms, echo times 36ms and 162ms, field of view 18cm, matrix 256×256).

Images were analyzed in two ways. First, the nature and severity of cerebral WMAs were assessed using a qualitative grading scheme (Inder, et al., 2003; Woodward, et al., 2006). Each MRI scan was independently rated by a pediatric neuroradiologist and neonatal neurologist. Inter-rater agreement was 95%, with discrepant cases assigned a consensus rating. WMAs were graded on five 3-point scales assessing: 1) the nature and extent of white matter signal abnormality; 2) periventricular white matter volume loss; 3) cystic abnormality; 4) ventricular dilatation; and 5) thinning of the corpus callosum. A composite WMAs score was computed and children classified as showing no (scores 5–6), mild (scores 7–9), or moderate–severe (scores 10–15) cerebral WMAs.

Second, images were quantitatively analyzed for volumetric estimates of different cerebral tissue subtype. A sequence of image processing algorithms was used to reduce imaging system noise and align T1 and T2 images (Huppi, et al., 1998). Each image was then segmented into cortical and subcortical gray matter, myelinated and unmyelinated white

matter, and cerebrospinal fluid, using a spatially varying model through alignment with an anatomical template of a 40-week-old infant (Warfield, Kaus, Jolesz, & Kikinis, 2000). The total cerebral tissue volume was computed as the sum of all gray and white matter. The intracranial cavity volume was computed as the sum of all gray matter, white matter, and cerebrospinal fluid within the skull. For regional volumes, each image was segmented using the Talairach parcellation scheme (Peterson, et al., 2000) into dorsal prefrontal, orbitofrontal, premotor, subgenual, sensorimotor, midtemporal, parieto-occipital, and inferior occipital with cerebellum, using a combination of one axial and three coronal planes. The axial plane was passed through the anterior commissure and posterior commissure line. The first coronal plane was positioned at the most anterior part of the genu of the corpus callosum, the second coronal plane at the anterior border of the anterior commissure, and the third coronal plane through the posterior commissure. Volumetric image processing was feasible for 82% ($n=90$) of VPT born infants, with remaining scans affected by motion artifacts and MRI signal intensity errors that limited registration and tissue segmentation. There were no significant differences in neonatal clinical and social background characteristics of infants included and excluded from this analysis. For the FT born group, volumetric processing was feasible for 8 out of 10 infants.

Results for volumetric analysis have been reported as absolute volume (ml) as well as relative proportion within the intracranial cavity (i.e., [absolute volume/intracranial cavity volume] \times 100). As the proportion of cerebral tissues differs greatly in absolute volume, results have also been reported as relative difference in order to estimate the magnitude of volumetric reduction for different tissue subtype. Relative differences were calculated by dividing the absolute mean difference for each tissue subtype by the absolute mean volume of the comparison group, after adjusting for the intracranial cavity volume.

Behavioral Inattention/Hyperactivity Screening (Ages 4, 6, 9 years)—At ages 4 and 6 (corrected) and 9 years (uncorrected), all study children were screened for behavioral attention/hyperactivity problems based on parent and teacher ratings using the Inattention/Hyperactivity subscale of the Strengths and Difficulties Questionnaire, SDQ (Goodman, 1997). This scale assesses child behavior over the last 6 months using 5-items rated on a 3-point Likert scale. The SDQ has been widely used in epidemiological research and clinical practice as a behavioral screening measure, and has been consistently shown to have good concurrent and predictive validity (Goodman & Scott, 1999; Mathai, Anderson, & Bourne, 2004). Specifically, the Inattention/Hyperactivity scale has moderate sensitivity (68%–74%) and good specificity (92%–93%) for a *DSM-IV* ADHD diagnosis across ages 5 to 15 years (Goodman, 2001).

For this study, at each age assessment, children were classified as showing clinically significant attention/hyperactivity problems if their parent or teacher ratings exceeded the 90th percentile (defined on the basis of the FT born group). This approach of determining the clinical cut-point is widely used internationally in epidemiological research, and has also been endorsed by follow-up studies of children born very preterm (Delobel-Ayoub, et al., 2009; Larroque, et al., 2011). To be included in the persistent attention/hyperactivity problems group, children were required to meet the clinical cut-point for problems at all three age assessments. Children with missing parent and teacher data at any age (VPT: $n=8$;

FT: $n=4$) were excluded from this analysis. However, to minimize data loss, children with only their parent (VPT: $n=4$; FT: $n=1$) or teacher (VPT: $n=14$; FT: $n=8$) data missing at a single time-point were classified as showing no problem, unless clear difficulties were reported by the same informant at both the preceding and subsequent assessment. These identified cases were also cross-validated against a *DSM-IV* ADHD diagnosis assigned by a child psychiatrist blinded to children's perinatal history and group status and based on a structured psychiatric interview at age 9 years. All children who met criteria for early-onset persistent attention/hyperactivity problems also received a diagnosis of ADHD. Children not meeting the criteria for persistent attention/hyperactivity problems but showed symptoms at least at one age assessment were included in the transient problems group. Two children with persistent problems and two other children with transient problems were on prescribed ADHD medication at age 9 years.

RESULTS

Rates of Inattention/Hyperactivity across Ages 4 to 9 Years

Table 2 describes the extent to which VPT and FT born children showed clinically significant attention/hyperactivity problems based on either parent or teacher report at ages 4, 6, and 9 years. Also shown are the proportions of children in each group characterized by transient and persistent attention/hyperactivity problems. At each cross-sectional assessment, VPT born children had relative risks of inattention/hyperactivity that were 1.6 to 2.2 times higher than their FT born peers (OR=1.8–3.0). Almost half of VPT and nearly a quarter of FT born children met the criteria for transient attention/hyperactivity problems (OR=2.6). Persistent problems were much less common across both groups, but especially among FT born children (13.1% vs. 2.8%; OR=7.7). These between-groups differences persisted even after statistical control for sex and family socioeconomic status.

Neonatal Cerebral WMAs and Persistent Inattention/Hyperactivity

Table 3 shows the relationship between cerebral WMAs identified on MRI at term equivalent and children's later risk of persistent attention/hyperactivity problems. This analysis was confined to VPT born children given the absence of WMAs in the subsample of FT children with an MRI scan. As shown, no significant associations were found between the severity of overall cerebral WMAs on term MRI, or any of the individual scales, and VPT children's later risk of persistent attention/hyperactivity problems ($p = .24$). This pattern of findings persisted after adjustment for postmenstrual age at MRI, sex, and family socioeconomic status.

Neonatal Global Cerebral Tissue Volumes and Persistent Inattention/Hyperactivity

Table 4 describes the volumetric MRI findings at term equivalent for VPT born children with persistent attention/hyperactivity problems, VPT children with transient or no problems, and the small subsample of FT born children who had MRI data. None of these FT children met criteria for persistent or transient problems. Results show for each groups, both the absolute volume of the four tissue subtypes and cerebrospinal fluid, as well as the proportion relative to the intracranial cavity. Differences across the three study groups were examined using general linear models, with planned comparisons between VPT born

children with persistent problems and the other two groups. Figure 1 supplements these results by illustrating the magnitude of volumetric reduction for different tissues.

Associations between the absolute volume of total cerebral tissue and the risk of persistent attention/hyperactivity problems failed to reach statistical significance ($p=.12$). However, a clear linear association was evident between the relative proportion of total tissue within the intracranial cavity and risk of persistent problems ($p=.001$). These between-groups differences were further confirmed by pairwise comparisons ($p .01$). Consistent with the total cerebral tissue loss, there were corresponding increases in the absolute volume and relative proportion of cerebrospinal fluid ($p .002$). Specifically, as shown in Figure 1, VPT born children with persistent problems had 4% less total cerebral tissue and 36% more cerebrospinal fluid than VPT children with transient/no problems, and 8% less total tissue and 144% more cerebrospinal fluid than FT children without problems, after adjusting for the intracranial cavity volume.

Examination of the nature of neonatal cerebral tissue volume loss showed that reduced myelinated white matter volume, although not statistically significant, showed a tendency to be associated with an increased risk of later persistent attention/hyperactivity problems ($p .11$). This was particularly apparent in Figure 1 which shows that VPT born children with persistent attention/hyperactivity problems had 1.0ml (7%) and 4.7ml (27%) less myelinated white matter than VPT and FT children without these problems, respectively, after adjustment for the intracranial volume. No significant associations were found between neonatal cerebral volumes (absolute and relative proportion) of cortical gray matter ($p .33$), subcortical gray matter ($p .94$), unmyelinated white matter ($p .32$), and later persistent inattention/hyperactivity risk. These findings persisted after controlling for postmenstrual age at MRI, sex, and family socioeconomic status. Moreover, associations between proportion of total cerebral tissue within intracranial cavity, cerebrospinal fluid, and later risk of persistent problems among VPT born children became stronger after covariate adjustment ($p=.004$).

Neonatal Regional Cerebral Tissue Volumes and Persistent Inattention/Hyperactivity

To examine possible region-specific variations in cerebral tissue loss, Table 5 shows the associations between regional tissue volumes at term equivalent and children's later risk of persistent inattention/hyperactivity. This analysis was also confined to VPT born children and the subsample of FT born children with an MRI scan. Results showed no significant association between absolute volume of neonatal regional total cerebral tissue across all the eight anatomical subregions and children's later risk of persistent problems. However, clear reductions in regional cerebral tissue volume were evident in terms of relative proportion of total tissue within each subregion ($p .02$). Specifically, compared to FT and VPT children with no or transient attention/hyperactivity problems, VPT born children with persistent problems had the largest volumetric reductions in the proportion of total tissue within the dorsal prefrontal ($p=.001$), orbitofrontal ($p=.02$), premotor ($p=.002$), sensorimotor ($p=.001$), and parieto-occipital ($p=.003$) subregions. As shown in Figure 2, of all subregions, total tissue in the dorsal prefrontal region showed the greatest volumetric reduction. VPT born children with persistent inattention/hyperactivity had 3.2ml (7%) and 8.2ml (16%)

reductions in total tissue in the dorsal prefrontal region relative to their VPT and FT born peers without persistent problems, respectively, after adjusting for the intracranial cavity volume. Although these results remained unchanged after adjustment for postmenstrual age at MRI, sex, and family socioeconomic status, stronger associations were evident between proportion of regional total cerebral tissue volume and risk of persistent problems within the VPT group (dorsal prefrontal: $p=.02$; orbitofrontal: $p=.07$; premotor: $p=.005$; parieto-occipital: $p=.05$). Furthermore, all reported associations (Tables 3-5) persisted following control for child IQ and severity of cerebral palsy at age 4 years.

Neonatal Predictors of Persistent Inattention/Hyperactivity

The extent to which other neonatal clinical and social factors (as listed in Table 1) may also account for increased risk of persistent attention/hyperactivity problems among VPT born children was examined. The neonatal clinical complications significantly associated with later inattention/hyperactivity risk were grade III/IV intraventricular hemorrhage identified on cranial ultrasound (OR=8.3; $p=.03$) and confirmed sepsis (OR=5.3; $p=.008$). Being born to a younger mother also appeared to place VPT born children at increased risk of persistent inattention/hyperactivity ($p=.04$).

Finally, the extent to which neonatal clinical, social, and neurological factors, including global total cerebral tissue volume loss in VPT children, made a unique and independent contribution to later risk of attention/hyperactivity problems was assessed using logistic regression. After taking into account all the variables listed in Table 1, the proportion of total cerebral tissue within intracranial cavity at term equivalent age remained an independent predictor of later persistent inattention/hyperactivity ($\beta=-0.14$; $p=.07$) along with confirmed sepsis ($\beta=1.69$; $p=.01$). No interactions were evident between these two risk factors. Jointly these two neonatal variables explained 24.1% (Nagelkerke R^2) of variance and correctly classified 85% of cases.

DISCUSSION

Consistent with previous research (Delobel-Ayoub, et al., 2009; Larroque, et al., 2011), current findings show that attention/hyperactivity problems associated with VPT birth emerge early and can be readily identified with standardized screening measures. When assessed at a single time-point, parents and teachers report fairly high rates of inattention/hyperactivity in both VPT (29%–43%) and FT (17%–22%) born children, with the odds of problems being 2–3 times greater for VPT children. In contrast, examination of more serious, early-onset and persistent attention/hyperactivity problems showed that these difficulties were relatively rare, especially among FT children compared to VPT children (3% vs. 13%). In line with these results, findings from the follow-up of a large population-based cohort of low birth weight children reported a prevalence of 12% for a lifetime ADHD diagnosis (i.e., symptoms present from age 5 years) when assessed at age 16 years using the DISC-IV structured interview completed with parents (Whitaker *et al.*, 2011). Together, these findings suggest that just over one in 10 children born VPT are at risk of persistent attention/hyperactivity problems during childhood. This rate is considerably lower than rates estimated on the basis of cross-sectional data, suggesting that for a significant proportion of

both VPT and FT children, attention/hyperactivity problems are likely to be transient as opposed to chronic.

Study findings also provide useful insights into the neonatal neurological correlates that may, at least in part, help to explain why children born VPT are at an elevated risk of persistent inattention/hyperactivity. In contrast to previous studies (Spittle, et al., 2011; Woodward, et al., 2006; Woodward, et al., 2012) linking neonatal cerebral WMAs with later adverse motor and cognitive outcomes, no such association was found for attention/hyperactivity problems. Rather, global cerebral tissue volume loss during the neonatal period appeared to be an independent predictor of later risk of persistent inattention/hyperactivity. This may explain why some VPT born children without obvious evidence of early white matter injury also exhibit ADHD symptoms and/or attention problems. These findings concur with a DTI study of 11-year-old VPT born children without ultrasound evidence of perinatal cystic periventricular leukomalacia or intraventricular hemorrhage (Nagy, et al., 2003). They found significant associations between attention problems and lower fractional anisotropy values in the corpus callosum and internal capsules suggesting disturbances in cerebral organization. Links between reduced cerebral tissue volume and ADHD symptoms have also been reported in the general population, with 7 out of 12 studies that were included in a recent review showing that children and adolescents at risk of ADHD have a 3%–5% reduction in total cerebral volume compared to control children without ADHD (Seidman, et al., 2005).

Regional analysis of neonatal cerebral tissue volume showed that VPT born children with persistent attention/hyperactivity problems had reduced cerebral tissue volume within the dorsal prefrontal, orbitofrontal, premotor, sensorimotor, and parieto-occipital regions at term equivalent. Several general population studies have shown frontal and parietal lobe involvement in the development of ADHD symptoms (Castellanos, et al., 2002; Seidman, et al., 2005). For example, a recent review found smaller frontal lobe volume was consistently documented in children with ADHD, with 9 out of 12 studies reporting significant volumetric reduction in the dorsolateral prefrontal cortex (Seidman, et al., 2005). Although the potential role of the parietal cortex in the pathogenesis of attention problems is not well understood, a few studies have shown reduced parietal lobe volume in children with ADHD (Castellanos, et al., 2002; Seidman, et al., 2005). From a theoretical perspective, the frontoparietal network, which is thought to have a key role in alerting, orienting, and executive attention networks, may have relevance for the pathophysiology of attention/hyperactivity problems in VPT born children (Fan, McCandliss, Fossella, Flombaum, & Posner, 2005). Although the occipital lobe has not generally been associated with ADHD/attention problems, this neuroanatomical region may be of interest due to its involvement in visual information processing.

Study findings emphasize the importance of cerebral growth and maturation prior to term, including the time spent in the Neonatal Intensive Care Unit, as a vulnerable period for alterations in cerebral structural development that may place VPT born children at risk of ADHD symptomatology and/or inattention/hyperactivity during early/middle childhood. Apart from one study linking reduced neonatal hippocampal volume with parent reported

inattention/hyperactivity at age 5 years (Rogers, et al., 2012), all previous studies have been based on neuroimaging data from VPT born adolescent samples.

Finally, study limitations need to be acknowledged while interpreting these findings. First, regional cerebral parcellation in this study was strictly based on anatomical localization with the commissure making it difficult to delineate regions based on their functional relevance. Given the paucity of longitudinal studies examining neonatal neurological correlates of later attention problems in this high-risk population, study findings provide useful insights, however, further replication is warranted. Second, no anthropometric data was collected on the day of infant MRI scan making it difficult to tease out the associations between infant's height, head size, cerebral tissue volumes, and later risk. Finally, the child behavior screening measure used in this study was limited by its inability to distinguish between inattention and hyperactivity symptoms. In light of increasing evidence to suggest that VPT born children may be at risk of a "pure" form of attention problems characterized by inattention rather than hyperactivity, extension of this study with more specific attention and hyperactivity measures will be important.

Future studies need to address the persistence of attention/hyperactivity problems in VPT born children using a continuum rather than a dichotomous approach as it may be likely that a few children have chronic problems but may not be reaching the stringent clinical cut-points. Furthermore, it will also be important to assess the extent to which VPT born children with transient inattention/hyperactivity may differ from those with no and persistent problems in terms of neonatal clinical and neurological risk factors. However, from a methodological perspective, caution is warranted regarding classification of children in the transient attention/hyperactivity problems group based on parent or teacher ratings on behavior screening measures due to the risk of over/under-estimation of child problems.

In conclusion, study findings suggest that VPT born children are at an increased risk of persistent attention/hyperactivity problems from early to middle childhood. However, rates of persistent problems are considerably lower than rates estimated based on cross-sectional data. VPT born children's increased risk of persistent attention/hyperactivity problems appears to at least in part, reflect neonatal disturbances in cerebral structural growth and maturation, particularly in the dorsal prefrontal, and to a lesser extent, orbitofrontal, premotor, sensorimotor, and parieto-occipital regions.

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KEY POINTS

1. VPT born children are at an increased risk of attention problems, but little is known about the persistence of these problems over time or the neonatal neurological factors that place these children at risk.
2. Study findings showed that VPT born children are at an increased risk of persistent attention/hyperactivity problems from age 4 to 9 years; although this risk is more modest than previously reported based on cross-sectional data.
3. Increased risk of persistent attention/hyperactivity problems in VPT born children can partly be accounted for by neonatal disturbances in cerebral structural development assessed using MRI. Specific abnormalities include reduction in the proportion of total tissue within the intracranial cavity particularly in the dorsal prefrontal, and to a lesser extent, orbitofrontal, premotor, sensorimotor, and parieto-occipital regions, along with concomitant increase of cerebrospinal fluid volume.

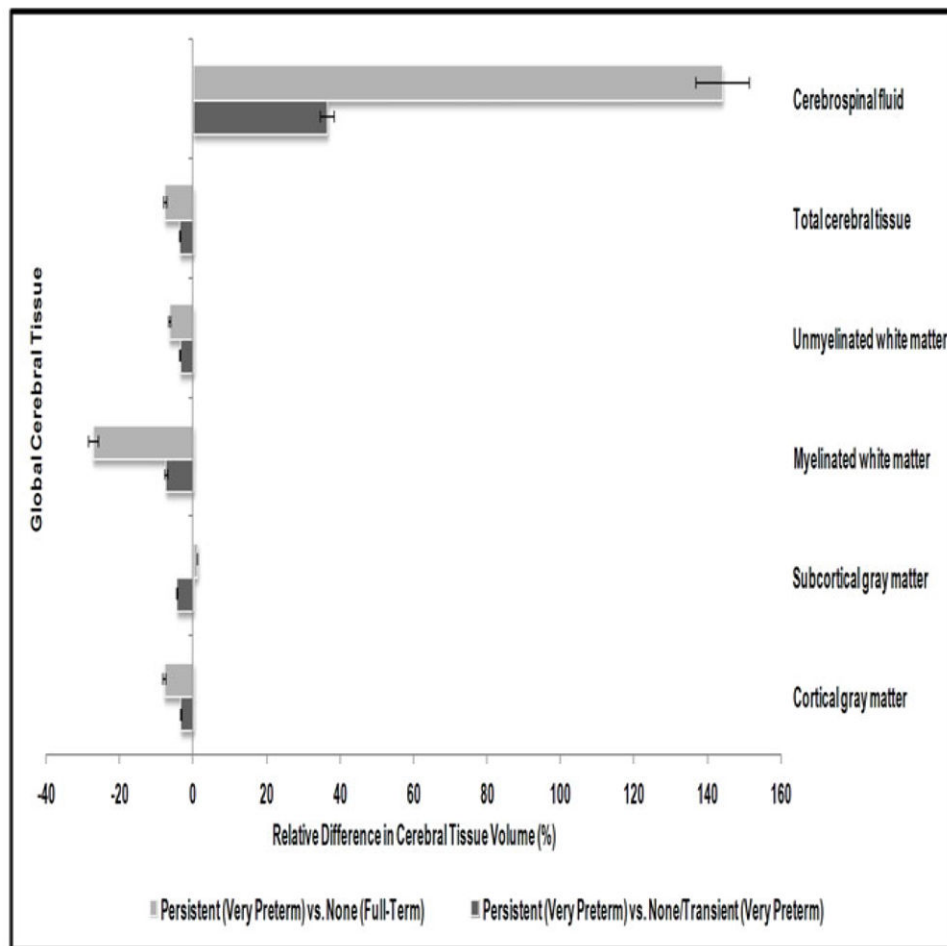


Figure 1. Relative difference in global cerebral tissue volume for very preterm born children with persistent attention/hyperactivity problems.

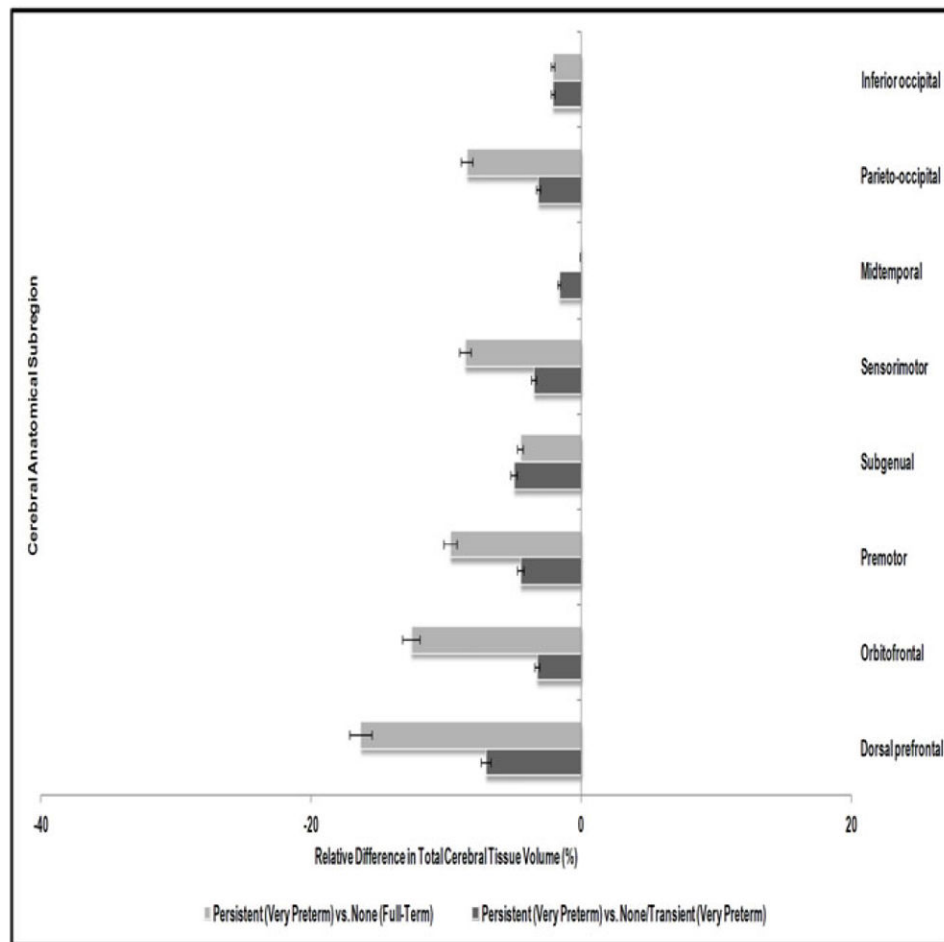


Figure 2. Relative difference in regional total cerebral tissue volume for very preterm born children with persistent attention/hyperactivity problems.

Table 1

Neonatal Clinical and Social Characteristics of the Sample

Measure	Full-Term (N=110)	Very Preterm (N=107)	<i>p</i>
Infant clinical characteristic			
Gestational age at birth, <i>M</i> ± <i>SD</i> , weeks	39.5 ± 1.2	27.8 ± 2.4	<.001
Birth weight, <i>M</i> ± <i>SD</i> , grams	3,579.5 ± 409.3	1,061.6 ± 314.2	<.001
Male sex, %	53.6	50.5	.64
Twin birth, %	3.6	33.6	<.001
Small for gestational age, %	0.9	10.3	.003
Antenatal corticosteroid use, %	–	84.1	
Postnatal dexamethasone use, %	–	5.6	
Oxygen therapy at 36 weeks, %	–	34.6	
Necrotizing enterocolitis, %	–	6.5	
Confirmed sepsis, %	–	28.0	
Patent ductus arteriosus, %	–	43.9	
Intraventricular hemorrhage grade III/IV, %	–	5.6	
Cystic periventricular leukomalacia, %	–	5.6	
White matter abnormalities on MRI			
None, %	–	24.5	
Mild, %	–	57.5	
Moderate–severe, %	–	17.9	
Social background characteristic			
Maternal age, <i>M</i> ± <i>SD</i> , years	31.0 ± 4.4	30.7 ± 5.4	.62
Maternal smoking during pregnancy, %	16.2	36.8	.001
Mother not a high school graduate, %	19.1	39.3	.001
Single parenthood, %	11.8	18.7	.16
Minority ethnicity, %	11.8	14.0	.63
Family socioeconomic status			
Professional/managerial, %	35.5	26.2	
Technical/skilled, %	54.5	43.0	
Semiskilled/unskilled/unemployed, %	10.0	30.8	.001

Table 2

Attention/Hyperactivity Problems among Full-Term and Very Preterm Born Children

Time-Point	Attention/Hyperactivity Problem, % (n)		p	Odds Ratio (95% Confidence Interval)	Adjusted ^a Odds Ratio (95% Confidence Interval)
	Full-Term (N=110)	Very Preterm (N=107)			
Age 4 years	18.7 (20)	29.1 (30)	.08	1.8 (0.9–3.4)	1.8 (0.9–3.4)
Age 6 years	22.2 (24)	43.3 (45)	.001	2.7 (1.5–4.8)	2.7 (1.4–5.0)
Age 9 years	17.3 (19)	38.8 (40)	<.001	3.0 (1.6–5.7)	2.7 (1.4–5.1)
Transient, Age 4 to 9 years	30.2 (32)	46.5 (46)	.002	2.6 (1.4–4.6)	2.5 (1.4–4.6)
Persistent, Age 4 to 9 years	2.8 (3)	13.1 (13)	.002	7.7 (2.1–28.6)	7.5 (1.9–29.0)

^a Adjusted for sex and family socioeconomic status.

Table 3

Neonatal Cerebral White Matter Abnormalities and Risk of Persistent Attention/Hyperactivity Problems among Very Preterm Born Children

Neonatal Cerebral White Matter Abnormality	Attention/Hyperactivity Problem, Age 4 to 9 Years, %		<i>p</i>
	None/Transient (<i>N</i> =85)	Persistent (<i>N</i> =13)	
White matter abnormality			
None	21.2	15.4	
Mild	62.4	53.8	
Moderate–severe	16.5	30.8	.34
White matter signal abnormality			
Normal	45.9	30.8	
Focal (2 regions)	40.0	46.2	
Extensive (2 regions)	14.1	23.1	.30
Periventricular white matter volume loss			
Normal	52.9	38.5	
Mild–moderate	41.2	46.2	
Diffuse	5.9	15.4	.24
Cystic abnormality			
Normal	86.2	84.6	
Focal (single, <2mm)	9.4	7.7	
Extensive (multiple, 2mm)	2.4	7.7	.50
Ventricular dilatation			
Normal	38.8	30.8	
Mild–moderate	45.9	53.8	
Marked	15.3	15.4	.83
Thinning of the corpus callosum			
Normal	27.1	15.4	
Focal	58.8	76.9	
Global	14.1	7.7	.81

Note. Reported associations persisted after adjustment for postmenstrual age at MRI, sex, and family socioeconomic status.

Table 4
 Neonatal Global Cerebral Tissue Volumes and Risk of Persistent Attention/Hyperactivity Problems

Neonatal Global Cerebral Tissue Volume, <i>M</i> ± <i>SD</i>	Attention/Hyperactivity Problem, Age 4 to 9 Years			<i>p</i>
	None (1)	None/Transient (2)	Persistent (3)	
Total cerebral tissue				
Absolute volume, ml	441.4 ± 25.2	410.1 ± 49.9	404.2 ± 39.6	.12
Relative percentage within intracranial cavity	94.6 ± 2.6	91.0 ± 4.0	87.8 ± 4.9	.001
Cortical gray matter				
Absolute volume, ml	193.4 ± 27.1	177.9 ± 38.3	176.5 ± 33.2	.36
Relative percentage within intracranial cavity	41.5 ± 5.9	39.3 ± 6.6	38.4 ± 6.4	.33
Subcortical gray matter				
Absolute volume, ml	12.3 ± 3.0	12.6 ± 4.2	12.3 ± 3.5	1.0
Relative percentage within intracranial cavity	2.6 ± 0.6	2.8 ± 0.9	2.7 ± 0.7	.94
Myelinated white matter				
Absolute volume, ml	17.8 ± 8.2	13.4 ± 5.7	12.9 ± 5.4	.09
Relative percentage within intracranial cavity	3.8 ± 1.6	3.0 ± 1.2	2.8 ± 1.2	.11
Unmyelinated white matter				
Absolute volume, ml	218.0 ± 26.2	206.2 ± 31.8	202.5 ± 31.5	.32
Relative percentage within intracranial cavity	46.7 ± 5.1	45.9 ± 6.0	43.9 ± 5.6	.34
Cerebrospinal fluid				
Absolute volume, ml	25.1 ± 12.7	41.0 ± 19.4	57.7 ± 26.5	.002
Relative percentage within intracranial cavity	5.4 ± 2.6	9.0 ± 4.0	12.2 ± 4.9	.001

Note. Reported associations persisted after adjustment for postmenstrual age at MRI, sex, and family socioeconomic status.

Table 5
Neonatal Regional Total Cerebral Tissue Volumes and Risk of Persistent Attention/Hyperactivity Problems

	Neonatal Regional Total Cerebral Tissue Volume, $M \pm SD$			Attention/Hyperactivity Problem, Age 4 to 9 Years			p
	None (1)	None/Transient (2)	Persistent (3)	Overall	(1) vs. (3)	(2) vs. (3)	
	Full-Term (N=6)			Very Preterm (N=67)			Very Preterm (N=13)
Dorsal prefrontal region							
Absolute volume, ml	51.4 ± 15.5	44.7 ± 9.6	44.8 ± 9.1	.19	.19	.96	
Relative percentage within intracranial cavity	92.1 ± 5.5	83.7 ± 8.3	78.8 ± 8.3	.001	.001	.05	
Orbitofrontal region							
Absolute volume, ml	11.5 ± 5.3	9.1 ± 3.8	8.7 ± 3.9	.16	.16	.76	
Relative percentage within intracranial cavity	93.5 ± 3.0	87.5 ± 8.4	83.8 ± 10.8	.02	.02	.16	
Premotor region							
Absolute volume, ml	56.6 ± 9.2	50.6 ± 8.3	50.0 ± 6.3	.10	.10	.79	
Relative percentage within intracranial cavity	93.0 ± 2.6	88.8 ± 5.1	85.0 ± 5.7	.002	.002	.02	
Subgenual region							
Absolute volume, ml	22.5 ± 6.3	22.6 ± 4.8	21.3 ± 4.3	.63	.63	.38	
Relative percentage within intracranial cavity	84.5 ± 6.6	84.8 ± 5.3	80.7 ± 5.2	.15	.15	.01	
Sensorimotor region							
Absolute volume, ml	69.5 ± 7.2	55.0 ± 12.1	57.7 ± 18.0	.07	.07	.50	
Relative percentage within intracranial cavity	96.9 ± 1.7	92.7 ± 4.1	89.6 ± 5.2	.001	.001	.01	
Midtemporal region							
Absolute volume, ml	32.5 ± 7.3	31.2 ± 5.6	30.4 ± 5.4	.46	.46	.68	
Relative percentage within intracranial cavity	91.5 ± 3.8	92.7 ± 2.9	91.3 ± 3.4	.93	.93	.15	
Parieto-occipital region							
Absolute volume, ml	126.0 ± 8.9	115.9 ± 16.6	115.5 ± 14.0	.18	.18	.94	
Relative percentage within intracranial cavity	96.7 ± 2.7	91.9 ± 5.0	89.1 ± 5.8	.003	.003	.06	
Inferior occipital region with cerebellum							
Absolute volume, ml	70.6 ± 13.5	80.3 ± 14.6	75.0 ± 11.6	.53	.53	.22	
Relative percentage within intracranial cavity	97.4 ± 1.5	96.5 ± 2.2	95.3 ± 5.7	.16	.16	.18	

Note. Reported associations persisted after adjustment for postmenstrual age at MRI, sex, and family socioeconomic status.