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Regional Cerebral Development at Term Relates to School-Age Social-Emotional Development in Very Preterm Children

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Abstract

Objective—Preterm children are at risk for social-emotional difficulties, including autism and attention deficit hyperactivity disorder. We assessed the relationship of regional brain development in preterm children, evaluated via MRI at term-equivalent postmenstrual age (TEA), to later social-emotional difficulties.

Method—MR images obtained at TEA from 184 very preterm infants (gestation <30 weeks or birthweight <1250 g) were analyzed for white matter abnormalities, hippocampal volume, and brain metrics. 111 infants underwent diffusion tensor imaging, which provided values for

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fractional anisotropy (FA) and apparent diffusion coefficient (ADC). Social-emotional development was assessed with the Infant Toddler Social and Emotional Assessment (ITSEA) at age 2 and the Strengths and Difficulties Questionnaire (SDQ) at age 5.

Results—Higher ADC in the right orbitofrontal cortex was associated with social-emotional problems at age 5 (peer problems, $p < 0.01$). In females, smaller hippocampal volume was associated with increased hyperactivity ($p < 0.01$), peer problems ($p < 0.05$) and SDQ total score ($p < 0.01$). In males, a smaller frontal region was associated with poorer prosocial ($p < 0.05$) scores. Many of the hippocampal findings remained significant after adjusting for birthweight z score, intelligence, social risk, immaturity at birth, and parental mental health. These associations were present in children who had social-emotional problems in similar domains at age 2 and those who did not.

Conclusions—Early alterations in regional cerebral development in very preterm infants relate to specific deficits in social-emotional performance by school-age. These results vary by gender. Our results provide further evidence for a neuroanatomical basis for behavioral challenges found in very preterm children.

Keywords

Preterm infant; Neurodevelopment; social-emotional development; orbitofrontal cortex; Hippocampus

INTRODUCTION

Preterm birth is a major public health issue, principally due to the high risk for adverse developmental outcomes in survivors. Between 30–60% of very preterm (VPT) children (born <30 weeks' gestation) will experience cognitive challenges and learning disabilities.^{1,2} Additionally, there is a growing literature reporting delays in social-emotional development with an increased prevalence of anxiety, depression, attention deficit hyperactivity disorder (ADHD), and autism.^{3–5} Indeed, children born <26 weeks are three times more likely to have a psychiatric diagnosis at age 11 compared to full-term peers.³ ADHD inattentive-type was the most common diagnosis, with rates among extremely preterm children four times higher than that of their peers. There were also significant increases in emotional disorders, anxiety disorders and autism.

As previously published, our cohort of VPT infants had higher internalizing and dysregulation scores and lower competence scores as measured by the Infant Toddler Social and Emotional Assessment (ITSEA) at age 2 years when compared with peers born at term.⁶ More recently, we have also found that early social-emotional difficulties at age 2 predicted comparable difficulties at age 5 and we have noted increased emotional symptoms, peer relationship difficulties, elevated hyperactivity/inattentive symptoms, (Treyvaud, Doyle, Lee et al., unpublished material, 2011) and overall social-emotional difficulties at age 5 as measured by the Strengths and Difficulties questionnaire (SDQ) compared to same age peers.⁷ Others have also noted similar social-emotional challenges at age 5.⁸ Similarly, parental reports of social-emotional problems at ages 2 and 6 years were predictive of psychiatric diagnoses at age 11.⁸

Preterm birth is also associated with brain injury and altered cerebral development. MRI-based studies have revealed that VPT infants commonly display a variety of white matter abnormalities, including diffuse signal abnormalities, loss of volume, enlarged ventricles, and delayed maturation.^{9–12} VPT infants at term-equivalent postmenstrual age (TEA) also exhibit gray matter abnormalities, including decreased gray matter volume and delayed cortical gyration.^{13–15} These alterations in brain structure by TEA are predictive of later

cognitive deficits,^{15–18} with some studies reporting that specific regional abnormalities are associated with particular cognitive delays, including deficits in IQ and working memory.^{16,17,19}

Evidence for a relationship between altered neonatal cerebral development and later cognitive deficits is emerging in the VPT population, however, less is known about the relationship between aberrant cerebral development and social-emotional outcomes in this group. A few studies have related abnormalities in cerebral development to psychiatric symptomatology in preterm adolescents^{20,21} including a reduction in hippocampal volume in preterm adolescents with ADHD.²² Additionally, white matter abnormalities and cerebellar hemorrhage during infancy have been associated with social deficits.^{6,23} Notably, a large proportion of preterm children that screened positive for autism had normal conventional MRIs, emphasizing the need for more sensitive, quantitative MRI approaches for detecting the neuroanatomical basis for social-emotional deficits in preterm infants.²⁴ The relative influence of aberrant neonatal cerebral development on social-emotional outcomes compared to other well-known risk factors more common among parents of preterm infants,^{25–27} including parental mental illness, lower maternal education, and lower socioeconomic status,^{28–30} also remains unclear.

The current study aims to address these issues by evaluating the relationship between cerebral development at TEA (determined using the MRI techniques of diffusion tensor imaging, regional brain volumes and brain metrics) and social-emotional outcomes at age 5 in a cohort of VPT children. We assessed whether alterations of development in brain regions implicated in social-emotional development by prior research, such as the frontal lobes and orbital frontal cortex (OFC),³¹ temporal cortex,³² cerebellum,³³ and hippocampus,³⁴ would be associated with impaired social-emotional outcomes at age 5, even after adjusting for sociodemographic factors. A secondary aim was to evaluate whether any associations between the neonatal brain markers and social-emotional outcomes at age 5 varied depending on whether these behavioral problems were also noted at age 2.

METHOD

Participants

The families were recruited for this study as part of the Victorian Infant Brain Studies (VIBeS) cohort between 2001 and 2003. Entry criteria included being born at less than 30 weeks gestation or weighing less than 1,250 g at birth. The VPT infants were born at or transferred shortly after birth to the Royal Women's Hospital, Melbourne, Australia. Infants were excluded if they had a major congenital abnormality associated with early mortality. The study was approved by the Research and Ethics Committees at the Royal Children's and Women's Hospital. Informed parental consent was obtained for all participants.

Magnetic Resonance Imaging

VPT infants that underwent an MRI scan of their brain at term equivalent postmenstrual age (TEA), 37 to 43 weeks, are included in this analysis. The MRI was performed without sedation or anesthesia using a 1.5T Signa LX Echospeed system (GE Healthcare, Milwaukee, WI). The sequences utilized included a 3D Fourier transform spoiled gradient recalled-echo sequence; a double-echo (proton-attenuation and T2-weighted) spin-echo sequence; and a line scan diffusion sequence with details previously published.³⁵ The MR images were analyzed for the following: 1) qualitative white matter abnormalities; 2) hippocampal volume 3) brain metrics; and 4) diffusion parameters apparent diffusion coefficient (ADC) and fractional anisotropy (FA).

Qualitative MR Analysis—An established qualitative scoring system was used to classify white matter as normal, mild, moderate, or severe.³⁶ All scans were scored by two raters who were blind to clinical status, with 94% inter-rater agreement.³⁵ White matter abnormality was graded using five items: the nature and extent of white matter signal abnormality, white matter volume loss, the presence of cystic abnormalities, ventricular dilatation, and thinning of the corpus callosum.

Quantitative MR Analysis

Hippocampal Volumetric Analysis: Details of the segmentation have been previously described.³⁷ The hippocampus was manually outlined by a single individual (D.T.) blinded to perinatal data. Each MR image underwent hippocampal segmentation twice, once in original orientation and again after being flipped in the left/right direction, to take into account possible hemispheric bias in the operator. The hippocampal volume used in analyses was the average of these two segmentations (original and flipped).

Brain Metrics: A detailed description of the application of this method to this cohort has been reported previously.³⁸ Of the original 15 parameters measured, bifrontal diameter, bilateral frontal heights, and transverse cerebellar diameter were selected as regional measures of interest. To test for reliability, brain metrics were repeated on 7 scans by 3 different observers, and the metrics were measured twice by each of the three observers on 3 scans. The intra-rater and inter-rater consistencies were high for all 3 measures, with ICCs above 0.8.

Diffusion Tensor Imaging Analysis—A full description of the DTI analysis is detailed elsewhere.³⁹ Data were analyzed using XPhase image analysis software (SE Maier, Boston, Mass) and Analyze (Mayo Clinic, Rochester, MN). Values for ADC and FA were calculated. Of the 12 manually selected regions of interest (ROIs), four -- bilateral frontal lobes on superior and inferior axial sections -- were used. The superior axial section was taken at a level just above the lateral ventricles and the inferior section was taken at a level through the basal ganglia and posterior limb of the internal capsule (PLIC). Intra-rater reliability was assessed in 12 infants and was high, with no statistical difference on test-retest ($p=0.7$). Additional ROIs were placed bilaterally in the OFC and the temporal lobes (Figure 1.). Intra-rater reliability was assessed in 5 infants, with ICCs of 0.9 for ADC and 0.6 for FA. All ROI placements were checked by an individual experienced in neonatal neuroimaging (T.I.).

Children's Social-Emotional Development

Children's social-emotional development was assessed at age 5 with the Strengths and Difficulties Questionnaire, Informant-Rated Version for Parents (SDQ) developed by Goodman.^{40,41} The SDQ is designed for children aged 3 to 16 years with 25 items divided between 5 subscales: emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems, and prosocial behavior. Each subscale contains 5 questions with 3-point response scales ('Not true'=0, 'Somewhat true'=1, 'Certainly true'=2), with a score range of 0–10. A total difficulties score from the first four subscales was calculated. For each subscale except prosocial behavior, higher scores indicate more impaired functioning. Scores can be classified into normal, borderline, or abnormal based on established cut-off scores.

The assessment of social-emotional development at age 2 years in this cohort using the ITSEA has been previously described.⁶ Briefly, the ITSEA is a 135 item parent-rated measure of children's social-emotional development with four domains: internalizing problems, externalizing problems, dysregulation, and social-emotional competence.⁴²

Research indicates that the ITSEA has good test-retest reliability and good criterion validity and supports the factor structure of the domains.⁴³

Sociodemographic Predictor Variables

The following factors were identified *a priori* and used as possible predictor variables for social-emotional development: gestational age, birthweight z-score, fluid intelligence, gender, parental mental health, and social risk.^{6,44,45} The Matrices subtest from the Kaufman Brief Intelligence Test-Second Edition (K-BIT 2) was collected at age five as a proxy for fluid intelligence. The K-BIT 2 scales have a mean of 100 and standard deviation of 15 and have good reliability and validity.⁴⁶ Parental mental health was assessed in the child's primary caregiver at the 2 year follow-up assessment using the 28-item self-administered General Health Questionnaire (GHQ-28) with only the total score used in the analysis.⁴⁷ Social risk was assessed using a composite measure assessing family structure, primary caregiver education, occupation and employment status of primary income earner, language spoken at home, and maternal age at infant's birth. Each of these six domains was scored on a 3-point scale where a score of 0 represented lowest risk, and a score of 2 represented highest risk.⁴⁸ The sum of the six domains formed the total social risk score.

Data Analysis

SPSS version 18 (SPSS Inc, Chicago, IL) and SAS version 9.2 (SAS Institute, Cary, NC) were used to analyze the data. To assess the relationship between brain measures at TEA and social-emotional development at age 5, measurements of the same type (i.e. all diffusion measures) were entered into a stepwise linear regression with SDQ subscales as outcome variables to determine the independently significant variables. Variables that were significant ($p < 0.05$) were then placed in univariate models that accounted for clustering between twins/triplets by entering this relationship as a random effect.⁴⁹ Adjustment for multiple comparisons was conducted by setting individual alpha levels for each SDQ scale equal to 0.05 divided by the number of brain measures tested for that scale. Univariate models with hippocampal volumes were also adjusted for total intracranial volume to differentiate the effect of absolute versus relative volume differences. The sociodemographic factors were entered in the models as covariates. Given known gender differences in brain measurements,⁵⁰ interactions between i) gender and hippocampal volumes and ii) gender and brain metrics were assessed. Significant interactions were analyzed separately, stratified by gender. Given our previously report of hippocampal asymmetry,⁵¹ left and right hippocampal volumes were analyzed separately. Analyses were repeated excluding children with moderate-severe white matter injury to ensure effects were independent of severity of white matter injury. To evaluate whether specific brain regions affect social-emotional development, separate exploratory univariate analyses were conducted for the metrics not selected in the analysis (e.g. biparietal diameter) to see if any showed a significant association with social-emotional development. We tested whether statistically significant associations between neonatal brain measures and SDQ scales varied based on whether the children had social-emotional difficulties at age 2 using two methods. First, we matched the SDQ scale with the corresponding ITSEA domain it was most related to in our prior study⁵² (SDQ emotional symptoms/ITSEA internalizing problems, SDQ conduct problems and hyperactivity-inattention/ITSEA externalizing, SDQ peer problems and prosocial behaviors/ITSEA competence). Given different measures were used at ages 2 and 5, we dichotomized the scales of both the ITSEA and SDQ based on the score equal to the 80th percentile (20th percentile for ITSEA competence and SDQ prosocial behavior) of the 73 term controls recruited for VIBeS.⁶ First, the univariate regression models were rerun only for those SDQ scales that had brain measures that were significantly associated with them. We parameterized the univariate regression models to test for differences in slopes between the ITSEA cut-off groups. Second, among only those who scored above the 80th percentile on

the SDQ scale at age 5, t-tests were used to analyze any differences in the significantly associated brain measure between those who also scored above and below the 80th percentile on the corresponding ITSEA scale at age 2.

RESULTS

Demographics

Two hundred and twenty-seven VPT children were recruited for the Victorian Infant Brain Studies (VIBeS) and 184 underwent MRI scans that were of sufficient quality for analysis. DTI acquisition commenced in the latter part of the study with 111 subjects having DTI acquisition. Nine infants had MRI scans either before 37 or after 43 weeks postmenstrual age and were excluded. Between August 2006 and June 2009, 195 ninety-five children were seen for the 5 year follow-up assessments (follow-up rate of 89%). Of the original VPT cohort, 7 infants were excluded from analysis (2 had died, 5 had severe, disabling cerebral palsy), 9 refused and 16 were inaccessible for follow-up (3 did not attend, 13 had relocated). The number of children with both SDQ and individual brain measures was as follows: hippocampal volumetric analyses $n=153$, brain metrics $n=165$ and DTI $n=80$. The children analyzed for this study had lower parental GHQ scores compared with those without complete SDQ data ($p=0.005$). There were no other significant differences in the clinical or sociodemographic characteristics. There were no significant differences between the subset that had DTI and the rest of the cohort on any demographic, clinical, or outcome measures.

The clinical characteristics of the VPT children included in the study are summarized in Table 1.

Association between MRI measures at TEA and Social-Emotional Development at age 5—Hippocampal volumes and brain metrics were analyzed

stratified by gender after analyses showed significant interactions between these two brain measures and gender on the SDQ outcomes.

After conducting the regression analyses with the hypothesized regions, the following MRI measures were candidate variables for SDQ scales: peer problems (right OFC ADC, left inferior temporal FA, right hippocampal volume for females), prosocial behavior (right OFC ADC, right superior frontal FA, bifrontal diameter in males, trans cerebellar diameter in females), hyperactivity/inattention (right inferior temporal ADC, bilateral frontal height in males, bilateral hippocampal volume in females), conduct problems (inferior left temporal FA, bilateral hippocampal volume in females) and total (bilateral hippocampal volume in females).

Exploratory analyses of other regions (i.e. biparietal diameter) found no associations with any SDQ scale

Table 2 displays the results of the univariate models and the multivariate models adjusted for the sociodemographic factors for all of the SDQ scales.

Peer Problems and Prosocial Behavior

Smaller right hippocampal volume and worse peer problems scores ($p=0.013$) were associated for females after controlling for total volume. On univariate analysis, higher ADC in the right OFC was associated with higher peer problem scores ($p=0.003$, α set to $p<0.017$), while there was a trend level association between smaller bifrontal diameter and poorer prosocial scores for males ($p=0.017$, α set to $p<0.01$). These latter two findings did not persist after multivariate adjustment.

Hyperactivity /Inattention

On univariate analyses, increased right inferior temporal lobe ADC and hyperactivity/inattention scores was not significant after Bonferroni correction ($p=0.049$, α set to $p<0.01$). Among females, smaller right and left hippocampal volumes predicted higher hyperactivity/inattention scores ($p=0.002$ and $p=0.003$ respectively). When correcting for total volume, right hippocampal volume became a trend ($p=0.02$). In males, smaller right frontal height was associated with higher hyperactivity/inattention scores but this was not significant after Bonferroni correction ($p=0.04$). On multivariate analyses, no predictors were significant after correction though left ($p=0.04$) and right ($p=0.06$) hippocampal volume remained trends.

Other SDQ domains

For females, smaller right and left hippocampal volumes were associated with poorer SDQ total scores on univariate ($p=0.006$ and $p=0.004$, α set to $p<0.025$) and multivariate ($p=0.02$ and $p=0.01$) analyses. There were also trends after adjustment for multiple comparisons (α set to $p<0.025$) between conduct scores and smaller bilateral hippocampal volumes in females ($p=0.03$ right and $p=0.045$ left), but this association weakened after adjusting for total intracranial volume ($p=0.08$ right and $p=0.12$ left).

Influence of White Matter Injury

Excluding children with moderate-severe white matter injury did not alter the associations between brain structure and social-emotional outcomes (data not shown).

Exploratory analyses of gender differences

Given there were notable gender differences in the relationships between regional MRI measures and some of the SDQ scales, particularly with hippocampal volume and hyperactivity/inattention (see Fig. 2), analyses were conducted to determine if this was secondary to gender differences in SDQ mean scores or in the proportion of those scoring in the abnormal range. There were no differences in the mean scores except males displayed higher hyperactivity/inattention scores ($t=-2.1$, $p=0.03$). There were no differences in the proportion of males or females scoring in the abnormal range on any scale.

Brain Measures and Continuity of Social-Emotional Symptoms

Comparison of the regression slopes between those who had elevated and normal related ITSEA domain scores at age 2 revealed no significant differences in any of the brain measure/SDQ scale relationships (See Figure 3). Among the subsample of VPT children with elevated SDQ scores at age 5, females above the 80th percentile for peer problems at age 5 and below the 20th percentile for the ITSEA competence domain at age 2 had smaller right hippocampal volumes ($t=2.38$, $p=0.03$) than those with better age 2 competence scores.

DISCUSSION

This study provides evidence that regional disruptions in brain development detectable at TEA in VPT children are associated with impaired social-emotional development at age 5 years. Social-emotional difficulties are associated with abnormalities in the frontal lobes and hippocampus that vary by gender. Specifically, inattention and hyperactivity symptoms are associated with decreased hippocampal volume in females, and decreased frontal lobe growth in males. Additionally, decreased hippocampal volume in females was associated with increased peer problems, conduct, and total SDQ scores. Some of the hippocampal relationships remained significant after adjusting for social risk, birthweight z score, cognitive development, gestational age, and parental mental health. This study did note

regional specificity in that the social-emotional development was related only to hypothesized regions.

This study is unique in its comparison of brain diffusion parameters during the neonatal period to later social deficits. The finding that higher ADC in the right OFC is associated with peer relationship difficulties is particularly salient as this region is known to be functionally involved with social regulation, social cognition and theory of mind which are disturbed in autism spectrum disorders (ASDs).⁵³ Indeed, the SDQ peer problems scale was most strongly associated with an ASD diagnosis three years later compared to an emotional, behavioral, or ADHD diagnosis.⁵⁴ Higher ADC in this region among older children with ASDs has been previously noted.⁵⁵ Similarly, associations between social functioning and the white matter of the right OFC,⁵⁶ and hypoactivation in the OFC when processing fearful faces⁵⁷ among children with ASD has been reported. Evidence has highlighted the particular importance of the right OFC in relation to social conduct.^{58,59}

Higher ADC is suggestive of disruption in the cerebral white matter. These findings, at TEA, may reflect prior injury to premyelinating oligodendrocytes and the subsequent failure of their development and ensheathment of axons³⁹ or axonal loss from broader neuronal disruption.⁶⁰ Such impairments in axonal organization may persist throughout child development contributing to these social-emotional deficits. Thus, detecting this disruption in cerebral white matter during the neonatal period may help identify infants that could benefit from early intervention services to improve social skills development.

This study also highlights gender differences in the relationships between regional brain development and social-emotional development. Indeed, for females, neonatal hippocampal volume remained a significant factor in most analyses after adjusting for many other well-known risk factors. The results also suggested trends between decreased frontal growth and prosocial behavior and inattention and hyperactivity in males. Animal models have suggested that hippocampal neurogenesis is particularly sensitive to prenatal stress and early maternal deprivation in females.^{61,62} Similarly, frontal and prefrontal regions are more sensitive to early maternal deprivation in males and relate to ADHD-like symptoms.⁶³ Different brain regions in males and females have been related to similar symptomatology.⁶⁴ Thus, the sexual dimorphism noted here may be secondary to different neuronal responses in males and females to the early stress of preterm birth and the NICU environment with abnormal development of different regions leading to similar social-emotional deficits. This hypothesis may also explain why gender differences have not been noted in full-term children.

The current study also indicates that the associations between the neonatal brain measures and age 5 social-emotional development were similar whether those difficulties were reported at age 2 and age 5 or only at age 5. This analysis was exploratory given the small sample size of children with reported social-emotional problems at both ages. Nevertheless, these results suggest that other factors may be related to the persistence of social-emotional difficulties detected at age 2 years. These regional brain abnormalities detected at term-equivalent may still hold promise as early biomarkers for social-emotional difficulties that emerge at preschool age but perhaps not for those that emerge as early as age 2. It is plausible that further brain maturation is necessary before the impact of these regional alterations on particular symptom domains becomes evident. Alternatively, it suggests that these early alterations in regional cerebral development are related to specific social-emotional domains like symptoms of inattention/hyperactivity rather than more global categories of internalizing, externalizing, dysregulation, and competence. Another interpretation is that these neonatal brain abnormalities may only relate to transient social-

emotional problems at age 5. While this seems less likely, further longitudinal assessments of this cohort will help clarify these findings.

A limitation of the current study includes the sole use of parental report of social-emotional development rather than a clinical interview. Prior work has shown high reliability and validity for the SDQ,⁶⁵ and it has adequate psychometric properties in distinguishing children with and without DSM-IV psychiatric disorders.⁶⁶ Nevertheless, the use of informants like teachers as well as clinical interviews to refine diagnoses should be utilized in future studies. Another possible limitation is that diffusion information was obtained from prespecified ROIs. While tract-based analysis and MR tractography would be useful to explore the associations between alterations in diffusivity and fiber tract maturation and social-emotional development, the white matter of the frontal and temporal ROIs in this study are not yet well-developed, making tractography technically challenging. Diffusion tractography could be applied to these children at later ages on follow-up. Additionally, parental mental health was assessed at age 2 and not age 5 and thus, its impact on the outcome in the models may be somewhat underestimated though a concurrent measure at age 5 would complicate an assessment of causality. A further limitation is the use of different social-emotional measures at ages 2 and 5. The domains of the two have been found to be similar and specific relationships between similar domains have been noted in this cohort.⁵² This study also has several strengths, including the large sample size and prospective design. Additionally, the imaging was conducted during the early neonatal period, prior to the onset of symptoms of social-emotional problems. Thus, these results suggest that previously identified cerebral abnormalities are likely related to the underlying pathology of social-emotional problems rather than secondary to prolonged abnormal cerebral functioning.

While requiring replication, these preliminary findings have possible clinical implications. Detecting these regional abnormalities could indicate the need for heightened clinical surveillance and early targeted interventions aimed at promoting social-emotional development for preterm infants as is currently done for cognitive and motor development. Finally, they may also improve the quality of the prognostic information provided for families of VPT infants as they are discharged from the hospital. Future directions for this research include ongoing follow-up of this cohort to assess both social-emotional development at later ages and the role of mediating and moderating environmental factors as well as further neuroimaging evaluations to map the persistence or modification of these structural changes in relationship to social-emotional development.

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Figure 1.

Left: Axial Apparent Diffusion Coefficient (ADC) image at the level of the orbits with Regions of interest (ROIs) placed in the bilateral Orbital Frontal Cortices. Middle: Superior Axial ADC image with ROIs placed in the bilateral temporal lobes. Right: Axial ADC image with ROIs placed in the bilateral temporal lobes where bilateral amygdalae first visible.

Figure 2. Scatterplots of Hippocampal Volume and Strength and Difficulties Questionnaire (SDQ) Hyperactivity-Inattention Scale. Note: Left panels represent females and right panels represent males.

Figure 3.

A: Mean z-scores of labeled brain measures and Strength and Difficulties Questionnaire (SDQ) scales with fitted regression lines for those above (left panel) and below (right panel) the term 80th percentile for the labeled Infant Toddler Social Emotional Assessment (ITSEA) domain at age 2. B: Mean of brain measures for those who were above and below the 80th percentile of the labeled ITSEA domains for the Very Preterm (VPT) subgroup scoring above the term 80th percentile for the SDQ peer problems (top row) and SDQ hyperactivity/inattention (bottom row) scales at age 5. ADC = Apparent Diffusion Coefficient

Table 1

Sample Characteristics

Characteristic	N=165
Birthweight, g, mean (SD)	980 (216)
GA at birth, weeks, mean (SD)	27.6 (1.9)
GA at MRI, weeks, mean (SD)	40.1 (1.2)
Male, <i>n</i> (%)	85 (52)
Multiple births, <i>n</i> (%)	68 (41)
Caesarean section delivery, <i>n</i> (%)	117 (71.3)
Apgar, 5 minutes, mean (SD)	8.2 (1.2)
Length of stay, days, mean (SD)	84.9 (31.6)
Moderate-severe WMI, <i>n</i> (%)	28 (17)
Total social risk, mean (SD)	2.5 (2.4)
Total GHQ score, mean (SD)	18.0 (10)
K-BIT 2 Matrices subtest, mean (SD)	95.9 (12.9)

Note: GA= gestational age, GHQ= General Health Questionnaire, K-BIT=Kaufman Brief Intelligence Test, MRI= Magnetic Resonance Imaging, WMI= White Matter Injury

Table 2

Imaging Predictors of Strengths and Difficulties Questionnaire (SDQ) Scales

	Univariate β (95% CI)	Multivariate β (95% CI)
SDQ Peer Problems^a		
ADC Rt. OFC	0.29(0.11 to 0.47) **	0.12(−0.11 to 0.34)
FA Lt. Inferior Temporal	−0.16(−0.32 to −0.009)	−0.15(−0.13 to −0.01)
Rt. Hippocampal vol.-Females ^c	−0.18(−0.36 to −0.004) *	−0.22(−0.44 to −0.004) *
SDQ ProSocial Behavior^b		
ADC Rt. OFC	−0.13(−0.31 to 0.05)	−0.13(−0.35 to 0.09)
FA Rt. Superior Frontal	0.08(−0.08 to 0.24)	0.05(−0.11 to 0.21)
Bifrontal diameter-Males	0.24(0.04 to 0.44)	0.12(−0.12 to 0.36)
Transcerebellar diameter-Females	0.15(−0.07 to 0.37)	−0.03(−0.23 to 0.17)
SDQ Hyperactivity^a		
ADC Rt. Inferior Temporal	0.21(−0.01 to 0.43)	0.15(−0.01 to 0.36)
Lt. frontal height-Males	−0.19(−0.38 to −0.02)	−0.19(−0.41 to 0.02)
Rt. frontal height-Males	−0.21(−0.41 to −0.01)	−0.16(−0.38 to −0.06)
Rt. Hippocampal vol.-Females	−0.30(−0.50 to −0.11) **	−0.21(−0.43 to 0.01)
Lt. Hippocampal vol.-Females	−0.28(−0.48 to −0.08) **	−0.22(−0.44 to 0.004)
SDQ Conduct^a		
FA Lt. Superior Temporal	−0.18(−0.38 to 0.02)	−0.18(−0.38 to 0.02)
Rt. Hippocampal vol.-Females	−0.22(−0.42 to −0.02) *	−0.17(−0.38 to −0.05)
Lt. Hippocampal vol.-Females	−0.20(−0.40 to −0.004)	−0.14(−0.36 to −0.08)
SDQ Total^a		
Rt. Hippocampal vol.-Females	−0.24(−0.40 to −0.08) **	−0.22(−0.40 to −0.04) *
Lt. Hippocampal vol.-Females	−0.24(−0.40 to −0.08) **	−0.22(−0.38 to −0.06) *

Note: Results presented are after Bonferroni correction. Multivariate models adjusted for birthweight z-score, cognitive development, social risk, immaturity, gender, and parental mental health. β is standardized estimate = number of standard deviations (SD) outcome will change with 1 SD change in predictor. ADC = Apparent Diffusion Coefficient; CI = confidence interval; FA= fractional anisotropy; Lt. = left; OFC = Orbital Frontal Cortex; Rt. = right.

^aHigher scores indicate more optimal behavior.

^bHigher scores indicate more problematic behavior.

^csignificant after adjusting for total volume

* p 0.05,

** p 0.01.