Psychological Medicine

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Growth of prefrontal and limbic brain regions and anxiety disorders in children born very preterm

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Abstract

Background. Children born very preterm (VP) display altered growth in corticolimbic structures compared with full-term peers. Given the association between the cortiocolimbic system and anxiety, this study aimed to compare developmental trajectories of corticolimbic regions in VP children with and without anxiety diagnosis at 13 years.

Methods. MRI data from 124 VP children were used to calculate whole brain and corticolimbic region volumes at term-equivalent age (TEA), 7 and 13 years. The presence of an anxiety disorder was assessed at 13 years using a structured clinical interview.

Results. VP children who met criteria for an anxiety disorder at 13 years ($n = 16$) displayed altered trajectories for intracranial volume (ICV, $p < 0.0001$), total brain volume (TBV, $p = 0.029$), the right amygdala ($p = 0.0009$) and left hippocampus ($p = 0.029$) compared with VP children without anxiety ($n = 108$), with trends in the right hippocampus ($p = 0.062$) and left medial orbitofrontal cortex ($p = 0.079$). Altered trajectories predominantly reflected slower growth in early childhood (0–7 years) for ICV ($\beta = -0.461$, $p = 0.020$), TBV ($\beta = -0.503$, $p = 0.021$), left ($\beta = -0.518$, $p = 0.020$) and right hippocampi ($\beta = -0.469$, $p = 0.020$) and left medial orbitofrontal cortex ($\beta = -0.761$, $p = 0.020$) and did not persist after adjusting for TBV and social risk.

Conclusions. Region- and time-specific alterations in the development of the corticolimbic system in children born VP may help to explain an increase in anxiety disorders observed in this population.

Introduction

With advances in neonatal intensive care, survival rates of infants born very preterm (VP) and very low birth-weight (VLBW) have increased (Doyle, 2004; Helenius, Gissler, & Lehtonen, 2019). However, many of these individuals continue to experience adverse long-term outcomes, with cognitive, attentional, socio-emotional and motor problems well documented (Anderson et al., 2011; Bhutta, Cleves, Casey, Cradock, & Anand, 2002; Bracewell & Marlow, 2002; Talge et al., 2010).

Higher rates of anxiety disorders have been documented in VP and VLBW children and adolescents (Botting, Powls, Cooke, & Marlow, 1997; Indredavik et al., 2004; Johnson et al., 2010; Treyvaud et al., 2013), however it is less clear whether this increased risk persists beyond adolescence. Rates of VP/VLBW-born adults that meet diagnostic criteria for an anxiety disorder vary across studies, with some reporting increased risk relative to term-born peers (Van Lieshout, Boyle, Saigal, Morrison, & Schmidt, 2015; Walshe et al., 2008) and others reporting no difference (Burnett et al., 2013; Johnson, O'Reilly, Ni, Wolke, & Marlow, 2019; Westrupp, Northam, Doyle, Callanan, & Anderson, 2011). When applying a dimensional approach to assessment of symptoms, Johnson et al. (2019) found increased broadband internalizing

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and anxiety symptoms in adults born VP or VLBW compared with normal birth weight peers, while other studies have found no difference in anxiety symptoms in adulthood (Burnett et al., 2013; Westrupp et al., 2011). Prospective longitudinal cohorts provide insights into the progression of clinical anxiety in this population. In the Bavarian Longitudinal Study, rates of diagnosed anxiety were increased in the VP/VLBW group at 8 years, but not at 6 or 26 years (Jaekel, Baumann, Bartmann, & Wolke, 2018). Conversely, rates of anxiety disorders were increased at 14, 19 and 26 years in those born VLBW in the Trondheim cohort (Indredavik et al., 2004; Laerum et al., 2017).

Mechanisms underlying the increased vulnerability to clinical anxiety following VP birth remain poorly understood. VP birth occurs prior to completion of the third trimester, a period of rapid brain growth and maturation (Dobbing, 1990; Volpe, 2009). Following this stressful birth event, infants are without placental support and rely on their own immature system to support brain development *ex-utero*. Neuroimaging studies have revealed high rates of white matter abnormalities and grey matter volume reductions in VP neonates compared with FT controls (Inder, Warfield, Wang, Huppi, & Volpe, 2005; Thompson et al., 2014), and during childhood (de Kieviet, Zoetebier, van Elburg, Vermeulen, & Oosterlaan, 2012); with grey matter volume reductions occurring in a region-specific manner (Alexander et al., 2019; Cismaru et al., 2016; Omizzolo et al., 2013; Peterson et al., 2000; Thompson et al., 2007).

Smaller volume of the amygdala – a structure involved in generating a response to fear stimuli – has been reported in individuals born VP compared with FT controls in cross-sectional studies at term-equivalent age (TEA) (Cismaru et al., 2016) and at 8 years of age (Peterson et al., 2000). Smaller hippocampal volumes have also been reported in VP individuals compared with FT controls in cross-sectional studies at 7 years and 14–15 years of age (Nosarti et al., 2002; Omizzolo et al., 2013). These regions form part of the wider, highly interconnected corticolimbic system which has been implicated in anxiety (Gold et al., 2017; Mueller et al., 2013; Newman et al., 2016; Ochsner et al., 2004; Strawn et al., 2013), and includes portions of the prefrontal and cingulate cortices. In VP compared with FT controls, we have recently reported slower volume growth from TEA to 7 years in the anterior cingulate cortex and lateral and medial orbitofrontal cortex in line with slower growth in total brain volume (Thompson et al., 2020).

Thus, the current literature suggests that VP children display slower growth in corticolimbic structures early in life. However, it is unclear whether altered corticolimbic growth in children born VP is associated with anxiety. The current study extends previous findings (Thompson et al., 2020) and aimed to compare corticolimbic region volume trajectories across childhood (TEA, 7 and 13 years) between VP children with and without an anxiety disorder diagnosis at 13 years. It was hypothesized that VP children diagnosed with anxiety disorders would display altered corticolimbic trajectories (especially during early childhood), compared with VP children without an anxiety disorder diagnosis at 13 years.

Methods

Participants

Participants were recruited as a part of the Victorian Infant Brain Study (VIBeS), a prospective longitudinal study consisting of infants born between July 2001 and December 2003 at the Royal Women's Hospital in Melbourne, Australia. Two hundred and twenty-four infants born VP (<30 weeks' gestation) or with VLBW (<1250 g) were recruited shortly after birth. Infants with congenital abnormalities were excluded from the study. This study was approved by the Royal Children's Hospital and Royal Women's Hospital Research Ethics committees and informed consent was obtained from children's parents/legal guardians.

Magnetic resonance imaging (MRI) acquisition

Infants were scanned at TEA (40 ± 2 weeks' gestational age) with a 1.5-Tesla General Electric Signa MRI scanner (Milwaukee, WI). Infants were fed, swaddled, fitted with earmuffs and placed in a vacuum fixation beanbag to reduce motion and scanned without sedation. T_2-weighted (1.7–3.0 mm coronal slices; repetition time 4000 ms; echo time 60/160 ms; flip angle 90°; field of view 220 × 160 mm; matrix 256 × 192, interpolated 512 × 512) whole-brain structural images were acquired. At the 7-year follow-up, structural T_1 (0.85 mm sagittal slices, repetition time 1900 ms, echo time 2.27 ms, flip angle 9°, field of view 210 × 210 mm, matrix 256 × 256) images were acquired using a 3 Tesla Trio Siemens MRI machine (Siemens, Erlangen, Germany) without sedation. At the 13-year follow-up, children were again scanned using the 3 Tesla Trio Siemens MRI machine (Siemens, Erlangen, Germany) without sedation and structural T_1 (0.9 mm^3 sagittal slices, repetition time 2530 ms, echo times 1.77, 3.51, 5.32, 7.2 ms, flip angle 7°, field of view 230 × 209 mm, matrix 256 × 230, interpolated 256 × 256) images were acquired.

Image pre-processing and volumetry

T_2-weighted images acquired at TEA were bias-corrected using N4ITK (Tustison et al., 2010) and brain extracted using Morphologically Adaptive Neonatal Tissue Segmentation software (MANTiS) (Beare et al., 2013; Beare et al., 2016). The neonatal M-CRIB atlas (Alexander et al., 2017), which replicates the widely used Desikan–Killiany atlas (Desikan et al., 2006) was used to parcellate regions at TEA and ensure compatibility with regions parcellated from 7 and 13 year scans (Supplementary Fig. 1a). Each of the 10 T_2-weighted images and corresponding parcellated images comprising the neonatal M-CRIB atlas (Alexander et al., 2017) were nonlinearly registered to each T_2-weighted image in the current sample using ANTS (Avants et al., 2011). M-CRIB atlas labels were then applied to each brain using pSTAPLE (Akhondi-Asl & Warfield, 2013). Regional brain volumes were selected for 16 bilateral corticolimbic regions of interest [amygdala, hippocampus, parahipppocampal gyrus, entorhinal cortex, rostral and caudal anterior cingulate gyri, medial orbitofrontal cortex (mOFC), and lateral orbitofrontal cortex (lOFC); Supplementary Fig. 1b]. T_1 images acquired at 7 and 13 years of age were bias corrected using N4ITK (Tustison et al., 2010), brain extracted using the Brain Extraction Tool (Smith, 2002) and parcellated using the FreeSurfer 6.0 automated parcellation and segmentation procedure (Fischl et al., 2002); manual edits to the surfaces were made according to FreeSurfer guidelines. At 7 and 13 years, volumes of limbic and prefrontal regions from the Desikan–Killiany cortical parcellation (Desikan et al., 2006) were used, corresponding to TEA regions of interest from the M-CRIB neonatal atlas (Supplementary Fig. 1b) (Alexander et al., 2017). Amygdala volumes from FreeSurfer's 'aseg' subcortical segmentation (Fischl et al., 2002) were used and hippocampal volumes were generated via the FreeSurfer 6.0 hippocampal subfields module (Iglesias et al., 2015); these were also compatible with the neonatal regions

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(Alexander et al., 2017). T_2-weighted images were used at TEA as a relatively high water content and limited myelination in the neonatal brain results in a reversal of tissue intensities on T_1- and T_2-weighted scans at this age (Holland, Haas, Norman, Brant-Zawadzki, & Newton, 1986). The quality of segmentations was assessed, and of the children who were scanned, 30 images at TEA, 7 images at 7 years and 1 image at 13 years had no usable volumetric data; this was primarily due to motion artefact. Intracranial volume (ICV) and total brain volume (TBV) were obtained by combining relevant M-CRIB regions at TEA (ICV: all regions; TBV: ICV – cerebrospinal fluid (CSF)) and with Statistical Parametric Mapping version 12 (http://www.fil.ion.ucl.ac.uk/spm/) at 7 and 13 years (ICV: grey matter + white matter + CSF; TBV: ICV – CSF).

Anxiety assessment

The 13-year follow-up included the *Development and Well-Being Assessment* (DAWBA; (Goodman, Ford, Richards, Gatward, & Meltzer, 2000)), a structured clinical interview completed by parents online with regards to their child's mental health including anxiety disorders. A computer algorithm identified potential cases based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). These cases were then reviewed by psychologists blinded to group membership and previous developmental assessments to determine if criteria for formal clinical diagnoses were met (Yates et al., 2020). A summary variable was created to reflect the absence or presence of any anxiety disorder (including generalized anxiety disorder (GAD), social anxiety disorder, separation anxiety disorder, specific phobia and agoraphobia).

Social risk

A family social risk score was calculated at 13 years of age based on family structure, education of primary caregiver, primary income earner employment status and occupation, language spoken at home and maternal age at birth (Roberts et al., 2008). Scores (0–2) were given for each domain (Roberts et al., 2008), and summed to provide an overall risk score (0–12). Overall scores $\geqslant 2$ were categorized as higher social risk, with scores <2 indicating lower social risk.

Statistical analyses

Statistical analyses were conducted using Stata 15.0 (StataCorp, TX). Group comparisons (VP anxiety, VP no anxiety) of sample characteristics were performed using two samples t tests and Fisher's exact tests. Prior to analysis, global and regional brain volumes of participants were standardized to the mean and S.D. of the relevant brain region. Thus, standardized beta coefficients (β) are reported throughout.

Linear mixed effects (LME) models were used to assess brain growth trajectories for each corticolimbic region of interest (by hemisphere) between groups (absence *v.* presence of an anxiety disorder at 13 years) across childhood [TEA (0 years), 7 and 13 years]. Group, age and a group-by-age interaction were included as fixed effects in the model, fitted with a random intercept and unstructured covariance structure; which provided the lowest Akaike information criterion (AIC) and Bayesian information criterion (BIC) values during model selection (Supplementary Table 1). Age was included as a discrete variable, given the narrow distribution of ages at each follow-up relative to the intervals between follow-up assessments. The models were fitted with robust standard errors to account for clustering of multiples, given the high number of multiple births in this sample (Carlin, Gurrin, Sterne, Morley, & Dwyer, 2005).

Firstly, overall group-by-age interactions were used to assess corticolimbic volume trajectories across childhood between groups (absence *v.* presence of anxiety disorder). For regions with significant overall group-by-age interactions, growth in early and late childhood between groups was assessed by extracting group-by-age interactions between 0–7 and 7–13 years from the LME models, respectively. In the case of significant interactions, group differences in volumes cross-sectionally (at 0, 7 or 13 years, as appropriate) were also extracted from the LME models. Secondary analyses (in regions where trajectory alterations were found) were adjusted for TBV (at the corresponding time point) and high social risk at 13 years to determine the extent to which these variables explained trajectory differences in regional brain volumes between groups. A false discovery rate (FDR) correction was applied for each set of inferences via the Benjamini and Yekutieli (2001) method to all p-values to account for increased type I error resulting from multiple comparisons across different brain structures. An alpha of 0.05 was set for all analyses.

Results

Sample characteristics

From 224 VP infants recruited shortly after birth, 197 (88%) VP children returned for the follow-up at 7 years and 179 (80%) returned for the follow-up at 13 years of age (Fig. 1). Reasons for attrition included families withdrawing from the study, moving out of state/internationally and loss of contact.

At 13 years of age, 13% ($n = 16$) of the cohort met criteria for one or more anxiety disorders, with generalized anxiety disorder (GAD) the most prevalent ($n = 8$, 6.4%), followed by social anxiety disorder ($n = 6$, 4.8%), specific phobia ($n = 4$, 3.2%) and separation anxiety disorder ($n = 1$, 0.8%). No participants met criteria for agoraphobia and three participants were diagnosed with comorbid GAD and social anxiety disorder. Children with usable MRI data for at least one time point (TEA, 7, 13 years) and DAWBA data at 13 years of age were included in the analysis ($n = 124$; Fig. 1). The characteristics of participants included in this study are presented in Table 1, and were similar between the anxiety and no anxiety disorder groups.

Global brain volume trajectories across childhood and anxiety disorder in VP children

Overall trajectories, trajectories during early and late childhood and subsequent cross-sectional analysis for each region are presented in Supplementary Table 2. Overall group-by-age interactions existed for ICV ($p < 0.0001$; Fig. 2*a*) and TBV ($p = 0.029$; Fig. 2*b*), indicating altered global brain volume trajectories in VP children diagnosed with an anxiety disorder compared with those who were not. Group-by-age interactions between 0 and 7 years were found for both ICV and TBV [$\beta = -0.461$, 95% confidence interval (CI) −0.826 to 0.097, $p = 0.020$; $\beta = -0.503$, 95% CI −0.92 to −0.086, $p = 0.020$, respectively; Fig. 2*a*, *b*] indicating slower global brain growth in early childhood for VP children with an anxiety disorder diagnosis compared with VP children without a diagnosis. However, ICV ($\beta = -0.224$, 95% CI −0.485 to 0.038, $p = 0.19$) and TBV ($\beta = -0.063$, 95% CI −0.30 to

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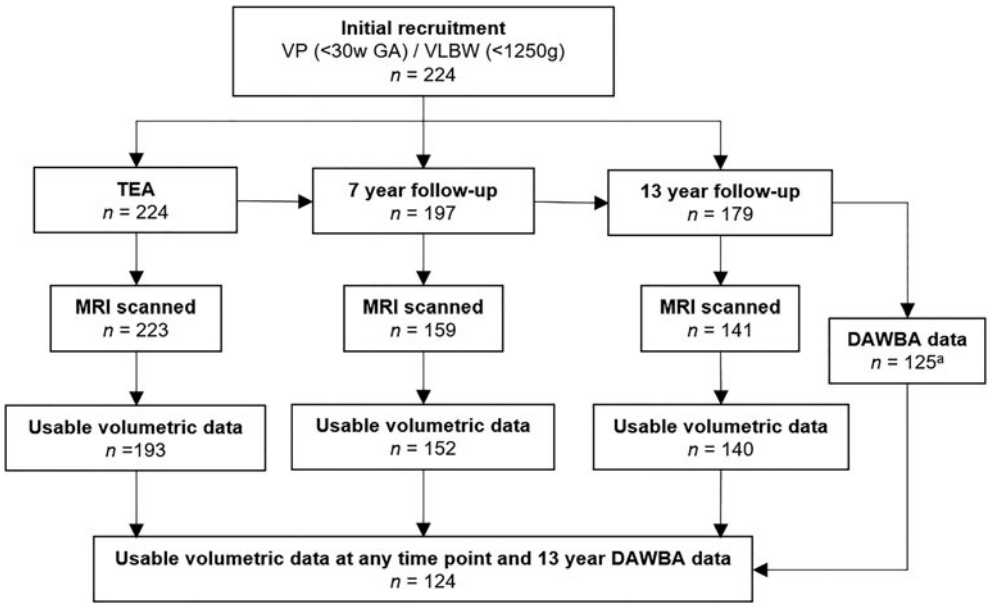

Fig. 1. Flow chart of attrition rates in current study. [a]*n* = 1 participant could not be included in analysis as had completed DAWBA at 13 years however had no usable volumetric data. VP, very preterm; GA, gestational age; VLBW, very low birth weight; TEA, term equivalent age; MRI, magnetic resonance imaging; DAWBA, development and wellbeing assessment; GAD, GAD.

Table 1. Participant characteristics

	Anxiety diagnosis (*n* = 16)	No anxiety diagnosis (*n* = 108)	*p*
Gestational age at birth (weeks), mean (s.d.)	28.1 (2.8)	27.3 (2)	0.17
Birthweight (g), mean (s.d.)	994 (253)	958 (239)	0.59
Small for gestational age[a], *n* (%)	4 (25)	8 (7.4)	0.049
Multiple births, *n* (%)	6 (37.5)	52 (48.2)	0.59
Male, *n* (%)	8 (50)	53 (49.1)	>0.99
Bronchopulmonary dysplasia,[b] *n* (%)	1 (6.3)	40 (37)	0.020
Antenatal corticosteroids administered, *n* (%)	15 (93.8)	97 (89.8)	>0.99
Postnatal corticosteroids administered, *n* (%)	0 (0)[c]	11 (10.2)	0.36
Infection,[d] *n* (%)	5 (31.3)[e]	36 (34.3)	>0.99
Cystic periventricular leucomalacia, *n* (%)	0 (0)	5 (4.6)	>0.99
Intraventricular haemorrhage grade 3 or 4,[f] *n* (%)	2 (13)	3 (2.8)	0.12
Moderate-to-severe brain abnormality,[g] *n* (%)	2 (12.5)	20 (18.5)	0.74
Postmenstrual age at neonatal MRI (in weeks), mean (s.d.)	40.9 (1.2)[c]	40.5 (1.3)[h]	0.33
Age at 7-year MRI (in years), mean (s.d.)	7.5 (0.3)[c]	7.6 (0.2)[i]	0.088
Age at 13-year MRI (in years), mean (s.d.)[j]	13.1 (0.3)	13.3 (0.4)[k]	0.13
Higher social risk at 13 years, *n* (%)	10 (62.5)	54 (50)[l]	0.43

[a]Birthweight more than two s.d. below the mean.
[b]Oxygen requirement at 36 weeks.
[c]*n* = 15.
[d]Proven necrotizing enterocolitis and/or sepsis.
[e]*n* = 105.
[f]Graded according to Papile, Burstein, Burstein, and Koffler (1978).
[g]Scored using Kidokoro system (Kidokoro, Neil, & Inder, 2013).
[h]*n* = 104.
[i]*n* = 87.
[j]DAWBA occurred at same age as 13-year MRI.
[k]*n* = 81.
[l]*n* = 106.
Note: All ages corrected for prematurity. *p*-values are presented for group comparisons assessed with 2 samples *t* tests and Fisher's exact tests.

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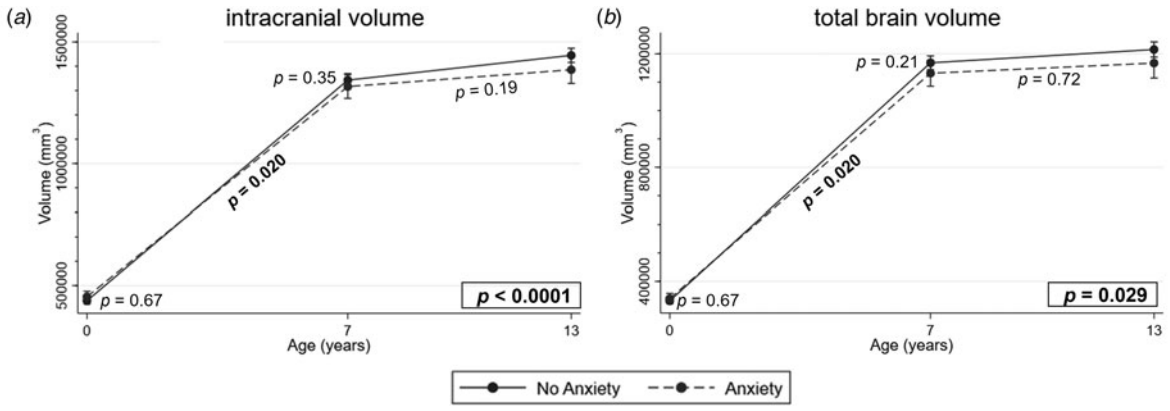

Fig. 2. Trajectory of global volumes across the first 13 years in very preterm individuals with and without anxiety disorder at 13 years. FDR corrected *p*-values for group-by-age interaction term in the LME model are presented in boxes in the bottom right corner for each region. Intracranial volume (ICV; a) and total brain volume (TBV; b) displayed significant overall group-by-age interactions ($p < 0.05$, indicated in bold) and thus were included in subsequent analysis of group-by-age interactions between 0–7 and 7–13 years (FDR corrected *p*-values presented below trajectory lines). Following significant group-by-age interactions between 0 and 7 years in ICV and TBV ($p < 0.05$ indicated in bold), group differences was explored cross-sectionally at 0 and 7 years, with no significant difference found at either time point (FDR corrected *p*-values presented next to 0 and 7 year data points). Error bars represent 95% confidence intervals.

0.173, $p = 0.72$) growth appeared fairly stable from 7 to 13 years. Cross-sectional analyses at 0 and 7 years indicated no group differences in ICV or TBV at 0 ($\beta = 0.237$, 95% CI −0.153 to 0.628, $p = 0.67$; $\beta = 0.165$, 95% CI −0.255 to 0.585, $p = 0.67$, respectively; Fig. 2) or 7 years of age ($\beta = -0.224$, 95% CI −0.694 to 0.245, $p = 0.35$; $\beta = -0.338$, 95% CI −0.815 to 0.138, $p = 0.21$, respectively; Fig. 2).

Corticolimbic volume trajectories across childhood and anxiety disorder in VP children

Overall group-by-age interactions were found in the right amygdala ($p = 0.0009$; Fig. 3*b*) and left hippocampus ($p = 0.029$; Fig. 3*c*), indicating that trajectories of these regions differed between VP children with and without an anxiety disorder diagnosis. There were trends for group differences in the trajectories of the right hippocampus ($p = 0.062$; Fig. 3*d*) and left mOFC ($p = 0.079$; Fig. 4*a*), therefore, these regions were also included in secondary analysis of growth trajectories in early and late childhood. Overall group-by-age interactions in all other corticolimbic regions were not observed (Figs 3*a*, *e–h*, 4*b–h*), indicating no alteration in trajectory and thus were not included in subsequent analysis.

Corticolimbic trajectories in early and late childhood and anxiety disorder in VP children

Slower growth in the left ($\beta = -0.518$, 95% CI −0.920 to −0.107, $p = 0.020$; Fig. 3*c*) and right ($\beta = -0.469$, 95% CI −0.832 to −0.105, $p = 0.020$; Fig. 3*d*) hippocampi and the left mOFC ($\beta = -0.761$, 95% CI −1.310 to −0.204, $p = 0.020$; Fig. 4*a*) in early childhood were observed between 0 and 7 years. There was no evidence of growth differences between groups from 0 to 7 years in the right amygdala ($\beta = -0.20$, 95% CI −0.76 to 0.367, $p = 0.49$; Fig. 3*b*). Trajectories remained similar between the groups in late childhood (7–13 years) in the left ($\beta = -0.058$, 95% CI −0.385 to 0.267, $p = 0.72$; Fig. 3*c*) and right ($\beta = -0.055$, 95% CI −0.289 to 0.179, $p = 0.72$; Fig. 3*d*) hippocampi, left mOFC ($\beta = 0.263$, 95% CI −0.038 to 0.564, $p = 0.19$; Fig. 4*a*) and right amygdala ($\beta = -0.421$, 95% CI −0.848 to 0.0005, $p = 0.19$; Fig. 3*b*).

Cross-sectional corticolimbic volumes at 0 and 7 years and anxiety disorder in VP children

Given slower growth in the left and right hippocampi and the left mOFC from 0 to 7 years in the anxiety *v.* no anxiety group, volumes at 0 and 7 years in these regions were assessed for group differences. Left and right hippocampi and left mOFC volumes did not differ between groups at 0 ($\beta = 0.129$, 95% CI −0.284 to 0.543, $p = 0.67$; $\beta = -0.004$, 95% CI −0.418 to 0.411, $p = 0.99$; $\beta = -0.214$, 95% CI −0.249 to 0.677, $p = 0.67$, respectively; Fig. 3c,d, 4a) but were smaller at 7 years in VP children with an anxiety disorder, although this did not reach statistical significance ($\beta = -0.389$, 95% CI −0.853 to 0.075, $p = 0.17$; $\beta = -0.472$, 95% CI −0.909 to −0.036, $p = 0.085$; $\beta = -0.547$, 95% CI −1.029 to −0.066, $p = 0.085$, respectively; Fig. 3*c*, *d*, 4*a*).

Corticolimbic volume trajectories across childhood and anxiety disorder in VP children after adjusting for TBV and social risk

Significant overall group-by-age interactions did not persist after adjusting for TBV and social risk (Supplementary Fig. 2).

Discussion

In this prospective longitudinal study, VP children diagnosed with an anxiety disorder at 13 years displayed altered trajectories for ICV and TBV and in various corticolimbic regions, including the left hippocampus and right amygdala, with trends in the right hippocampus and the left mOFC. More specifically, VP children with an anxiety disorder demonstrated slower growth during early childhood (0–7 years) for ICV, TBV, bilateral hippocampi and left mOFC, relative to VP children without an anxiety disorder. Cross-sectional analysis did not reveal group differences at 0 years but there was some evidence for smaller volumes in bilateral hippocampi and left mOFC at 7 years although this did not reach statistical significance, likely due to power limitations. Conversely, there was no difference between groups in volume trajectories during late childhood (7–13 years). This suggests that alterations in global and corticolimbic region volumes earlier in development may relate, at least in part, to later presentation of an anxiety disorder in VP individuals. Group differences in the trajectories of the left and right hippocampus, left mOFC and right amygdala were

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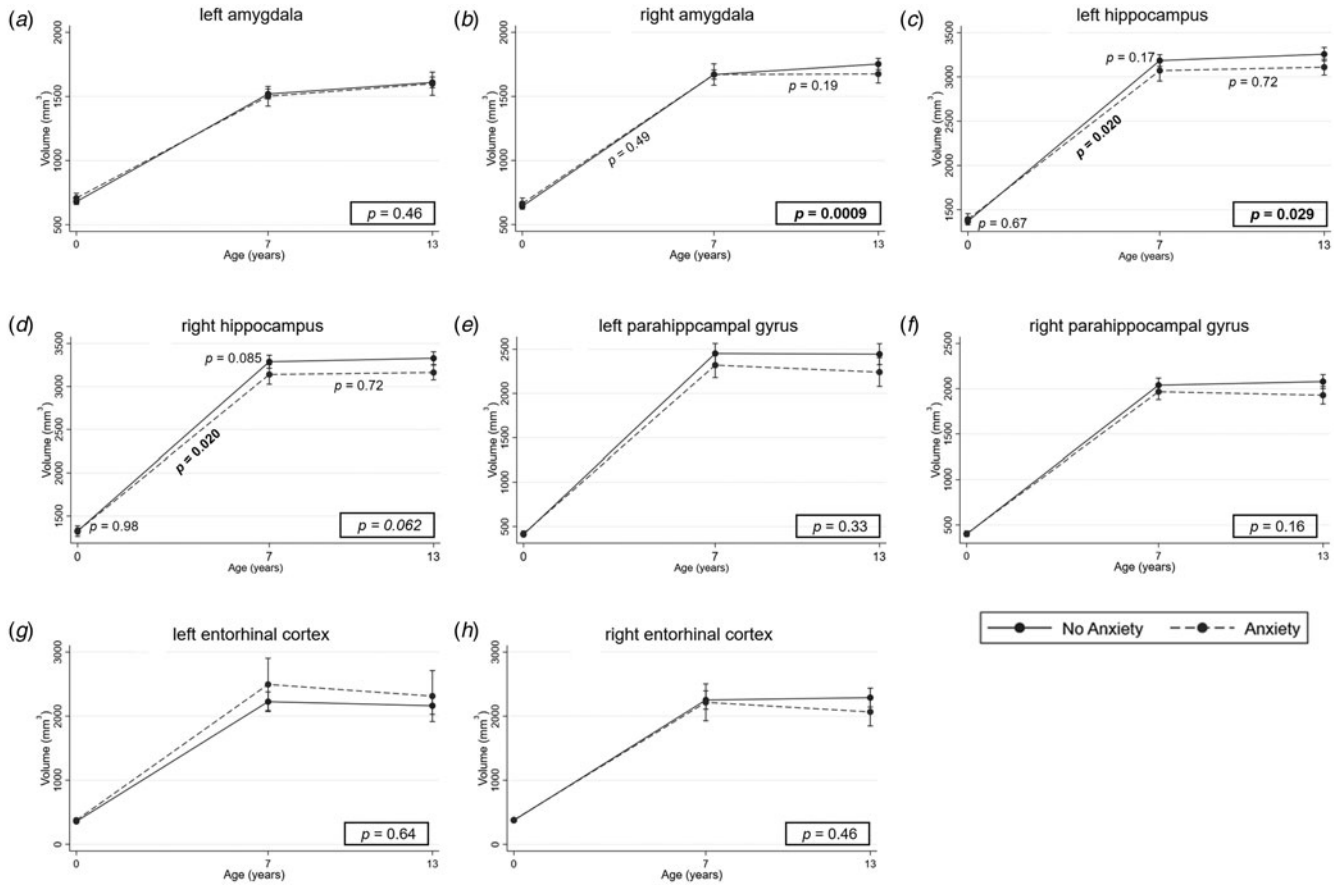

Fig. 3. Trajectory of limbic region volumes across the first 13 years in very preterm individuals with and without anxiety disorder. FDR corrected *p*-values for group-by-age interaction term in the LME model are presented in boxes in the bottom right corner for each region. The right amygdala (b) and left hippocampus (c) displayed significant overall group-by-age interactions ($p < 0.05$, indicated in bold) and the right hippocampus (d) displayed a trend ($p < 0.10$, indicated by italics) and thus was included in subsequent analysis of group-by-age interactions between 0–7 and 7–13 years (FDR corrected *p*-values presented below trajectory lines). Following a significant group-by-age interaction between 0 and 7 years in the left and right hippocampi (c–d) ($p < 0.05$ indicated in bold), group differences were explored cross-sectionally at 0 and 7 years, with no significant difference found at either time point (FDR corrected *p*-values presented next to 0 and 7 year data points). Error bars represent 95% confidence intervals.

attenuated when controlling for TBV and high social risk, which likely reflects the alterations in TBV trajectories reported.

Global reductions in cerebral grey matter have been documented shortly after birth in VP infants (Inder et al., 2005; Padilla, Alexandrou, Blennow, Lagercrantz, & Aden, 2015), as well as across childhood (for review see de Kieviet et al., 2012). We have reported slower growth from TEA to 7 years in ICV, TBV and bilateral cortical grey matter and subcortical grey matter volumes in VP compared with FT controls (Monson et al., 2016; Thompson et al., 2020). The current study extends these findings, with significant group-by-age interactions indicating altered ICV and TBV trajectories in those with anxiety. Subsequent analysis identified slower growth in these global measures from TEA to 7 years in VP children who meet criteria for an anxiety disorder at 13 years compared with those who do not. Hence, altered growth in global measures of brain structure documented in the VP population in early childhood may provide a biomarker of anxiety disorder in this population.

Links between regional brain volumes and the presentation of anxiety disorder in individuals born VP are relatively unexplored. In school-age children born preterm, albeit those born between 34 and 36 gestational weeks, smaller temporal-lobe volumes have been associated with later anxiety symptoms (Rogers et al., 2014). The current study extends this work by mapping the volume growth trajectory in key corticolimbic regions across the first 13 years, thus providing additional evidence of region-specific alterations in VP children diagnosed with an anxiety disorder. These regions are likely differentially affected by VP birth given the diversity in emergence and maturation across regions in both prenatal and postnatal life.

The amygdala has been the focus of research investigating the neurobiological underpinnings of anxiety in preterm individuals (Rogers et al., 2017), given its role in processing emotion, and reports of altered size (De Bellis et al., 2000; Milham et al., 2005; Schienle, Ebner, & Schafer, 2011), activation (Monk et al., 2008) and connectivity (Kim, Gee, Loucks, Davis, & Whalen, 2011; Qin et al., 2014) in the wider population of individuals experiencing anxiety. VP neonates display smaller amygdala volumes than term-born peers, which has been associated with fear processing capabilities at 1 year of age (Cismaru et al., 2016). Smaller amygdala volumes are also evident in preterm VLBW children compared with term-born children at 8 years of age (Peterson et al., 2000). In the current study, group differences in overall volume trajectories were lateralized to the right amygdala. Alterations to the right amygdala, including volume reductions and hyperactivity have been documented in anxiety disorders such as social anxiety disorder, GAD and panic disorder (Asami et al., 2009; Hölzel et al., 2013; Irle et al., 2010; Lipka,

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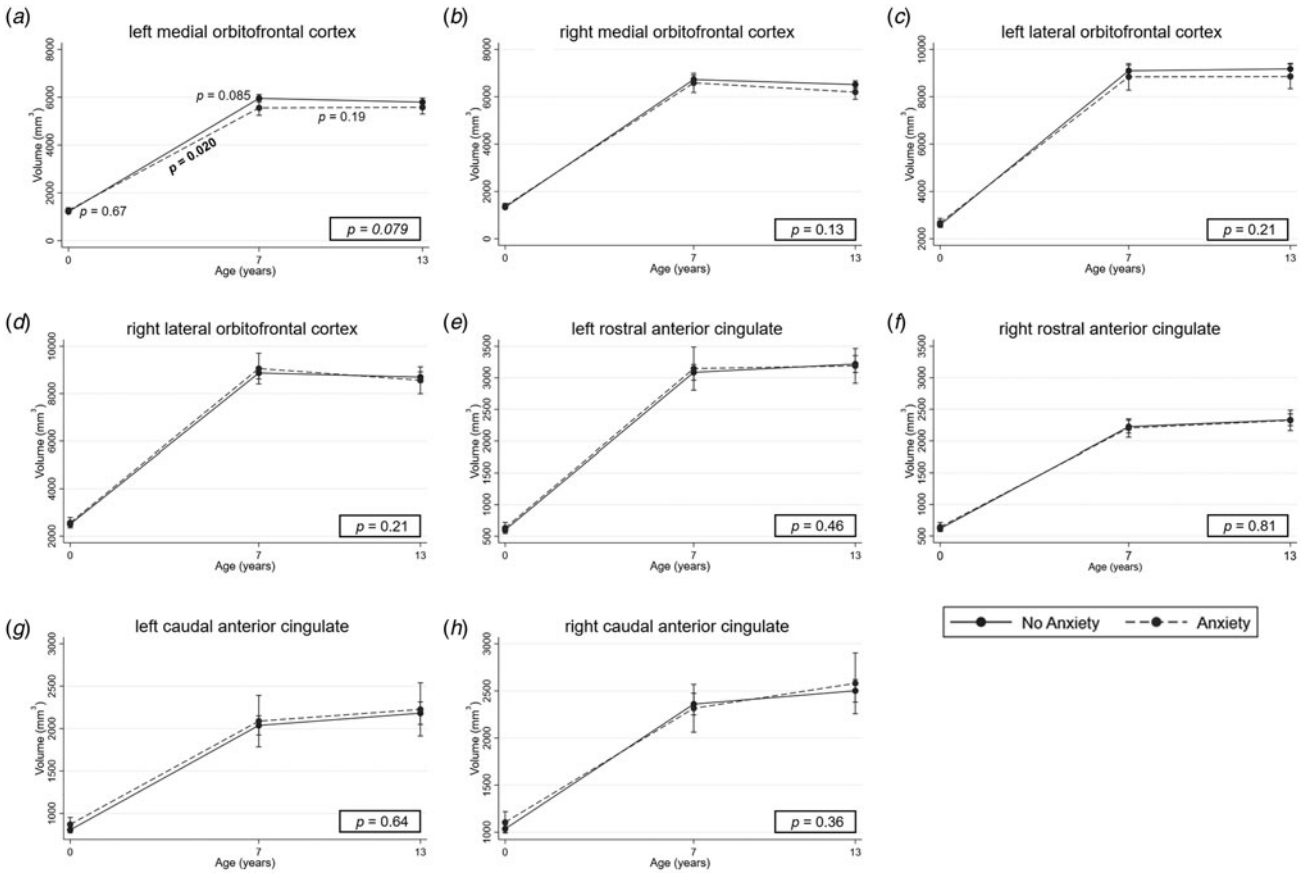

Fig. 4. Trajectory of cortical region volumes across the first 13 years in very preterm individuals with and without anxiety disorder at 13 years. FDR corrected *p*-values for group-by-age interaction term in the LME model are presented in boxes in the bottom right corner for each region. The left medial orbitofrontal cortex (a) displayed a trend ($p < 0.10$, indicated by italics) and thus was included in subsequent analysis of group-by-age interactions between 0–7 and 7–13 years (FDR corrected *p*-values presented below trajectory lines). Following a significant group-by-age interaction between 0 and 7 years ($p < 0.05$ indicated in bold), group differences were explored cross-sectionally at 0 and 7 years, with no significant difference found at either time point (FDR corrected *p*-values presented next to 0 and 7 year data points). Error bars represent 95% confidence intervals.

Miltner, & Straube, 2011). Stimulation of the right amygdala has been implicated in inducing predominantly negative emotions (especially fear); contrasting the left amygdala which elicits both positive and negative emotions (Lanteaume et al., 2007). Thus, altered trajectories in the right but not left amygdala in the anxiety group may highlight a tendency towards fear conditioning. While the anxiety group appeared to diverge from the trajectory of the no anxiety group from 7 to 13 years, subsequent analysis revealed no group differences in right amygdala trajectories in early or late childhood. It is possible that this was due to low statistical power given the small anxiety group.

Findings of altered trajectory of left and right hippocampal volumes and slower growth from birth to 7 years in VP children later diagnosed with an anxiety disorder are consistent with temporal-lobe findings by Rogers et al. (2014) and extend on long-lasting reductions in hippocampal volumes documented in VP individuals relative to FT peers during childhood and adolescence (de Kieviet et al., 2012; Peterson et al., 2000). The hippocampus is highly vulnerable to hypoxic and ischaemic insults (Golan et al., 2009; Schmidt-Kastner & Freund, 1991), providing a possible mechanism of damage. Hippocampal alterations in individuals born VP are not apparent shortly after birth (Thompson et al., 2008) given that much of hippocampal development occurs in the first two years postnatally (Utsunomiya, Takano, Okazaki, & Mitsudome, 1999). However, the current study indicates that impaired hippocampal development during early childhood has functional implications. Studies investigating functional implications of hippocampal alterations following VP birth have largely focused on cognition (Thompson et al., 2013), given widely reported impairments in cognitive functioning (Brydges et al., 2018; Gimenez et al., 2004; Peterson et al., 2000; Twilhaar et al., 2018) and the role of this region in learning and memory processes. The current study extends these findings to include socio-emotional outcomes, namely anxiety disorder. The anterior portion of the hippocampus is involved in emotionally driven and anxiety-related behaviours (Bannerman et al., 2004). Consistent with the current findings, the hippocampus has been implicated in the pathophysiology of anxiety disorders, with reduced volumes reported in paediatric populations diagnosed with one or more anxiety disorders (Gold et al., 2017; Mueller et al., 2013). Hippocampal morphology resembling that of an adult by 5 years of age (Kretschmann, Kammradt, Krauthausen, Sauer, & Wingert, 1986). Therefore, as expected, left and right hippocampal volume trajectories remained fairly stable from 7 to 13 years in the current study. Parallel trajectories between groups in late childhood indicate that the hippocampus remained smaller in the anxiety group following slower growth from 0 to 7 years and suggest a disrupted developmental course rather than a delay in the growth of this region, in line with previous postulations for overall brain volume trajectories during this period (Thompson et al., 2020).

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In the current study, the anxiety disorder group displayed altered left mOFC volume trajectories compared with the no anxiety disorder group. Specifically, the anxiety disorder group displayed slower growth from TEA to 7 years of age, but not from 7 to 13 years. The final trimester of pregnancy is a critical period of OFC gyrification (Ganella et al., 2015), thus our results suggest that early alterations to this development may have later functional implications. The mOFC has projections to the basolateral nuclei of the amygdala and plays a critical role in regulation of amygdala activation, particularly reactivity to negative emotional stimuli (Ducharme et al., 2014). Consistent with the current findings, self-report of generalized anxiety symptoms corresponds to less expansive surface area in early childhood and decreased cortical thickness in this prefrontal region across childhood in the general population (Newman et al., 2016). While these measures provide more specific indices of cortical dysmaturation, limited resolution in our neonatal scans did not enable investigation of cortical thickness or surface area longitudinally. GAD was the most prevalent anxiety disorder in the current study and similar left OFC volume decreases are noted in children diagnosed with GAD in the general population (Strawn et al., 2013).

Cross-sectional analysis at 0 and 7 years in regions where VP children with an anxiety disorder displayed altered trajectories from 0 to 7 years did not reveal group differences at either timepoint, suggesting the benefit of assessing trajectories of growth in addition to cross-sectional assessment of volumes. Alterations to growth in VP children with an anxiety disorder did not persist from 7 to 13 years. Maturation of the OFC is dynamic across childhood, with a rapid volume growth in early childhood, which 'peaks' at approximately 11–12 years and is followed by a decrease in adolescence (Shaw et al., 2008). Thus, additional MRI scanning across late childhood would be beneficial to investigate this OFC trajectory in greater detail and determine how this 'catch up' of OFC volumes in the anxiety group occurs in the context of volume increase, peak and decrease across this period.

It must be noted, that in the current cohort, altered amygdala, hippocampal and mOFC trajectories in the anxiety group did not persist after adjustment for TBV and social risk. This suggests that growth in these regions may not contribute to a later diagnosis of anxiety disorders beyond differences in TBV and that the role of socio-environmental factors in the development of anxiety disorders should also be considered. It would be of benefit to include socio-environmental factors such as parenting, parent–child relationships and parental mental health in future models of brain growth in this population, given that such factors may moderate mental health outcomes (Clark, Woodward, Horwood, & Moor, 2008; Treyvaud, Lee, Doyle, & Anderson, 2014; Treyvaud et al., 2009, 2010, 2020).

Grey matter alterations observed in VP individuals have been proposed to occur secondary to white matter microstructural changes (Volpe, 2019). Limbic and prefrontal regions are highly interconnected via white matter fibre projections, including the uncinate fasciculus, cingulum bundle and fornix. In people diagnosed with an anxiety disorder (Phan et al., 2009) and individuals born VP (Constable et al., 2008; Kelly et al., 2016; Vandewouw, Young, Shroff, Taylor, & Sled, 2019), altered microstructural properties in the uncinate fasciculus, a key connection between the OFC, amygdala and hippocampus, have been noted. Thus, microstructural properties of limbic tracts should be investigated as a possible mechanism for altered corticolimbic volumes between individuals born VP with and without anxiety.

A major strength of the current study was the use of a large prospective longitudinal VP cohort, which enabled the characterization of brain development across the first 13 years of life in a population with a high risk of anxiety. Repeated brain imaging in the same cohort of children is preferable to multiple cross-sectional or case–control studies of different cohorts in evaluating the dynamic changes across brain development, given environmental influences. This was possible through the use of compatible MRI parcellation schemes at the neonatal (Alexander et al., 2017) and childhood time points (Desikan et al., 2006), which enabled comparison of brain region volumes longitudinally.

There are some limitations in the current study. While the relatively small sample size of the anxiety disorder group was representative of the population, it may have limited the potential to detect significant group differences in cross-sectional regional brain volumes. Additionally, a contemporary healthy term-born control group is not included in this study, as volume trajectories of the full-term control and the total VP group in this cohort were previously assessed (Thompson et al., 2020). Due to advances in technology across the 13-year study, scanners and acquisition parameters differed across time points. While these differences could have introduced variability, assessment of total grey matter volume appears to be relatively robust across scanners (Heinen et al., 2016). It is unclear however, if this remains for smaller grey matter structures. Although these limitations are inherent in prospective longitudinal designs, repeated scanning of this cohort across the first 13 years of life provides a novel contribution to the current body of literature examining the neurobiological basis of anxiety disorders in this population. Grey matter development across childhood occurs in a non-linear fashion, however we did not consider it appropriate to apply a non-linear model due to the high clustering around the three time points. Thus, time was treated as a discrete variable. Follow-up during additional time points in similar studies, especially across the first 7 years of life when brain growth is most dynamic, would be beneficial.

We also acknowledge limitations in combining all DSM-5 anxiety disorders into a single outcome of anxiety disorder diagnosis. While each anxiety disorder has components of fear, the age of onset and underlying neural mechanisms may be distinct for the various anxiety disorders. Three VP children diagnosed with anxiety at 13 years also met criteria for major depressive disorder. Major depressive disorder often occurs comorbidly with anxiety disorders (Cummings, Caporino, & Kendall, 2014) with increased rates reported in the preterm cohorts (Burnett et al., 2011). The median age of onset of depressive disorders is later than that of anxiety (Kessler et al., 2005), thus follow-up in adulthood may enable a more detailed investigation of the trajectories of regional volumes and their role in comorbid depression, as well as separation into specific anxiety disorders.

In conclusion, the trajectory of region-specific corticolimbic volumes in VP individuals with anxiety appears to be altered in early childhood compared with VP individuals without an anxiety disorder. This builds on previous research which identified altered brain development during early childhood in VP compared with FT children and demonstrates the importance of early brain development in the socio-emotional outcome of VP children.

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Data sharing. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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