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Alterations in cortical thickness development in preterm-born individuals: Implications for high-order cognitive functions

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ABSTRACT

Very preterm birth (gestational age <33 weeks) is associated with alterations in cortical thickness and with neuropsychological/behavioural impairments. Here we studied cortical thickness in very preterm born individuals and controls in mid-adolescence (mean age 15 years) and beginning of adulthood (mean age 20 years), as well as longitudinal changes between the two time points. Using univariate approaches, we showed both increases and decreases in cortical thickness in very preterm born individuals compared to controls. Specifically (1) very preterm born adolescents displayed extensive areas of greater cortical thickness, especially in occipitotemporal and prefrontal cortices, differences which decreased substantially by early adulthood; (2) at both time points, very preterm-born participants showed smaller cortical thickness, especially in parahippocampal and insular regions. We then employed a multivariate approach (support vector machine) to study spatially discriminating features between the two groups, which achieved a mean accuracy of 86.5%. The spatially distributed regions in which cortical thickness best discriminated between the groups (top 5%) included temporal, occipitotemporal, parietal and prefrontal cortices. Within these spatially distributed regions (top 1%), longitudinal changes in cortical thickness in left temporal pole, right occipitotemporal gyrus and left superior parietal lobe were significantly associated with scores on language-based tests of executive function. These results describe alterations in cortical thickness development in preterm-born individuals in their second decade of life, with implications for high-order cognitive processing.

Introduction

Developmental patterns of cortical maturation following very preterm birth (VPT, <32 weeks of gestation) have not been systematically investigated. Results of cross-sectional studies demonstrated alterations in cortical thickness in VPT samples from childhood to adulthood, with the majority of studies conducted during adolescence. Overall, compared to controls, VPT individuals tend to show developmental delay of cortical thinning in parietal, temporal, and frontal cortices (Martinussen et al., 2005; Frye et al., 2010; Nagy et al., 2011; Skranes et al., 2012; Bjuland et al., 2013; Murner-Lavanchy et al., 2014). These cortical alterations are spatially located in brain areas displaying typical patterns of cortical thinning in healthy controls from early childhood to adolescence, which vary in their maturational trajectories according to layers and cortical regions (Shaw et al., 2008).

Cortical thickness, defined as the distance, at a given point, between the inner and outer boundaries of the cortex (MacDonald et al., 2000), is used as a proxy for neuronal density, although cortical thickness in brain areas with different cytoarchitectonical properties is differentially associated with its underlying neuronal structures (la Fougere et al., 2011). The cellular basis for reduction in cortical thickness from childhood to adolescence is not fully understood, but a possible explanation is greater organization of the brain through synaptic pruning, reflecting the refinement of neural circuits involved in cognitive processing and regional specialization of function (Knudsen, 2004; Raznahan et al., 2011). Cortical thickness is therefore used as an index of neurodevelopment (Shaw et al., 2008), and has been associated with cognitive functions (Sowell et al., 2004).

Being sensitive to both genetic and environmental influences (Lenroot and Giedd, 2008), deviations from typical cortical development

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have been observed in developmental and psychiatric disorders including autism (Ecker et al., 2013) and schizophrenia (Greenstein et al., 2006), but also in individuals experiencing subclinical symptoms including autistic and antisocial traits (Wallace et al., 2012). In VPT samples cortical alterations have been associated with IQ, performance on tasks involving executive function, working memory, perceptual skills, and with internalizing and externalizing behaviour (Martinussen et al., 2005; Lohaugen et al., 2009; Skranes et al., 2012; Zubiaurre-Elorza et al., 2012; Bjuland et al., 2013).

The studies conducted to date have been cross sectional in design, thus excluding mapping of cortical thickness development with age, which enables the investigation of changes within individuals. An increased understanding of whether cortical trajectories can be used to predict neurodevelopmental outcomes represents a challenge with important clinical relevance.

As cortical development continues beyond adolescence (Gogtay et al., 2004; Kochunov et al., 2011; Lebel and Beaulieu, 2011; Petanjek et al., 2011) we studied longitudinal changes in cortical thickness in preterm born individuals and controls, during the time spanning from mid-adolescence to the beginning of adulthood in order to identify within- and between-group developmental patterns. We then identified spatially discriminating features between the groups at early adulthood based on spatially distributed differences in cortical thickness at mid-adolescence, using a pattern classification approach. Finally we explored the association between cortical thickness changes within the spatially distributed regions in which cortical measurements best discriminated between the groups and cognitive outcome at early adulthood.

Based on results of the studies mentioned earlier (Martinussen et al., 2005; Frye et al., 2010; Nagy et al., 2011; Skranes et al., 2012; Bjuland et al., 2013), we hypothesized that preterm-born individuals would display differential longitudinal cortical thickness changes from controls during the late part of adolescence, especially in parietal, temporal and frontal cortices. We further hypothesized that cortical thickness changes in regions vulnerable to long-term alterations following VPT birth would have implications for cognitive outcome, with the potential to represent a biomarker of important changes in cortical development, potentially influencing brain functioning and cognitive outcomes.

Materials and methods

Study population

We studied two cohorts of participants born before 33 weeks of gestation and admitted consecutively to the Neonatal Unit of University College London Hospital (UCLH) (Nosarti et al., 2008). The first cohort drew on all individuals born in 1979–82 who were enrolled for long-term follow-up (Nosarti et al., 2004). The second cohort included a selected group of individuals born in 1983–84 (Allin et al., 2007). This selection was necessitated by an expansion in capacity of UCLH in 1983, which prevented inclusion of the entire consecutive series due to limited research resources. The selection criteria were: all individuals born at 28 or less weeks of gestation, as well as a random sample of one in four of those born from 29 to 33 weeks of gestation. A hundred and sixty VPT participants were studied at a mean age of 15 years (i.e., mid-adolescence) and 67 at a mean age 20 years (i.e., early adulthood, 51 of whom were also studied at mid-adolescence). Eighty-eight controls were studied at mid-adolescence and 42 at early adulthood (21 of whom were also studied at mid-adolescence). Inclusion criteria were full-term birth (38–42 weeks) and birth weight >2500 grams. Exclusions criteria were a history of neurological conditions including meningitis, head injury and cerebral infections.

Neuropsychological assessment

All study participants were assessed at Time 2 with the following well-validated measures: 1) the Wechsler Abbreviated Scale of Intelligence (WASI) was used to provide estimates of full-scale IQ (Wechsler, 1999); 2) the Visual Reproduction test of the Wechsler Memory Scale-Revised (WMS-R) assessed memory functions, i.e. immediate and delayed recall of non-verbal material (Wechsler, 1987); the California Verbal Learning Test (CVLT) examined verbal memory, and specifically short term memory (Recall, list A), interference of prior learning on new learning and memory (Recall, list B) and recognition (Recognition hits) (Dellis et al., 1987); (3) executive function (EF) was assessed with two language based tests: the Controlled Oral Word Association Test (COWAT) (Benton and Hamsher, 1976), which measures phonemic fluency, mental flexibility and the ability to use different cognitive strategies, such as clustering (Spreen and Strauss, 1991); and the Hayling Sentence Completion Test (HSCT), which measures response initiation and inhibition (Burgess and Shallice, 1997). 'Global EF' and 'Global memory' scores were then calculated as the sum of domain-specific Z scores; for VPT participants these were obtained using means and SDs from controls, which by default were set to 0 and 1. Only variables where VPT individuals showed significant differences from controls were used, therefore 'Global EF' was made up of HSCT (Scaled) and COWAT scores and 'Global memory' was made up of CVLT (Recognition hits) and WMS (Immediate and Delayed) scores.

Magnetic resonance imaging

At mid-adolescence assessment, MRI was performed at two sites. For the 1979–82 cohort and controls a 1.5 Tesla GE Signa Horizon machine (General Electric Medical Systems, Milwaukee, WI, USA) was used at the Institute of Neurology, London. The 1983–84 cohort and controls were scanned using a 1.5 Tesla GE Signa N/Vi system at the Maudsley Hospital, London. At both sites, three-dimensional T1-weighted MR images were acquired in coronal plane, with the spoiled gradient recalled pulse sequence (flip angle 35°, field of view 240 mm, echo time 5 ms, repetition time 35 ms). Each image contained 124 slices with a matrix size of 256 × 256, slice thickness of 1.5 mm and slice gap of 0 mm.

At early adulthood assessment, all participants were scanned at the Maudsley Hospital with the same scanning protocol used at mid-adolescence.

Quality control was carried out using previously described criteria to ensure adequate quality of the T1-weighted volume images, such as avoidance of wraparound artefacts and minimal levels of subject motion (Simmons et al., 2011).

Cortical surface extraction

The cortical surfaces were extracted from the T1-weighted MR images using the CIVET pipeline (version 1.1.9) (Ad-Dab'bagh et al., 2006; Zijdenbos et al., 2002), according to the following steps: 1) T1-weighted MR images were linearly registered to MNI-Talairach stereotaxic space using the ICBM152 volumetric template as the registration target (Collins et al., 1994). 2) Images were corrected for signal intensity non-uniformity (Sled et al., 1998) and 3) a brain mask was calculated from each input image (Smith, 2002). 4) Then, images were segmented into grey matter, white matter, cerebrospinal fluid (CSF) and background (Zijdenbos et al., 1998) and 5) partial volumes in each voxel was estimated (Tohka et al., 2004). 6) A *non-linear* transformation was calculated from the images in stereotaxic space to the ICBM152 template, and major structures were identified (Collins et al., 1995). 7) Cortices were extracted using a fully automated method, known as Constrained Laplacian Anatomic Segmentation using Proximity (CLASP) algorithm. Cortical extraction was performed in three steps in stereotaxic space aligned with the ICBM152 template (Kim et al., 2005). First, white matter surface was established by deforming a spherical polygon model to the border between grey and white matter. Then, a Laplacian field was formed between the white matter surface and the inner boundary of the CSF. Lastly, grey matter surface was initiated by forming itself on the white matter surface and expanded, guided