NeuroImage: Clinical 6 (2014) 180–191

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Preterm birth and structural brain alterations in early adulthood

Chiara Nosarti[a,*], Kie Woo Nam[a], Muriel Walshe[a], Robin M. Murray[a], Marion Cuddy[a], Larry Rifkin[a], Matthew P.G. Allin[a]

[a]Department of Psychosis Studies, Institute of Psychiatry, King's Health Partners, King's College London, De Crespigny Park, SE58AF London, UK

ARTICLE INFO

Article history:
Received 17 April 2014
Received in revised form 5 August 2014
Accepted 10 August 2014
Available online 13 August 2014

Keywords:
Very preterm
White matter
Grey matter
Brain volume
Cognitive outcome

ABSTRACT

Alterations in cortical development and impaired neurodevelopmental outcomes have been described following very preterm (VPT) birth in childhood and adolescence, but only a few studies to date have investigated grey matter (GM) and white matter (WM) maturation in VPT samples in early adult life. Using voxel-based morphometry (VBM) we studied regional GM and WM volumes in 68 VPT-born individuals (mean gestational age 30 weeks) and 43 term-born controls aged 19–20 years, and their association with cognitive outcomes (Hayling Sentence Completion Test, Controlled Oral Word Association Test, Visual Reproduction test of the Wechsler Memory Scale-Revised) and gestational age. Structural MRI data were obtained with a 1.5 Tesla system and analysed using the VBM8 toolbox in SPM8 with a customized study-specific template. Similarly to results obtained at adolescent assessment, VPT young adults compared to controls demonstrated reduced GM volume in temporal, frontal, insular and occipital areas, thalamus, caudate nucleus and putamen. Increases in GM volume were noted in medial/anterior frontal gyrus. Smaller subcortical WM volume in the VPT group was observed in temporal, parietal and frontal regions, and in a cluster centred on posterior corpus callosum/thalamus/fornix. Larger subcortical WM volume was found predominantly in posterior brain regions, in areas beneath the parahippocampal and occipital gyri and in cerebellum. Gestational age was associated with GM and WM volumes in areas where VPT individuals demonstrated GM and WM volumetric alterations, especially in temporal, parietal and occipital regions. VPT participants scored lower than controls on measures of IQ, executive function and non-verbal memory. When investigating GM and WM alterations and cognitive outcome scores, subcortical WM volume in an area beneath the left inferior frontal gyrus accounted for 14% of the variance of full-scale IQ ($F = 12.9$, $p < 0.0001$). WM volume in posterior corpus callosum/thalamus/fornix and GM volume in temporal gyri bilaterally, accounted for 21% of the variance of executive function ($F = 9.9$, $p < 0.0001$) and WM in the posterior corpus callosum/thalamus/fornix alone accounted for 17% of the variance of total non-verbal memory scores ($F = 9.9$, $p < 0.0001$). These results reveal that VPT birth continues to be associated with altered structural brain anatomy in early adult life, although it remains to be ascertained whether these changes reflect neurodevelopmental delays or long lasting structural alterations due to prematurity. GM and WM alterations correlate with length of gestation and mediate cognitive outcome.

1. Introduction

Due to its rapidly developing and complex characteristics, the preterm brain is vulnerable to exogenous and endogenous insults in the third trimester of gestation (Volpe, 2009), during which the volume of the whole brain more than doubles and the volume of cortical grey matter (GM) increases approximately four-fold (Huppi et al., 1998). Therefore, attention has increasingly focused on the quality of life of survivors, who are at greater risk of brain damage and consequent neurological disorders, neuropsychological, and behavioural impairments in childhood and later in life (Ball et al., 2013; Beauchamp et al., 2008; Bjuland et al., 2013; Johnson and Marlow, 2011; Ment et al., 2009; Pavlova and Krageloh-Mann, 2013; Taylor et al., 2011).

Long-lasting and widespread alterations in brain structure in their second decade of life have been reported in individuals who were born very preterm (VPT; <32 weeks of gestation) and/or with a very low birth weight (VLBW; <1500 g). Volume reductions have been described by our group and others in hippocampus (Cheong et al., 2013; Nosarti et al., 2002), caudate nucleus (Abernethy et al., 2002; Nosarti et al., 2008), thalamus (Cheong et al., 2013; Gimenez et al., 2006a), corpus callosum (Narberhaus et al., 2008; Nosarti et al., 2004; Taylor et al., 2011) and cerebellum (Allin et al., 2001; Taylor et al., 2011). Using voxel based morphometry (VBM), we conducted the largest study to date which demonstrated widespread GM and white matter (WM) alterations especially in frontal and temporal lobes in mid-adolescence, which mediated cognitive impairment (Nosarti et al., 2008). Other

* Corresponding author.
E-mail address: chiara.nosarti@kcl.ac.uk (C. Nosarti).

http://dx.doi.org/10.1016/j.nicl.2014.08.005

studies in similar samples obtained consistent findings (Gimenez et al., 2006b; Nagy et al., 2009), whereas investigations on cortical morphology reported a thinner inferior frontal cortex in VPT adolescents vs. controls (Frye et al., 2010). Such findings could be interpreted within a 'neuroplastic' framework, which posits that developmental changes in any brain region may result in a cascade of alterations in many other regions (Hack and Taylor, 2000).

Despite strong evidence that neurodevelopmental anatomical alterations are present in VPT/VLBW children and adolescents, little is known about the nature and course of their brain development when they reach adulthood. Both increases and decreases in GM and WM volumes have been described in VPT/VLBW young adults compared to controls, especially in internal capsule, insula, prefrontal cortex, medial temporal/parahippocampal gyrus and putamen (Allin et al., 2004). Reductions in cortical surface area and cortical thickness alterations in prefrontal, temporal and parietal regions have also been found (Bjuland et al., 2013; Skranes et al., 2013). Finally, changes in WM microstructure, as assessed by diffusion tensor imaging, have been reported in several areas including the corpus callosum, corticospinal tracts, cortical association tracts, cerebellar penducle and corona radiata (Allin et al., 2011; Eikenes et al., 2011).

A question which remains unanswered is whether the structural brain differences observed between VPT individuals and controls at a given time point represent delays in the course of maturation (i.e., trajectory of brain development) or long-lasting brain alterations (Nosarti et al., 2008). The results of studies published to date suggest that such differences diminish with time. In the VPT/VLBW cohort from the University Hospital in Trondheim, Norway, cortical thickness deviations seemed to be more pronounced at age 15 (Martinussen et al., 2005) compared to age 20 (Bjuland et al., 2013), and we previously reported that the surface area of the corpus callosum did not differ between VPT born individuals at age 19 compared to controls, while it was significantly smaller in the VPT group when the same sample was studied in mid-adolescence (Allin et al., 2007).

It is important to study the association between structural brain alterations and cognitive/behavioural outcome measures (Allin et al., 2011; Bjuland et al., 2013; Eikenes et al., 2011; Skranes et al., 2013), as this could contribute to elucidate the causes underlying the increased risk in VPT/VLBW young adults of experiencing medical and social disabilities (Moster et al., 2008), executive function deficits (Nosarti et al., 2007), psychiatric disorder (Nosarti et al., 2012) and neurological abnormalities, even in the absence of neurodevelopmental impairments (Miskovic et al., 2009).

The current study aimed to assess regional GM and WM volumes in VPT-born young adults and controls using VBM. We hypothesized that VPT individuals would display WM and GM alterations predominantly in frontal, temporal, and occipital regions and cerebellum, as observed in a larger cohort in adolescence (Nosarti et al., 2008), but that by early adulthood these alterations would be less extensive than at previous assessment (Allin et al., 2007; Bjuland et al., 2013). We further hypothesized that GM and WM volumes in regions where significant between-group differences are observed would be associated with gestational age as well as with neurodevelopmental outcome (Cheong et al., 2013; Nosarti et al., 2008; Taylor et al., 2011).

2. Materials and methods

2.1. Study population

We studied a cohort of individuals who were born in 1983–84 before 33 weeks of gestation and admitted consecutively to the Neonatal Unit of University College London Hospital (UCLH). A total of 302 individuals were enrolled for follow-up (Allin et al., 2006). At 14–15 years, 90 individuals received a comprehensive cognitive and behavioural assessment and had an MRI scan (Nosarti et al., 2008). At age 19–20 years, 93 individuals were assessed and had an MRI scan. Seventy-four VPT individuals (82.2%) received an MRI scan at both time points. Results of diffusion tensor MRI analyses in the sample which forms the basis of the current study are reported elsewhere (Allin et al., 2011).

For the assessment at 14–15 years, 71 controls were recruited by advertisement in the local press (South London) and selected according to age and socio-demographic characteristics. At age 19–20 years 50 controls were assessed; 34 (47.9%) controls received an MRI scan at both time points. The remaining 19 controls were also recruited by advertisement in the local press and selected according to age and socio-demographic characteristics. Inclusion criteria were full-term birth (38–42 weeks) and birth weight >2500 g. Exclusion criteria were any history of neurological problems including meningitis, head injury and cerebral infections.

Reasons for attrition between follow-up studies included unavailability of current contact details, participants' unwillingness to participate in the study and contraindications for MRI including the presence of metallic implants.

Ethical approval for the study was obtained from the Institute of Psychiatry, King's College, London, Ethics Committee (Research). Written informed consent for the assessment, including MRI, was obtained from all participants.

2.2. Neurodevelopmental, behavioural outcome data and socio-economic status

The Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999) was used to provide estimates of full-scale IQ and comprised four scales: Vocabulary, Similarities, Matrix Reasoning and Block Design; the Visual Reproduction test of the Wechsler Memory Scale-Revised (WMS-R) (Wechsler, 1987), which assesses immediate and delayed recall of non-verbal material, was used to assess learning and memory; the Controlled Oral Word Association Test (COWAT) (Benton and Hamsher, 1976) (phonemic fluency) and the Hayling Sentence Completion Test (Burgess and Shallice, 1997) were used to assess executive function and in particular cognitive flexibility. A 'global executive' score was calculated as the sum of *Z* scores from the HSCT and the COWAT; and a 'non-verbal memory' score was calculated as the sum of *Z* scores from the WMS-R immediate and the WMS-R delayed tests. For VPT participants *Z* scores were obtained using means and SDs from controls, which by default were set at 0 and 1. The Clinical Interview Schedule-Revised (CIS-R) (Lewis et al., 1992) was used to measure the frequency and severity of non-psychotic psychiatric symptoms.

Socio-economic status (SES) was measured by Her Majesty's Stationary Office Standard Occupational Classification criteria (Her Majesty's Stationery Office (HMSO) 1991). The following SES bands were used: I−II = managerial and professional; III = intermediate (e.g., small employers and own account); IV−V = working (i.e., lower supervisory and technical, routine).

2.3. Analysis of neonatal, socio-demographic, cognitive and behavioural data

Data were analysed with IBM® SPSS® Statistics 21.0. Neonatal characteristics (gestational age, birth weight, neonatal ultrasound classification) and socio-demographic variables (age at assessment, sex and SES) were analysed with Chi-square tests or univariate analysis of variance, as applicable. 95% confidence intervals were calculated. Between-group differences in cognitive and behavioural measures were assessed by univariate analysis of covariance adjusting for age at assessment. Between-group differences in WASI sub-scores were analysed with multivariate analysis of covariance, using age at assessment as a confounder.

2.4. MRI data acquisition

Magnetic resonance imaging was performed using a 1.5 Tesla system (General Electric Medical Systems, Milwaukee, WI). Three-