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White matter alterations to cingulum and fornix following very preterm birth and their relationship with cognitive functions

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ABSTRACT

Very preterm birth (VPT; < 32 weeks of gestation) has been associated with impairments in memory abilities and functional neuroanatomical brain alterations in medial temporal and fronto-parietal areas. Here we investigated the relationship between structural connectivity in memory-related tracts and various aspects of memory in VPT adults (mean age 19) who sustained differing degrees of perinatal brain injury (PBI), as assessed by neonatal cerebral ultrasound. We showed that the neurodevelopmental consequences of VPT birth persist into young adulthood and are associated with neonatal cranial ultrasound classification. At a cognitive level, VPT young adults showed impairments specific to effective organization of verbal information and visuospatial memory, whereas at an anatomical level they displayed reduced volume of memory-related tracts, the cingulum and the fornix, with greater alterations in those individuals who experienced high-grade PBI. When investigating the association between these tracts and memory scores, perseveration errors were associated with the volume of the fornix and dorsal cingulum (connecting medial frontal and parietal lobes). Visuospatial memory scores were associated with the volume of the ventral cingulum (connecting medial parietal and temporal lobes). These results suggest that structural connectivity alterations could underlie memory difficulties in preterm born individuals.

Introduction

Very preterm birth (VPT; < 32 weeks of gestation) has been associated with neurological, social and emotional problems (Johnson and Marlow, 2014; Van Hus, 2014), as well as impairments in several cognitive abilities, including executive function (Burnett et al., 2013, Kroll et al., in press), language processing (Lewis et al., 2000) and various aspects of memory (Nosarti and Froudist-Walsh, 2016; De Haan, 2010).

Memory is an abstract construct, which refers to the retention of learning or experience (Blakemore, 1988) and is a core component of cognitive function. Key processes involved in memory include (a) registration (or reception), which is closely associated with selective attention, (b) storage, and (c) retrieval. Therefore, memory is one of the elementary processes that is likely to contribute to the development of global cognitive abilities, with a key role in learning (Rose et al., 2004).

Memory deficits have been reported following very preterm birth, as early as at term equivalent (Therien et al., 2004), with childhood studies focusing on working memory and episodic memory (see Nosarti and Froudist-Walsh, 2016; Anderson, 2014 for recent reviews). Working memory refers to the capacity to temporarily store information for everyday activities, whilst episodic memory refers to remembering specific past events embedded in a spatial and/or temporal framework. Overall, existing evidence suggests that VPT individuals show impairments in episodic memory (Narberhaus et al., 2008; Isaacs et al., 2000) and working memory in childhood and adolescence (Nosarti and Froudist-Walsh, 2016; Schneider et al., 2014; Thompson et al., 2014). Some studies have additionally reported deficits in visual reproduction tests (Aanes et al., 2015; Nosarti et al., 2014), which require a rapid processing of information and its effective organization for subsequent recall.

From a cognitive neuroscience perspective, different neural networks subserve different memory components. For example, working memory involves predominantly frontal and parietal cortices (D'Esposito, 2007), which are reciprocally connected by the dorsal cingulum (Catani et al., 2013) and superior longitudinal fasciculi

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(Petrides and Pandya, 2002). On the other hand, the hippocampus is a critical region for episodic memory. The hippocampus lies at the end of convergent processing streams of visual, auditory (from temporal cortex) and spatial information (from parietal areas), and is thus ideally located to bind different types of information in order to form memories of discrete episodes (Rolls, 2015). Other areas that form the episodic memory system include the medial temporal, posterior cingulate and prefrontal, cortices (connected via the cingulum bundle), and the thalamus and mammillary bodies (connected to the hippocampus via the fornix) (Rugg and Vilberg, 2013).

Memory impairments in VPT individuals could be understood in the context of the observed neurodevelopmental structural and functional brain alterations in networks supporting memory functions. For instance, the periventricular location of the hippocampus and its protracted neurogenesis (Sullivan et al., 2001), makes it particularly vulnerable to perinatal brain injury (PBI) associated with very preterm birth, such as intraventricular haemorrhage (IVH; Khwaja and Volpe, 2008).

Reductions in volume of the hippocampus, as well as the interconnected thalamus and posterior cingulate cortex, have been observed at term-equivalent age in VPT infants and have been related to the degree of prematurity (Ball et al., 2012). Smaller bilateral hippocampal volume in VPT samples compared to controls have been described from childhood to adult life (Aanes et al., 2015; Brunnemann et al., 2013; Nosarti et al., 2002), although in some studies significant between-group differences disappeared when correcting for intracranial volume (Omizzolo et al., 2013; Fraello et al., 2011). Hippocampal volume at term has been associated with working memory at age two (Woodward et al., 2005) and with episodic memory abilities at age seven (Thompson et al., 2013, 2014; Omizzolo et al., 2013). However, in the same study cohort, both hippocampal volume at 7 years of age and longitudinal volumetric changes between term and age 7 were not associated with episodic memory, suggesting that children with early hippocampal damage may have had limited resources for the development of subsequent memory functions.

Structural and functional alterations in the fornix, corpus callosum, superior longitudinal fasciculus, dorsal cingulum and the parahippocampal, entorhinal and perirhinal cortices following VPT birth have been further documented in adolescence and early adulthood and have often correlated with memory ability (Froudist-Walsh et al., 2015; Nosarti et al., 2014; Salvan et al., 2014; Skranes et al., 2012; Allin et al., 2011; Narberhaus et al., 2008).

Here we used diffusion magnetic resonance imaging (MRI) tractography to study white matter fasciculi that are important for memory function: the cingulum, which connects the medio-temporal lobe (enthorinal cortex) to the prefrontal cortex (cingulate gyrus), subdivided into dorsal cingulum (DC; connecting medial frontal and parietal cortex, including the cingulate gyrus) and ventral cingulum (VC; connecting medial temporal and parietal cortex, including the retrosplenial cortex), and the fornix, which is the principal efferent neural pathway of the hippocampus and connects it to the mamillary bodies and the septal region.

We hypothesized that each of these white matter fasciculi would be reduced in volume in VPT young adults, and particularly those who experienced high-grade PBI. This was based on our previous finding that the most severe pervasive and tract-specific white matter alterations following VPT birth were seen in individuals who suffered PBI in the form of intraventricular haemorrhage and ventricular dilatation (Froudist-Walsh et al., 2015; Nosarti et al., 2014). Moreover, we hypothesized that cingulum and fornix alterations would be associated with scores on verbal and visual memory tests which we previously reported as being lower in VPT adults compared to controls (Nosarti et al. 2014, Allin et al. 2011).

Table 1
Participants' neonatal, socio-demographic characteristics and IQ, by group.

	VPT-N (n=64)	VPT-PBI (n=20)	Controls (n=48)	Statistics
Gestational age, weeks[a]	29.20	27.65	40.10	H=7.482 p=0.006
Birth weight, grams[a]	1328.22	1060.25	3310.54	H=7.775 p=0.005
Males/Females	35/29	10/10	26/22	X^2=2.423 p=0.659
Age at assessment[b]	19.8 (1.24)	19.4 (0.68)	19.1 (1.24)	H=10.525 p=0.005
SES[c]				X^2=5.292 p=0.507
I-II	28 (43.8%)	9 (45%)	27 (7%)	
III	25 (39.1%)	8 (40%)	12 (25%)	
IV-V	9 (14.1%)	3 (15%)	9 (18.8%)	
Unclassified	2 (3.1%)	0 (0%)	0 (0%)	
Full scale IQ[d]	96 (12.71)	98.47 (15.98)	105.81 (13.85)	H=11.828 p=0.003

[a] VPT-N compared to VPT-PBI.
[b] Information was missing for 1 control participant and 2 participants from VPT-N group. Statistically significant differences were found between the VPT-N and control groups (H=21.744, p=0.008).
[c] Parental socio-economic status (SES) was measured by the Classification of Occupation (CO80, Her Mayesty' Stationery Office, 1980), with I as the highest and V as the lowest socio-economic group.
[d] Statistically significant differences were found between the VPT-N and control groups (H=−23.66, p=0.003).

Methods

Participants

VPT participants were drawn from a cohort of infants who were born before 33 gestational weeks in 1982–1984. All individuals were admitted within 5 days of birth to the Neonatal Unit at University College London Hospital, where they received neonatal cranial ultrasound daily for the first 4 days of life, at 1 week, and weekly until they were discharged from hospital. All infants who survived were enrolled into a longitudinal follow-up study (n=302). Results of other neuroimaging studies in the subject sample which forms the basis of the present study are reported in Nosarti et al. (2014), Nam et al. (2015), and Allin et al. (2011).

At 19–20 years, 94 individuals underwent neuropsychological assessment and 87 received diffusion MRI (Allin et al. 2011). Exclusion criteria were severe visual, hearing and motor impairment. Socio-demographic and neonatal characteristics of the study sample are shown in Table 1. VPT participants were further subdivided on the basis of their neonatal cranial ultrasound classification. Hemorrhages confined to the germinal matrix, and those spreading to the brain parenchyma or lateral ventricles were combined together as periventricular hemorrhage (PVH) (Stewart et al., 1983) and their grade was defined according to Papile et al. (1978). Ventricular dilatation was described as a visible dilatation of one or both lateral ventricles with cerebrospinal fluid, although insufficient to meet the criteria for hydrocephalus. Those VPT participants with normal neonatal cranial ultrasound results (n=30) and with uncomplicated PVH (grade I-II), without ventricular dilatation (n=34) were grouped together and were labelled VPT-N (in total, n=64); those individuals with high-grade PVH (grade III-IV) and/or ventricular dilatation were labelled VPT-PBI (n=20). There were no instances of periventricular leukomalacia. Please refer to Nosarti et al., 2011 for further details on neonatal cranial ultrasound classification. 48 age-matched term-born individuals were also assessed. The inclusion criterion for this group was full term birth (37–42 completed weeks of gestation); exclusion criteria were birth complications (for example, low birth weight < 2500, endotracheal mechanical ventilation, prolonged gestation (> 42 weeks), severe visual, hearing and motor impairment).

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