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Corpus callosum and prefrontal functions in adolescents with history of very preterm birth

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Abstract

Very preterm (VPT) birth can account for thinning of the corpus callosum and poorer cognitive performance. Research findings about preterm and VPT adolescents usually describe a small posterior corpus callosum, although our research group has also found reductions of the anterior part, specifically the genu. The aim of the present study was to investigate the functional implications of this concrete reduction. Fifty-two VPT adolescents were compared with 52 adolescents born at term; there were no significant differences in age and gender, and socioeconomic status was similar between the groups. All participants underwent a magnetic resonance imaging (MRI) study and assessment of prefrontal functioning and vocabulary. The VPT group showed significant reductions of the genu, isthmus and splenium, as well as a significantly worse performance on category verbal fluency, executive functions, everyday memory and vocabulary. Although several parts of the corpus callosum correlated with some prefrontal functions, the genu was the part which principally explained these correlations. The subtest Vocabulary only correlated with the splenium. The relationship between genu and prefrontal functions and between splenium and vocabulary may be due to the fact that these parts of the corpus callosum connect prefrontal and posterior parietal cortex, respectively. The work presented here provides evidence of specific associations between reductions in the anterior corpus callosum (genu) and lower prefrontal functioning in VPT adolescents.

Keywords: Genu; Prefrontal skills; Low performance; Adolescence; Correlations

1. Introduction

Very preterm (VPT) individuals have an increased risk of brain abnormalities, especially prominent in white matter, which are evident in both childhood (Hüppi et al., 1998; Inder et al., 1999; Nagy et al., 2003) and adolescence (Giménez, Junqué, Narberhaus, Bargalló et al., 2006; Stewart et al., 1999). The corpus callosum is the main interhemispheric commissure of the brain (Tomasch, 1954). In humans it begins to develop 9 weeks after conception and continues to grow post-natally, showing morphological changes related to the ongoing myelination of interhemispheric fibers (Volpe, 2001).

Magnetic resonance imaging (MRI) studies have demonstrated thinning of the corpus callosum in VPT or preterm children and adolescents (Narberhaus, Segarra, Caldú, et al., 2007; Nosarti et al., 2004; Peterson et al., 2000; Stewart et al., 1999). Such injury may be partly explained by the vulnerability of the developing corpus callosum to hypoxic-ischemic damage, possibly due to intrinsic vulnerability of immature oligodendrocytes (Back et al., 2001).

Peterson et al. (2000) reported that 8-year-old VPT subjects showed a generalized corpus callosum reduction, including the anterior and posterior regions. In a qualitative MRI study of 14–15-year-old VPT individuals, Stewart et al. (1999) reported a reduction predominantly in the posterior corpus callosum. In the same sample, Nosarti et al. (2004) confirmed this result through a quantitative MRI technique able to detect even subtle cerebral abnormalities. More recently, and also using this technique, our research group has consistently found reductions of both the

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posterior and anterior corpus callosum, specifically the genu, in preterm and VPT adolescents (Narberhaus, Segarra, Caldú, et al., 2007).

In the corpus callosum, the region which extends from the rostrum to the posterior part of the midbody is predominantly made up of fibers interconnecting the prefrontal cortex (Park et al., in press). This fact enhances the importance of studying cognitive functions that are highly dependent on the prefrontal cortex, namely prefrontal functions.

Preterm adolescents seem to perform significantly worse than term born subjects in phonetic verbal fluency (Giménez, Junqué, Narberhaus, Botet et al., 2006; Taylor, Minich, Bangert, Filipek, & Hack, 2004) and category verbal fluency (Allin et al., 2001; Giménez, Junqué, Narberhaus, Botet et al., 2006). For other prefrontal functions, studies report contradictory results. For instance, while Tideman (2000) and Rushe et al. (2001) described no significant differences in attention/concentration, Taylor, Klein, Minich, and Hack (2000) found specific difficulties on this cognitive function. As regards executive functioning, Taylor et al. (2000, 2004) reported significant differences between preterms and controls on several different measures. Tideman (2000) also showed a significantly worse performance, but only on one specific task the Trail Making Test (TMT) B, mainly measuring planning and cognitive flexibility (Baron, 2004). In contrast, Rushe et al. (2001) and, recently, Saavalainen et al. (2006) observed no differences in executive functions between groups assessed through the TMT B and the Stroop test, respectively. Related to the above mentioned studies, it is noteworthy that Taylor et al. (2000, 2004) differ from the others in that they explore specifically extremely and very low birth weight subjects.

Additionally some studies report a significantly worse performance in preterm adolescents compared to term controls in everyday memory, as assessed by the Rivermead Behavioural Memory Test (RBMT) (Narberhaus, Segarra, Giménez, et al., 2007). This test mainly evaluates episodic memory, prospective memory and orientation, so the medial temporal lobe and finally the prefrontal cortex are involved (Kahn et al., 2005; Lezak, Howieson, & Loring, 2004; Rami et al., 2003; Umeda, Nagumo, & Kato, 2006).

Corpus callosum reduction has been related to a worse general cognitive performance in VPT children (Peterson et al., 2000) and adolescents (Caldú et al., 2006). Only two studies have analyzed the relationship between prefrontal functions and corpus callosum in VPT adolescents. Results showed an association between phonetic verbal fluency and the mid-posterior surface area (Nosarti et al., 2004), and between everyday memory and total corpus callosum area (Caldú et al., 2006). However, in this study the authors did not analyze the possible correlations between prefrontal functions and each part of the corpus callosum, while Nosarti et al. (2004) only found this relationship for VPT boys ($n = 33$). To our knowledge there is no study addressing the issue about the relationship between the different parts of the corpus callosum and prefrontal functioning in VPT adolescents.

The specific aim of the present study was to examine the functional implications of the reductions in the anterior corpus callosum, specifically the genu. We hypothesised that a smaller genu would be associated with worse prefrontal functioning in VPT adolescents compared to the term control group.

2. Method

2.1. Participants

Subjects with a history of prematurity were selected from the population born between 1982 and 1994 at the Hospital Clínic i Provincial, and between 1988 and 1989 at the Hospital Vall d'Hebron, both in Barcelona (Spain). In the archives of these hospitals 488 cases of prematurity were currently available at their databases. Inclusion criteria for the present study were: gestational age <33 weeks (VPT) and age at assessment between 11 and 18 years; remaining 278 cases, from which the clinical histories were inaccessible in 44 cases.

This resultant cohort was then reduced for several reasons: missing clinical data or exitus (72), no updated address or telephone number (75), refusal to participate in the study (5) or presence of one or more of the exclusion criteria (30). These exclusion criteria were: (a) full intelligence quotient (FIQ) below 70; (b) history of traumatic brain injury, cerebral palsy or other neurological diagnosis; (c) motor or sensory impairment that precluded neuropsychological assessment; (d) metal orthodontic prosthesis; (e) claustrophobia or anxiety levels high enough to require sedation. The available clinical data allow us to confirm that these subjects lost for investigation did not differ from those studied in birth weight, gestational age, gender ratio, mode of delivery nor in condition at birth.

The final sample thus comprised 52 VPT adolescents (27 girls/25 boys). Seventy-five percent presented hypoxic risk with apneas and/or hyaline membrane disease, requiring oxygen therapy. Only seven cases presented intraventricular haemorrhage grade III and/or IV. None of the other cases presented relevant complications in the peri/neonatal period.

Fifty-two controls (26 girls/26 boys) born at a gestational age ≥37 weeks and with normal pre-, peri- and post-natal data were recruited. This control group was mainly composed of relatives or acquaintances of the study sample, and their educational level and socio-economic status were similar. There were no significant differences between VPT subjects and controls in age at assessment ($t = -0.20$; $p = 0.84$) or gender ($\chi^2 = 0.08$; $p = 0.81$) (Table 1).

All participants underwent a magnetic resonance imaging (MRI) study and a neuropsychological assessment. According to the neuroradiologist (NB) no subject had parenchymal lesions. FIQ of the VPT individuals (*mean*: 101, *range*: 75–135) and controls (*mean*: 114, *range*: 92–141) were normal.

The study was approved by the Ethics Committee of the University of Barcelona and all the subjects or their family gave written informed consent prior to participating in the study.

2.1.1. MRI acquisition and analyses

T1-weighted morphological images were acquired on a 1.5 T Signa GE (Milwaukee, WI) using a 3D FSPGR-IR sequence (TR = 12 ms; TE = 5.2 ms; TI = 300 ms; 1 NEX; FOV = 24 cm × 24 cm; matrix size = 256 × 256), yielding partitions of 1.5 mm in thickness. All the images were reoriented in order to place them in the same position. A mid-sagittal slice in which the anterior and posterior commissures, as well as the fornix, were clearly identifiable was selected in order to draw the corpus callosum, which was semi-automatically segmented into seven parts following the approach described by Witelson (1989) and using Analyze 6.0 (Biomedical Imaging Resource, Mayo Clinic). This computer pro-

Table 1
Sample characteristics

	Mean (S.D.), range	
	VPT ($n = 52$)	Controls ($n = 52$)
Gestational age (in weeks)	29.69 (2.02), 25–32	39.58 (1.49), 37–43
Birth weight (g)	1273 (337.7), 690–2160	3421 (428), 2340–4300
Age at assessment (in years)	14.21 (1.74), 11–18	14.29 (2.22), 10–19