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Delay of cortical thinning in very preterm born children

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ABSTRACT

Background: Cortical gray matter thinning occurs during childhood due to pruning of inefficient synaptic connections and an increase in myelination. Preterms show alterations in brain structure, with prolonged maturation of the frontal lobes, smaller cortical volumes and reduced white matter volume. These findings give rise to the question if there is a differential influence of age on cortical thinning in preterms compared to controls.
Aims: To investigate the relationship between age and cortical thinning in school-aged preterms compared to controls.
Study design and outcome measures: The automated surface reconstruction software FreeSurfer was applied to obtain measurements of cortical thickness based on T1-weighted MRI images.
Subjects: Forty-one preterms (<32 weeks gestational age and/or <1500 g birth weight) and 30 controls were included in the study (7–12 years).
Results: In preterms, age correlated negatively with cortical thickness in right frontal, parietal and inferior temporal regions. Furthermore, young preterms showed a thicker cortex compared to old preterms in bilateral frontal, parietal and temporal regions. In controls, age was not associated with cortical thickness.
Conclusion: In preterms, cortical thinning still seems to occur between the age of 7 and 12 years, mainly in frontal and parietal areas whereas in controls, a substantial part of cortical thinning appears to be completed before they reach the age of 7 years. These data indicate slower cortical thinning in preterms than in controls.

1. Introduction

Important maturational events take place in the third trimester of pregnancy [1]. Since very preterm born children are born in this crucial phase, they are particularly vulnerable to primary injuries and secondary maturational difficulties. Various methods have been used to identify structural alterations in the preterm brain. Studies using magnetic resonance imaging (MRI) have reported lower cortical gray and white matter volumes, lower cerebellar volumes as well as smaller corpus callosum and hippocampus size in preterm born infants [2,3], children [4–7] and adolescents [8,9]. Furthermore, a smaller cortical surface area was observed in 7–10 year-old preterm children when compared to age-matched term born controls [7]. A voxel-based morphometry study found atypical gray and white matter distribution in preterm adolescents aged 14–15 years [10]. Diffusion tensor imaging studies detected alterations in white matter fiber tract organization throughout the brain, suggesting differences in structural connectivity [11] as well as widespread microstructural white matter abnormalities in very preterm born children compared to same-aged term born controls [12]. The structural alterations in very preterm born children raise the question if the process of cortical thinning differs between preterms and controls.

Cortical thickness is thought to be an indicator of the number of neurons per cortical column (groups of neurons which connect the six horizontal layers of the neocortex vertically) as well as glial support and dendritic arborization [13]. From early childhood to adolescence, decrease of cortical thickness co-occurs with the pruning of dispensable neurons and synapses [14]. This process leads to more efficient synaptic connections. The normal developmental cortical thinning does not occur simultaneously over the whole cortex. Findings concerning synaptic density, which is indirectly related to cortical thickness, suggest that during the course of development a synaptic loss occurs first in primary sensory and motor regions and later in multimodal association areas [15,16]. More recent studies confirmed this pattern using neuroimaging of cortical thinning in healthy children [14,17], others found contradictory results. Correspondingly, a longitudinal MRI study found not only regional specific *thinning* but also *thickening* in circumscribed perisylvian language relevant regions in 45 healthy

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children between 5 and 11 years of age [18]. Since the process of cortical thinning varies over different cerebral regions, it is important to examine cortical thickness over the whole cortex *and* on a regional level.

A cross-sectional study investigated the development of cortical thinning in children with very low birth weight and term born controls at 18–22 months and 3–4 years of age [19]. At both age groups, children with very low birth weight displayed greater mean cortical thickness compared to control children. Although the difference did not reach statistical significance, the authors suggest that their results point to a delay in normal cortical thinning following prematurity, up to the age of four years. Correspondingly, a longitudinal study comparing 55 preterm children (born with 600 to 1250 g birth weight) with 20 term born control children at 8 and 12 years of age, identified different gray and white matter volume changes over time between the study groups: In preterms, gray matter volumes decreased and white matter volumes increased less than in controls, which suggests a different gray and white matter development in preterms than in controls [20]. To the authors' knowledge, no study has investigated the effect of age on global and regional cortical thinning in a sample of school-aged very preterm born children in a cross-sectional study design. Based on the existing findings, we hypothesize that age is differentially associated with cortical thinning in preterms and controls between 7 and 12 years of age. We further assume that the normal developmental cortical thinning is delayed in very preterm born children compared to their term born peers, even in our sample of relatively healthy very preterm born children.

2. Methods

This study reports on a subset of data from the NEMO (NEuropsychology and meMOry) research project at the Children's University Hospital in Bern, Switzerland. The NEMO project examines cognitive development in very preterm born children including behavioral and neuroimaging data. The study protocol was approved by the local ethics committee. All children and caregivers provided informed written consent to the research and publication of the results prior to participation, consistent with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

2.1. Very preterm group

Medical reports of all very preterm born children (<32 weeks of gestation and/or <1500 g birth weight) born between 1998 and 2003 at the Children's University Hospital Bern, Switzerland were reviewed. Native German speakers aged 7 to 12 years with normal neonatal ultrasound, no or mild periventricular leukomalacia (grade I or II), no or mild neonatal cerebral lesions (hemorrhage grade I), no chronic illness, no pervasive developmental disorders, and Full-scale IQ > 85 in the neuropsychological follow-ups were included. A total of 247 children fulfilled the inclusion criteria and were contacted by letter out of which 75 children agreed to participate in the study. Fifty-five very preterm born children completed the MRI assessment. Fourteen preterms had to be excluded (technical problems n = 4, movement n = 10) resulting in 41 preterms for inclusion in the analysis.

2.2. Control group

Term born controls from the same year cohorts were recruited by means of announcements in the hospital. Forty-two children completed the MRI examination, twelve children were excluded (technical problems n = 2 and movement, n = 10), resulting in 30 controls included in the analysis.

Handedness was enquired by telephone interview prior to the first assessment. Socioeconomic status (SES) was defined as mother's and father's education level at the time of the neuropsychological assessment (no graduation = 1, college = 2, college of higher education = 3, university degree = 4). Full-scale IQ was assessed using the short form of the German version of the 'Wechsler Intelligence Scale for Children, Fourth Edition' [21].

2.3. MR imaging

Children underwent a one-hour MRI assessment at the Department of Diagnostic and Interventional Neuroradiology, University Hospital Bern.

2.3.1. Image acquisition

MRI was performed on a Verio3-T whole body scanner (Siemens Erlangen, Germany) equipped with a 40 mT/m gradient system and a CP standard head coil (12 channels). The scanner was equipped with the Syngo MR 2002B (VA17) software. Anatomical imaging was obtained using a T1-weighted, 3D-MPRAGE sequence (TR 2300 ms, TE 2.98 ms, TI 900 ms, 0 mm gap, FoV 256, 1 mm voxel resolution, 160 contiguous sagittal slices) with an acquisition duration of 5.21 min, recommended by ADNI (http://www.adni-info.org/).

2.3.2. Image analysis

The FreeSurfer software package (version 5.1.0, http://surfer.nmr.mgh.harvard.edu) was used for an automated cortical reconstruction of the T1-weighted images. The method used to create a three-dimensional cortical surface model of cortical thickness using intensity and continuity information has been previously described in detail [22]. Briefly, the automated processing included removal of non-brain tissue, Talairach transformation, intensity normalization, tessellation of the gray matter/white matter boundary, topology correction and surface deformation to detect gray matter/white matter and gray matter/cerebrospinal fluid boundaries. The resulting representation of cortical thickness was measured as the shortest distance between tissue boundaries (gray matter/white matter and gray matter/cerebrospinal fluid). Thickness measures were mapped to the inflated surface of the reconstructed brain in order to allow for visualization of data across the entire cortical surface without being obscured by cortical folding. To ensure the accuracy of the automated segmentation, each scan was reviewed to check the delineation of gray and white matter differentiation. Where necessary, pial surface correction and/or white matter corrections were made according to the FreeSurfer guidelines. Small pial surface corrections (i.e. over 3–5 slices) were made in 13 preterms and 15 controls and a white matter correction was made in one control child. Morphologically homologous cortical locations were accurately matched across subjects by morphing each reconstructed brain to an average spherical surface representation which optimally aligned sulcal and gyral features across subjects while minimizing metric distortion [23]. To reduce noise-induced variations and registration errors in measurements, a full width half maximum (FWHM) Gaussian blurring kernel of 15 mm was applied to smooth the thickness estimates. The applied method has been methodologically evaluated and has been applied in various settings, showing reliability even across different scanner platforms in terms of spatial localization and cortical thickness results [24].

2.3.3. Statistics

Pearson's chi square test (IBM SPSS Statistics 21.0) was used to examine group differences for categorical data. Unpaired two-sided t-tests were used to calculate group differences for continuous, normally distributed data. Cohen's delta coefficient d served as a measure of effect size, with $r = 0.20$ representing a small, $r = 0.50$ a medium and $r = 0.80$ a large effect. In order to compare mean global cortical thickness of both groups over the *whole* hemispheres, unpaired two-sided t-tests were used within SPSS. Associations of mean global cortical thickness with age were calculated for each group with Pearson correlations (data was distributed normally), $p < .05$ was considered statistically significant.

Using the high-resolution surface-based averaging techniques of the FreeSurfer software, thickness maps were averaged within both groups