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Entorhinal cortical thinning affects perceptual and cognitive functions in adolescents born preterm with very low birth weight (VLBW)

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ABSTRACT

Background: The entorhinal cortex serves as an important gateway between the cerebral cortex and the hippocampus by receiving afferent information from limbic, modality sensory-specific, and multimodal association fibers from all the brain lobes.
Aim: To investigate whether thinning of entorhinal cortex is associated with reduced perceptual, cognitive and executive skills in very low birth weight (VLBW) adolescents.
Study design: Prospective, geographically based follow-up study of three year cohorts of preterm born VLBW children.
Subjects: Forty-nine VLBW (birth weight ≤ 1500 g) and 58 term-born control adolescents were examined at the age of 14–15 years.
Outcome measures: Perceptual and cognitive functions were assessed with Visual motor integration test, Grooved Pegboard test, Wechsler Intelligence Scale for Children-III and different executive function tests (Wisconsin card sorting test, Trail Making test, Knox cube test). An automated MRI technique at 1.5 T for morphometric analyses of cortical thickness was performed. Areas with cortical thinning in left and right entorhinal cortex in the VLBW group were chosen as regions of interest to look for associations between cortical thickness and clinical findings.
Results: Thinning of the entorhinal cortex was correlated with low performance on perceptual and cognitive scores in the VLBW adolescents, but not in controls. In addition, thinning of the entorhinal cortices correlated with reduced performance on several executive tests, including perceptual speed and aspects of working memory.
Conclusions: Entorhinal cortical thinning is related with low IQ and reduced perceptual and executive functions in VLBW adolescents.

1. Introduction

The medial temporal lobe includes a system of anatomically related structures where the hippocampus lies at the end of a cortical processing hierarchy; the entorhinal cortex (ERC) is the major source of its cortical projections. This system is principally concerned with long-term memory, but also critically involved in complex functions such as sensory representation and spatial orientation [1]. Recently it was stated that the ERC may act as the nodal point between hippocampus and a variety of multimodal association areas of the cortex such as parietal, temporal, and prefrontal cortex [2].

Computational automated morphometric MRI methods with high reliability have detected correlates between cortical thinning and cognitive task performance in healthy individuals and in different patient groups (schizophrenia, Alzheimer's disease (AD), epilepsy) [3–5], and entorhinal shrinkage has been associated with cognitive decline in healthy elderly persons and in AD patients [6].

Children born very preterm or with very low birth weight (VLBW: birth weight ≤ 1500 g) are prone to perinatal brain injury and have an increased risk of developing motor and cognitive impairments during childhood and adolescence [7]. These impairments include reduced skills in perceptual and higher cognitive tasks that measure executive functions, attention and memory functions [8,9]. Quantitative MR

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studies have revealed both white and gray matter abnormalities in VLBW children, and the MR pathology seems to persist into adolescence and early adulthood, as do clinical problems [10–12]. We have previously published areas of cortical thinning and thickening in a cohort of VLBW children at 14–15 years of age and found that regional thinning in areas corresponding to the ERC was more pronounced in those with low IQ compared with those with normal IQ in the VLBW group, and in the most immature of the preterm born children [13]. The ERC area therefore seemed interesting to investigate further with quantitative measurements of mean thickness versus different aspects of cognitive functions.

The aim of the present study was to investigate whether ERC thinning is associated with reduced perceptual, cognitive and executive/attentional skills in VLBW adolescents. We hypothesized that aberrant development of this important cortical area would interfere with higher order cognitive and perceptual functions in these adolescents.

2. Methods

This study is part of a hospital-based follow-up study from birth where three year cohorts of prematurely born VLBW children from a defined geographic region in Norway were compared with randomly selected term born controls from the same geographic area examined at regular intervals with a battery of clinical tests and different MRI techniques.

2.1. Participants

The study population consisted of 49 VLBW and 58 control adolescents examined at 15 years of age. The Regional Committee for Medical Research Ethics approved the study protocol and written informed consent was obtained.

(See Appendix for more information about the study population).

2.2. Neuropsychological assessment battery

An estimate of the adolescents' intelligence quotient (IQest) was calculated using four subtests of *Wechsler Intelligence Scale for Children* (WISC)-third edition: Arithmetic, Vocabulary, Block design and Picture arrangement [15]. We defined low IQ as an estimated IQ score < 2 standard deviations (SD) of the mean in the control group.

Visual–motor function was assessed by the *Developmental Test of Visual–Motor Integration* (VMI–IV), including supplementary tests to evaluate visual perception and motor coordination [14]. Poor performance/impairment was defined as score < −2 SD from the mean scores of the control group. Attention and executive function were assessed with the, *Wisconsin Card Sorting Test (WCST), version III* [17], *Knox-Cube test* [18], and *Trail Making Test* [19], while the *Grooved Pegboard (GP) test* [16] was used to assess both motor coordination and processing speed. (See Appendix for more information about each of the neuropsychological tests).

2.3. MR imaging

The scanning was performed on a 1.5 T Siemens Symphony Sonata, Siemens AG, Erlangen, Germany. The imaging for the morphometric analyses was a 3D inversion recovery MPRAGE sequence with 128 sagittal partitions, slice thickness of 1.33 mm, square FOV of 256 mm, and acquisition duration of 8.5 min. An automated cortical surface reconstruction method developed by Dale and Fischl was performed to construct cortical thickness for each subject's entire brain [20,21]. The method has been described before, and statistical significant cortical thickness difference maps between the two groups of adolescents were generated [13]. Several significantly thinner areas were found in the VLBW adolescents (Fig. 1). Thinner areas in the right and left medial temporal lobe corresponded to an area that covered most of the ERC. These areas, labeled white in Fig. 1C and D, were used as regions of interest (ROIs) in the present study. The regions of interest were mapped back to each participant by using a high-dimensional spherical morphing procedure to find the homologous regions across subjects. A mean thickness for each of the two entorhinal cortical areas was then recorded for every VLBW participant.

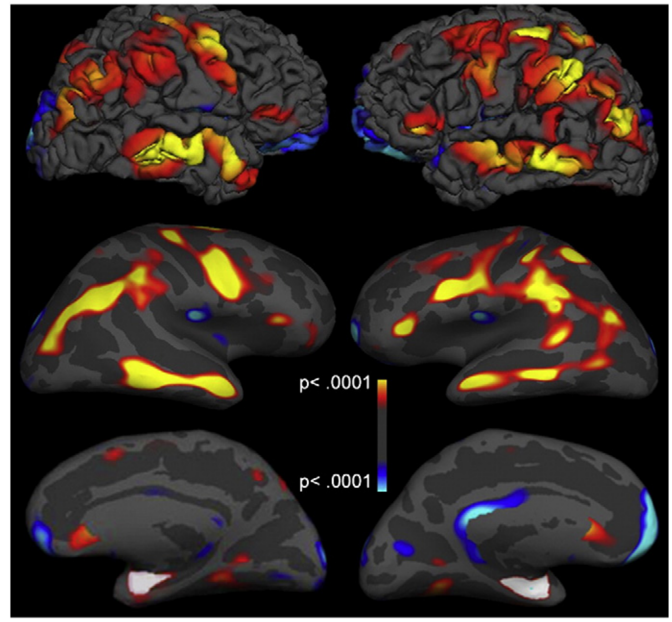

Fig. 1. Statistical difference maps of cortical thickness between 49 VLBW and 58 control adolescents are overlaid on the surface reconstruction with uninflated (upper panel) and inflated (middle and lower panel) brains. Dark gray areas correspond to sulci and light gray areas are gyri. Areas with statistically significant thickness difference between groups are shown in color, and the color scale shows the dynamic range of the changes, red to yellow represents an increasing thinning of the cortex in the VLBW group, and full yellow corresponds to a statistical difference in cortical thickness with a p-value ≤ 0.0001. Blue represents a statistically significant thickening of the cortex in the VLBW group; light blue corresponds to a statistical difference in cortical thickness with a p-value ≤ 0.0001. Areas of regional thinning of the entorhinal cortex (regions of interest) are marked in white in the lower panel.

2.4. Statistics

The associations between the individual mean thickness calculations in the ROI and the neuropsychological test scores in the VLBW group were explored by linear regression analysis. For continuous variables Pearson's r was used for correlation analyses between ERC thickness and IQ measurements, while Spearman's rho were performed for the neuropsychological test results since these are not normally distributed. For the correlation analyses the two-tailed significance threshold was set to $p < 0.02$ to adjust for multiple comparisons. In addition, we explored the relationship between thickness and neuropsychological test scores when the scores were dichotomized into those indicating normal and abnormal/low function (more than 2 SD from mean value of controls) using the Mann–Whitney *U* test. Adjustments for socio-economic status (SES) and IQ were performed for the neuropsychological tests, since low test results may be influenced by both these factors. Here p-values ≤ 0.05 were considered significant.

3. Results

3.1. Clinical and MRI findings

The clinical characteristics, test results and MRI findings for the study groups are shown in Table 1. Age at MRI examination was about 12 months higher in both groups of children when comparing with