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Long-term attention deficits combined with subcortical and cortical structural central nervous system alterations in young adults born small for gestational age

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ABSTRACT

Background: Being born small for gestational age has been associated with neurodevelopmental disabilities and smaller gray matter volumes in childhood. However, it is not known if these changes persist in adults and whether SGA has any impact on attention memory and IQ.
Aims: The goal of this study was to evaluate the association between birth weight and gray matter anatomy in adults born small for gestational age at term, in relation to IQ, attention and memory.
Materials and methods: This prospective follow-up study at age 20 included 39 adults born small for gestational age at term and 37 adults born appropriate for gestational age at term. Detailed neurocognitive skills were assessed (IQ, attention and memory). Anatomical images were analyzed using Voxel-Based-Morphometry and FreeSurfer.
Results: Adults born small for gestational age at term had lower performances in subtests assessing attention and executive functions. They also showed smaller total intracranial volume; smaller volumes and surface areas in the frontal lobe, inferior/middle parietal and temporal gyrus; smaller cerebellum, thalamus and basal ganglia volumes. Interestingly, all these structures correlated with attention subtests.
Conclusion: These results highlight the persistent effects of being born small for gestational age on attention and associated brain structures.

1. Introduction

Being born small for gestational age (SGA), either being born preterm or at term, was linked to decreased IQ, academic achievement and learning abilities; visomotors skills; as well as difficulties in attention, memory, executive function and emotional regulation in children and adults [1–8]. Moreover, decreased total brain volume has been observed in SGA children and adults [9].

The Kangaroo Mother Care program is a human-based care intervention devised to complement neonatal care for low birth weight and premature infants. Kangaroo position (skin-to-skin contact on the mother's chest) offers thermal regulation, physiological stability, appropriate stimulation and enhances bonding and breastfeeding. Kangaroo nutrition is based on breastfeeding and kangaroo discharge policy relies on family empowerment and early discharge in kangaroo position with close ambulatory follow-up [10].

One study in 4 to 7 years-old SGA children born at term reported smaller cerebellum, globus pallidus, putamen and hippocampus volumes [11]. One study in 15 years-old SGA adolescents born at term showed smaller cerebellum and thalamus volumes, but no difference in the amygdala and hippocampus volumes [12]. In 20 years-old SGA adults born at term, Ostgard et al. (2014) reported smaller frontal lobe, cingulate, temporal and parietal lobes surface area, as well as smaller putamen volume. However, they found no difference regarding cortical

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thickness and they did not assess cortical volumes [13].

The objective of this study was to investigate subcortical volumes, as well as cortical volume, thickness and surface area in 20 years-old SGA adults born at term. Participants were from the Colombian Kangaroo Mother Care cohort [10]. In addition to cortical thickness and surface area measurements [13], cortical volumes were assessed using two complementary methods for anatomical structural measurements (voxel-based and surface-based morphometric analyses). Moreover, to test the relationship between structure and function, we measured IQ, attention/executive functions and memory of the participants.

2. Methods

2.1. Participants

This study is part of a larger prospective research program on low birth weight, prematurity and the Kangaroo Mother Care program in Bogota, Colombia [14]. This program involved fetal assessment and long-term postnatal follow-up of several hundred newborns at the Clinica San Pedro Claver. In this cohort, newborns were born between 1993 and 1994 with a weight of < 2001 g. Among these newborns, 39 term infants participated in the follow-up study until adulthood. The present study included 76 adults, with 39 adults born at term, small for gestational age (SGA, mean birth weight: 1817 g ± 400 g) and 37 adults born at term, appropriate for gestational age (AGA, mean birth weight: 3032 g ± 800 g) and equivalent in terms of socio-economic status. The SGA group was defined by a birth weight below the 10th percentile, adjusted for gestational age [15]. Control subjects were defined as adults with birth weight between the 10th and 90th percentile. We defined SGA adults whose height at 12 months of age was equal to or above the 3rd percentile as having experienced catch-up growth [16,17]. In the SGA adults, 15 experienced catch-up growth, 22 not. The study protocol was approved by an ethical committee, and written informed consent was obtained for all participants.

2.2. Measures

Maternal age at birth; gender and parental education and incomes were recorded. Developmental physical data included weight, height and head perimeter at birth, 41 weeks of GA, 3, 6, 9, 12 months of corrected age and 20 years.

Cognitive and neuropsychological tests were administered to all participants at the time of testing. Intelligent Quotient (IQ) was measured with the *Weschler Abbreviated Scale of Intelligence* (*WASI-II*) [18]. The *California Verbal Learning Test-2nd edition* (*CVLT-2*) was used to assess memory [19]. Nine subtests of the *Test-battery of Attentional Performance* (*TAP 2.2.*) [20] were used to evaluate attention/executive function of the youth: alertness (focus attention), divided attention, sustained attention, working memory and go/nogo (selective attention/inhibition) subtests.

2.3. Image acquisition and processing

Structural brain images were acquired on a 3 T MRI scanner, with whole-brain, high resolution T1-weighted MPRAGE images acquired in the sagittal plane (TR = 8,52 ms, TE = 4.13 ms, matrix size = 250 × 256 × 160 mm, voxel size = 0.97 × 0.97 × 1 mm, FOV = 74 mm). The two-dimensional DICOM files of each brain were organized into volumetric three-dimensional files using the MRIcron software package (http://www.mccauslandcenter.sc.edu/mricro/mricron/).

2.3.1. Voxel-based morphometry (VBM)

The structural T1 images were firstly processed using the Computational Anatomy Toolbox (CAT12; developed by Christian Gaser, University of Jena) within the SPM12 software package (Wellcome Department of Cognitive Neurology, London, UK) and MATLAB R2016a, 9.0.0 (MathWorks, Natick, MA, USA) [21,22]. First, all T1-weighted anatomical images were manually reoriented to place the anterior commissure (AC) at the origin of the three-dimensional Montreal Neurological Institute (MNI) space. The images were then segmented into gray matter, white matter, and cerebrospinal fluid [23]. Segmentations were then inspected for their quality and homogeneity was checked with the CAT12 toolbox. One participant was excluded because of the anatomical image inhomogeneity and motion. Images were normalized to Montreal Neurological Institute (MNI) space using a diffeomorphic non-linear registration algorithm (diffeomorphic anatomical registration through exponentiated lie algebra toolbox-DARTEL) [24]. Images were modulated by the Jacobian transformed tissue probability maps (to obtain volume differences in gray matter) and smoothed with a Gaussian kernel of 8 mm full width at half maximum before statistical analyses.

2.3.2. Surface-based morphometry (SBM)

We assessed cortical volumes, thickness and surface area, as well as sub-cortical volumes using the FreeSurfer software (version 5.3.0) in the Canadian Brain Imaging Research Platform (CBRAIN) [25]. FreeSurfer, a fully automated surface-based pipeline, was used to process the T1 images into a common stereotactic space, in which volumes, cortical thickness and surface area values could be derived on a participant-by-participant basis [26] Cortical and sub-cortical segmentation procedure involved the assignment of a neuroanatomical label to each voxel in a MRI volume using voxel intensity, a probabilistic atlas estimated from a manually labeled training set, and Bayesian classification rules [26]. This technique was previously shown to be comparable in accuracy to manual tracing [27,28]. Cortical thickness was automatically quantified within FreeSurfer on a vertex-by-vertex basis by computing the average shortest distance between the white matter boundary and the pial surface (i.e. the cerebral spinal fluid boundary) at each point on the cortex [29]. Segmentation boundaries were visually inspected by a trained rater and, if necessary, errors due to segmentation miss classification were reprocessed.

2.4. Statistical analyses

Developmental, demographic, cognitive and neuropsychological data were analyzed in SPSS v.20 (Armonk, NY) with 2 sample *t*-tests comparing the two groups (small for gestational age, SGA vs. appropriate for gestational age, AGA), when data were normally distributed. If not, a non-parametric U Mann-Whitney test was used. With categorical data, a non-parametric Chi^2 test was used.

A whole brain VBM analyses was performed with a Gaussian random field threshold set at $\alpha = 0.001$ with an extent of at least 130 contiguous voxels (based on the expected voxels per clusters $< k > = 128.81$ for this analysis). Clusters were considered significant at $p < 0.05$, FWE-corrected. For FreeSurfer analyses, we extracted ROIs based on anatomical atlas and evaluated their gray matter volume, cortical thickness and surface area. Bonferroni's correction for multiple comparisons was applied with a significance level of $p < 0.0022$ ($p < 0.05/23$ number of comparisons in each hemisphere) to subcortical volume; cortical volume, thickness and surface area analysis of 19 regions. Two sample *t*-tests between groups (SGA vs. AGA), and sex as covariate of no interest, were performed in SPM12 and SPSS 20, respectively.

With Spearman's correlations, we then assessed how significant extracted VBM peak voxels and significant FreeSurfer gray matter volume, cortical thickness and surface area were related to the neurocognitive significant differences between groups. Correlations were considered significant at $p < 0.05$.

Exploratory, we performed a whole brain VBM analyze to differentiate participants who presented catch-up growth or not.