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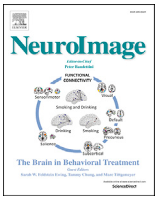

Hemispheric asymmetry and homotopy of resting state functional connectivity correlate with visuospatial abilities in school-age children

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ABSTRACT

Hemispheric specialization of cognitive functions is a developmental process that shapes the brain from the gestational stage to adulthood. Functional connectivity of the resting brain has been largely used to infer the hemispheric organization of the spontaneous brain activity. In particular, two main properties have been largely explored throughout development: hemispheric asymmetry of functional connectivity and homotopic functional connectivity. However, their relation with specific cognitive processes typically associated with hemispheric specialization, such as visuospatial abilities, remains largely unexplored. Such relationships could be particularly relevant for the quest of developmental cognitive biomarkers in childhood, a significant maturation period of visuospatial abilities. Moreover, the relation between asymmetry and homotopy of brain functional connectivity is not well understood. We have examined these two properties in a sample of 60 typically developing children between 6 and 10 years of age, and explored their relation with visuospatial abilities. First, we identified a strong negative relation between homotopy and asymmetry across the brain. In addition, these properties showed areas in the posterior portion of the brain, with significant correlation with performance in visual memory and visual attention tasks. These results highlight the relevance of the hemispheric organization of spontaneous brain activity for developmental cognition, particularly for visuospatial abilities.

Introduction

Hemispheric specialization of the brain is a developmental process that shapes its functional and structural properties from the gestational stage to adulthood, and has been largely associated with language and visuospatial abilities (Everts et al., 2009; Kasprian et al., 2010; Perani et al., 2011). In addition, unbalanced hemispheric lateralization has been associated with developmental disorders, such as dyslexia (Bishop, 2013; Paulesu et al., 2014), autism spectrum disorder (Anderson et al., 2010; Travers et al., 2012; Van Hecke et al., 2015), as well as attention disorders such as neglect syndrome (Stone et al., 1993; Corbetta and Shulman, 2011; Jiaojian Wang et al., 2016).

Neuroimaging techniques have allowed the exploration of the hemisphere-dependent structural and functional brain architecture and its relation with cognitive, sensory and motor functions (Saenger et al., 2012; Gotts et al., 2013; Hervé et al., 2013; Santarnecchi et al., 2015). In particular, functional connectivity of the resting brain has been largely used to infer the organization of the spontaneous brain activity throughout the lifespan (Nielsen et al., 2013; Alcauter et al., 2014; Agcaoglu et al., 2015), and has provided strong evidence of the relation of asymmetric resting state networks and performance in language-related tasks (Koyama et al., 2010; Martin et al., 2015; Alcauter et al., 2017). It has been even suggested as a promising predictor of success for interventions in children with dyslexia (Richlan et al., 2011; Schurz et al., 2014). Hemispheric functional organization in terms of resting state functional connectivity can be explored in terms of two main properties: asymmetry and homotopy. Asymmetry compares the connectivity patterns of a brain region with those of its contralateral counterpart (Tomasi and Volkow, 2012a; Nielsen et al., 2013). Meanwhile, homotopy is referred to the synchronicity of the spontaneous brain activity of homologous brain regions (Anderson et al., 2010; Zuo et al., 2010). So far, these two methods have shown that homotopy tends to decrease from childhood to adulthood (Zuo et al., 2010), whereas asymmetry shows a slightly increase during childhood (Nielsen et al., 2013), suggesting that hemispheric lateralization strengthens during childhood. However, these two properties have been explored in isolation, and their relation with developmental cognition remains largely unexplored (Gotts et al., 2013; Santarnecchi et al., 2015).

Few studies have explored the relationship between hemisphere-dependent functional connectivity and visuospatial abilities in adult

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samples (Gotts et al., 2013; Santarnecchi et al., 2015). Gotts et al. (2013) found that intra- and inter-hemispheric functional connectivity of the ventral temporal cortex showed a positive correlation with the performance in visuospatial tasks of a brief intelligence scale (WASI; Wechsler, 1999). Meanwhile, Santarnecchi et al. (2015), using a score of general intelligence, found that lower homotopic functional connectivity in sensorimotor areas was related with higher performance. Nevertheless, no previous studies have addressed this goal during childhood, despite being the period of greatest maturation of such abilities. Indeed, visual attention and visuospatial memory strengthen during childhood, rising to maximum performance around the end of the first decade of life (Wimmer et al., 2015), allowing accurate and rapid distinction of external stimuli as well as spatial orientation and navigation (Del Giudice et al., 2000; Tzuriel and Egozi, 2010).

The present work aims to characterize the hemispheric functional organization of the typically developing brain, and its impact on developmental cognition. Specifically, we computed the asymmetry of intra-hemispheric functional connectivity and inter-hemispheric homotopic functional connectivity at the voxel level and explored their relation with visuospatial abilities in typically developing children between 6 and 10 years old. The findings may contribute to the general interest of identifying potential biomarkers for typical and altered cognitive development.

Methods and materials

Subjects

The participants in this study took part in a larger study that assessed the relationship of brain connectivity and cognitive abilities in school-age children (Moreno et al., 2014; Alcauter et al., 2017). Those with available resting state functional MRI and high resolution T1 images (see below for details) were selected for this study, resulting in a sample of 66 children (age range: 6.7–9.8 years old; 30 boys, 36 girls). Six subjects with excessive motion artifacts in the fMRI session were excluded for further analyses (see below), resulting in a sample of 60 children (average age: 8.46 ± 0.77 years old; 25 boys, 35 girls). Group average, sex and age effects were tested for the functional connectivity properties in this dataset. Finally, brain-cognition relations were explored in a subset of 43 participants (average age: 8.51 ± 0.75 years old; 16 boys, 27 girls) that completed a neuropsychological battery (see below).

Original inclusion criteria consisted of birth after full-term gestation (at least 37 weeks) and being enrolled in elementary school. Exclusion criteria consisted of school grade repetition or any neurological or psychiatric impairment identified with the MINI International Neuropsychiatric Interview for Children and Adolescents (MINI-KID; Sheehan et al., 2010) and a general medical examination. Written informed consent from parents and assent from children were required. Experimental protocols followed the principles of the Declaration of Helsinki and were approved by the institutional bioethics committee ("Comité de Bioética del Instituto de Neurobiología").

Neuropsychological assessment

Participants were assessed with a battery of neuropsychological tests (ENI, from the Spanish "Evaluación Neuropsicológica Infantil", which can be translated as Neuropsychological Assessment for Children; Matute et al., 2007).

The ENI explores a wide variety of cognitive abilities. ENI natural scores are standardized into percentile scores according to a reference population for each year of age. For this study, only visuospatial domains were explored. Visuospatial evaluation includes five different domains: visual short and long-term memory, visual perception, spatial orientation, and visual attention. Briefly, visual memory is evaluated by the reproduction of geometrical figures, instantly (short-term) and 30 min after the presentation (long-term). Visual perception is assessed in terms of the correct identification of facial expressions in a set of pictures of children and identification of objects within a set of altered images (superimposed, uncompleted, blurred or split in smaller elements). Spatial orientation was evaluated in terms of the ability to follow directions on a cartoon city map. Visual attention is evaluated based on correct identification of specific figures or a set of alphabetic characters immersed in a pool of similar figures or alphabetic characters (Supplementary Table 1). Sex effects on visuospatial performance were tested with a two sample *t*-test. In addition, age effects were tested with Pearson's correlation analyses.

Imaging

MR images were acquired with a 3T MR GE750 Discovery scanner (General Electric, Waukesha, WI), using a 16-channel-array head coil. A total of 150 whole brain fMRI volume images were obtained using a gradient recalled echo T2* echo-planar imaging sequence (TR/TE = 2000/40 ms, voxel size 4 x 4 x 4 mm^3) with an acquisition time of 5 min. Participants were instructed to keep their eyes closed and not to fall asleep. This sequence was always run at the beginning of the MRI session to facilitate participants to stay awake. Subsequently, in order to obtain an anatomical reference, high resolution structural T1-weighted images were acquired using a 3D spoiled gradient recalled (SPGR) acquisition (TR/TE = 8.1/3.2 ms, flip angle = 12.0, voxel size 1 x 1 x 1 mm^3).

Preprocessing

Images were preprocessed using FMRIB's Software Libraries (FSL v.4.1.9; Smith et al., 2004; Jenkinson et al., 2012). Preprocessing of resting state fMRI datasets included slice timing and head motion correction, brain extraction, regression of confounding variables, spatial normalization, and band-pass temporal filtering (0.01–0.08 Hz). Each functional dataset was registered to its corresponding structural image with a rigid-body transformation, followed by a non-lineal registration to a symmetric pediatric brain atlas, the 7–11 years old NIHPD atlas (NIHPD-7-11; Fonov et al., 2011). A rigorous confounding regression strategy was implemented in order to minimize motion effects. For each fMRI volume, the relative displacement (i.e., relative to the precedent volume) was estimated and summarized into a single vector through the root mean square (RMS) of the six rigid-body registration parameters (Satterthwaite et al., 2013). Those volumes with more than 0.25 mm relative RMS displacement were regressed out from the time series (i.e., spike regression). Subjects with less than 120 non-affected volumes (i.e., 4 min) were excluded from further analyses. Confounding variables also included the average signal of white matter (WM) and cerebrospinal fluid (CSF), six motion parameters, the derivative of these eight parameters, and the square of these sixteen variables, as suggested by Satterthwaite et al. (2013). In addition, five principal components of WM and CSF were also included as confounding variables to further minimize the effect of physiological noise, a method described as *aCompCor*, which has been shown to be as effective as including respiration and cardiac readings as confounding variables (Behzadi et al., 2007; Chai et al., 2012). The preprocessing approach here used is known to significantly attenuate the effect of head motion on the low frequency fluctuations of the BOLD signal in pediatric samples (Ciric et al., 2017).

Hemispheric asymmetry and homotopic functional connectivity

An asymmetry index (ASI) was computed as the normalized difference of intra-hemispheric weighted degree (WD) for every pair of mirror voxels within a symmetrical gray matter mask (see below), according to the following equation: $ASI = (WD_R - WD_L)/(WD_R + WD_L)$; where R and L subindices account for right and left hemispheres, respectively. Thus, a negative asymmetry index would indicate higher WD in the left hemisphere, while a positive value would indicate higher WD in the right hemisphere. The weighted degree (WD) is a basic measure of graph theory, which is defined for a node as the sum of the magnitudes of its significant connections (edges in graph theory). Functional connectivity