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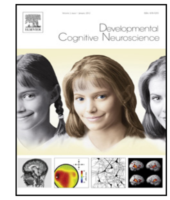

Dorsal anterior cingulate cortex in typically developing children: Laterality analysis

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ABSTRACT

We aimed to elucidate the dACC laterality in typically developing children and their sex/age-related differences with a sample of 84 right-handed children (6–16 years, 42 boys). We first replicated the previous finding observed in adults that gray matter density asymmetry in the dACC was region-specific: leftward (left > right) in its superior part, rightward (left < right) in its inferior part. Intrinsic connectivity analysis of these regions further revealed region-specific asymmetric connectivity profiles in dACC as well as their sex and age differences. Specifically, the superior dACC connectivity with frontoparietal network and the inferior dACC connectivity with visual network are rightward. The superior dACC connectivity with the default network (lateral temporal cortex) was more involved in the left hemisphere. In contrast, the inferior dACC connectivity with the default network (anterior medial prefrontal cortex) was more lateralized towards the right hemisphere. The superior dACC connectivity with lateral visual cortex was more distinct across two hemispheres in girls than that in boys. This connection in boys changed with age from right-prominent to left-prominent asymmetry whereas girls developed the connection from left-prominent to no asymmetry. These findings not only highlight the complexity and laterality of the dACC but also provided insights into dynamical structure–function relationships during the development.

1. Introduction

Based on its cytology, imaging characteristics and connections, the dorsal anterior cingulate cortex (dACC) is thought to play a crucial role in the development of human cognitive function and guiding human behaviors (Rushworth et al., 2007). It has been associated with cognitive control functions including attention modulation, competition monitoring, complex motor control, motivation, novelty, error detection, working memory, anticipation of cognitively demanding tasks, and the modulation of reward-based decision making (for review, see Shenhav et al., 2013). Functional abnormalities associated with the dACC have been consistently reported in ADHD (Bush et al., 1999; Cao et al., 2009; Castellanos et al., 2008; Durston, 2003; Rubia et al., 1999; Tamm et al., 2004; Tian et al., 2006; Yang et al., 2011; Zang et al., 2007), which is considered as a neurodevelopmental disorder (Bush et al., 2005; Castellanos et al., 2002).

Seldon has proposed that during human development, white matter grows outward and expands to the overlying cortex similar to a balloon, affecting the capacity of the cortex (Seldon, 2005). The different rates of expansion in particular brain regions create regional differences in cortical thickness, volume, surface area, neuronal density, curvature and folding patterns. A varying rate of expansion between homologous regions causes lateralization, which represents a natural feature of the human brain. Many

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studies have reported the lateralization of the human brain, such as the leftward asymmetry of the precentral gyrus and the middle frontal, anterior temporal and superior parietal lobes, the rightward asymmetry of the inferior posterior temporal lobe and the inferior frontal gyrus (Luders et al., 2006) as well as larger right-than-left frontal petalias and larger left-than-right occipital petalias (Chiu and Damasio, 1980; LeMay, 1977). We recently demonstrated a specific pattern of gray matter density (GMD) asymmetry of the dACC in a large sample of healthy adults, indicating leftward GMD asymmetry in the superior dACC but rightward GMD asymmetry in the inferior dACC (Wang et al., 2013). Such an asymmetry has not been explored in typically developing children (TDC).

With increasing age, cortical thinning is observed in the occipital, parietal and somatosensory areas (Mufuler et al., 2011). This age-related GMD loss in TDC is explained by cortical maturation to increase functional efficiency and variety (Gogtay et al., 2004; Sowell et al., 2001, 2003, 2004). The dACC is typically considered to have strong reciprocal interconnections with the lateral prefrontal, parietal, and premotor and supplementary motor cortices (Bush et al., 2000). According to the evidence for age-related cortical thinning and the cortical expansion theory, we hypothesized that the GMD asymmetry in the dACC during childhood is associated with age.

Decreased lateralization of task activation in children and adolescents compared to adults has been detected for many tasks, including attention (Booth et al., 2003; Bunge et al., 2002; Moses et al., 2002) and language tasks (Holland et al., 2001; Szaflarski et al., 2006). The dACC connects with many brain networks involving language, attention and cognitive control, which are highly asymmetric in adults (Aboitiz et al., 1995; Corbetta and Shulman, 2002; Coull and Nobre, 1998; Garavan et al., 1999; Toga and Thompson, 2003). Increased functional connectivity between the left dACC and the left inferior frontal gyrus has been reported during a language-processing task, whereas increased connectivity between the right dACC and the right parietal areas during a visuo-spatial processing task was detectable (Stephan et al., 2003), suggesting that the brain regions associated with cognitive control in the dACC are restricted to the ipsilateral hemisphere. Computerized neurocognitive tests have provided strong evidence that substantial improvement with age occurred for executive functions, and relevant age–sex interactions (Gur et al., 2012). We thus further hypothesized that the morphologic asymmetry in the dACC would lead to its functional asymmetry with age and sex effects in TDC.

To directly test our hypotheses, we employed resting-state magnetic resonance imaging (rfMRI) as the method measuring intrinsic functional connectivity (iFC) (Biswal et al., 1995, 2010), which has been used to examine the ACC circuitry in human brains (Castellanos et al., 2008; Margulies et al., 2007; Tian et al., 2006; Yan et al., 2009). This tool has been proved valuable in studying neurodevelopment processes (Fair et al., 2007; Gao et al., 2013, 2014, 2015; Kelly et al., 2009; Betzel et al., 2014). With an approach similar to our previous study on asymmetric iFC pattern of the dACC in adults (Yan et al., 2009), we elucidate the dACC asymmetry profiles on both GMD and iFC in TDC as well as their interactions with age and sex.

2. Materials and methods

2.1. Participants

All participants are parts of a large longitudinal sample for the study of the normative growth curves of the brain in China, the Chinese Color Nest Program (CCNP). The CCNP data collection is currently undergoing, including three waves of multi-modal neuroimaging data from 198 participants across five years (2012–2017). We have shared part of the CCNP wave-1 data to the public via the Consortium for Reliability and Reproducibility (CoRR) (Zuo and Xing, 2014; Zuo et al., 2014). Before the experiments, all participants or their guardians provided written informed consent. The Institutional Review Board of the Institute of Psychology of the Chinese Academy of Sciences approved the experiments. All participants had no history of head injury, psychiatric or neurological disorder or substance abuse according to their self-reports and their handedness was assessed using Annett's Inventory (Annett, 1976). We collected the wave-1 data from 162 participants at the time of manuscript preparation. A total of 42 participants were excluded from the samples based on the following criteria: (1) non-right-handed (13 participants); (2) poor anatomical image quality (2 participants); (3) bad spatial normalization based on visual inspection (4 participants); and (4) excessive head motion (23 participants). To match age and sex of samples, we finally selected 84 TDC from the 120 participants passing above criteria (6–16 years old, 42 males).

2.2. Data acquisition

All data were acquired using a 3T Siemens MR scanner (Magnetom Trio Tim equipped with syngo software) at Southwest University, Chongqing, China. To minimize head motion, foam pads and belts were used. T1-weighted image data were acquired using a magnetization prepared rapid gradient echo (MP-RAGE) sequence (176 sagittal slices, time repetition = 2600 ms, time echo = 3.02 ms, slice/gap thickness = 1/0 mm, in-plane matrix = 256 × 256, field of view = 256 × 256 mm^2, and flip angle = 8°). Two rfMRI scans were acquired for each participant using a single-shot gradient-recalled echo planar imaging (EPI) sequence (repetition time = 2500 ms, echo time = 30 ms, flip angle = 80°, 38 axial slices, field of view = 216 × 216 mm^2, in-plane matrix = 72 × 72, slice thickness = 3 mm, and slice overlapping = 10%) and were separated by the T1 scan. Each rfMRI scan contains 184 functional volumes in a total scan time of 460 s. The participants were instructed to rest with their eyes open and to look at a fixation point on the screen while not thinking of anything in particular or falling asleep. The rfMRI with smaller head motion measured by the mean frame-wise displacement (mean FD) as defined in (Power et al., 2012) was selected for subsequent analyses.

2.3. Overall strategy of laterality analysis

Similar to our previous studies (Wang et al., 2013; Yan et al., 2009), our analytic strategy consisted of eight fundamental stages: (1) creating a group-specific symmetric templates of gray matter, EPI image, and brain tissue mask for spatial normalization and iFC analyses; (2) preprocessing of the structural MRI and rfMRI scans; (3) generating individual GMD maps; (4) performing analysis of variance (ANOVA) with repeated measures to detect the differences in GMD between left and right sides of the brain, side-age, side-sex and side-sex-age interactions; (5) extracting peak coordinates for the dACC showing significant differences in left-right GMD asymmetry to define 3 mm-radius spheres as seed regions for subsequent iFC analysis; (6) generating individual iFC maps of the left and right dACC seeds; and (8) solving a similar ANOVA with repeated measures in (4) to determine the differences between the individual iFC maps of the left dACC seeds and the LR-flipped individual iFC maps of the right dACC seeds as well as their interactions with age and sex. The steps of image analysis are illustrated in Fig. 1, and the details of each of these steps are fully described in the subsequent sections.