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Trade-off of cerebello-cortical and cortico-cortical functional networks for planning in 6-year-old children

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ABSTRACT

Childhood is a critical period for the development of cognitive planning. There is a lack of knowledge on its neural mechanisms in children. This study aimed to examine cerebello-cortical and cortico-cortical functional connectivity in association with planning skills in 6-year-olds ($n = 76$). We identified the cerebello-cortical and cortico-cortical functional networks related to cognitive planning using activation likelihood estimation (ALE) meta-analysis on existing functional imaging studies on spatial planning, and data-driven independent component analysis (ICA) of children's resting-state functional MRI (rs-fMRI). We investigated associations of cerebello-cortical and cortico-cortical functional connectivity with planning ability in 6-year-olds, as assessed using the Stockings of Cambridge task. Long-range functional connectivity of two cerebellar networks (lobules VI and lateral VIIa) with the prefrontal and premotor cortex were greater in children with poorer planning ability. In contrast, cortico-cortical association networks were not associated with the performance of planning in children. These results highlighted the key contribution of the lateral cerebello-frontal functional connectivity, but not cortico-cortical association functional connectivity, for planning ability in 6-year-olds. Our results suggested that brain adaptation to the acquisition of planning ability during childhood is **partially** achieved through the engagement of the cerebello-cortical functional connectivity.

Introduction

Planning is a complex ability that involves the evaluation and selection of a sequence of thoughts and actions to achieve a desired goal. Considering the central role of planning for navigating daily life, it is unsurprising that the success of developing proper planning skills during childhood is predictive of later academic achievement and social maturity (Gerstle et al., 2016; Hughes, 1998; Zorza et al., 2016). While the crucial period for developing early planning skills is during mid-childhood, between 6- and 8-years-old (Luciana and Nelson, 2002; Welsh et al., 1991), the neural development associated with the acquisition of planning ability remains unknown.

Planning ability not only involves multiple cognitive processes such as attention, inhibition, and working memory, but also internal rehearsal and temporal sequencing, which have long been considered functions subserved by the cerebral cortex. However, evidence from both neuroimaging and lesion studies supports a more distributed account of these functions that includes the cerebellum. Planning ability can be investigated using the Tower of London task (Shallice, 1982), which requires participants to imagine a complex sequence of steps to move blocks from one position to another under specific constraints. Prior MRI and positron emission tomography (PET) studies investigating the Tower of London task have found both the prefrontal and parietal cortex (Beauchamp et al., 2003; Newman et al., 2003; Nitschke et al., 2017; Schall et al., 2003; Wagner et al., 2006) as well as the lateral cerebellum (VI, VIIa/b) to be involved (Beauchamp et al., 2003; Schall et al., 2003; Stoodley and Schmahmann, 2009). Further support for the cerebellar role in planning can be found in lesion studies, which have observed that focal damage in

Abbreviations: ALE, Activation likelihood estimation; SOC, Stockings of Cambridge; FC, functional connectivity; ICA, independent component analysis.

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the lateral cerebellum results in planning deficits in both adults (Grafman et al., 1992; Schmahmann and Sherman, 1998) and children (Cantelmi et al., 2008; Levisohn et al., 2000). Notably, the lateral cerebellum — including lobules VI, VIIa and VIIb — has direct anatomical connections with the prefrontal and parietal association cortex (Kelly and Strick, 2003; Middleton and Strick, 2000; Schmahmann and Pandya, 1997), supporting the notion of a cerebello-cortical functional system underlying planning ability.

Resting-state functional MRI (rs-fMRI) provides a great advantage for assessing functional organization of the brain (Buckner et al., 2013), especially in children, because of the minimal task compliance required during acquisition. Prior rs-fMRI investigation of developmental differences within the cerebello-cortical system has found that the cerebellum is more integrated with the frontal and parietal association cortex during mid-childhood, while adults have greater integration within cortico-cortical functional networks (Kipping et al., 2017). This asynchronous neurodevelopment of cerebello-cortical and cortico-cortical networks provides a basis for investigating the development of cognitive planning. We hypothesize that children with better planning ability would show decreased cerebello-cortical, and increased cortico-cortical integration.

To investigate this hypothesis, we compared cerebello-cortical and cortico-cortical connectivity strength between children with good performance in a planning task and children with poor performance in a planning task. Planning ability was assessed using the Stockings of Cambridge task (SOC) (Luciana and Nelson, 2002; Robbins et al., 1998), which is a computerized version of the Tower of London task (Shallice, 1982). Independent component analysis (ICA) was used to identify the cerebellar and cortical functional components that were then employed to generate the cerebello-cortical and cortico-cortical functional connectivity maps. Activation likelihood estimation (ALE) meta-analysis was conducted on existing task-fMRI studies to identify brain regions related to planning as anatomical references, which were then used to select planning-relevant cerebello-cortical and cortico-cortical functional connectivity maps. Our results confirmed the differential cerebello-cortical integration in planning ability during childhood, and introduced a novel perspective on the large-scale systems involved in acquiring this crucial ability during mid-childhood.

Methods

Research involving human participants and/or animals

All procedures performed in studies involving human participants were in accordance with the ethical standards of Institutional Review Board of the National University of Singapore.

Informed consent

Informed and written consent was obtained from all individual participants' parents included in the study.

Participants

Children aged 6–7 years ($n = 76$; age $= 6.45$ years $\pm$ 0.32 years) were recruited from an existing population-based study (Dirani et al., 2010; Zhong et al., 2014). All of the children in this study were born at 37–41 weeks (*mean* = 38.9 weeks, *SD* = 1.1 weeks) with normal birth weight (i.e., 2500–4630 g, *mean* = 3241.3 g, *SD* = 370.6 g). Data for birth weight and gestational age were obtained from medical record booklets and had been reported by a hospital physician or nurse at or shortly after the time of birth. IQ was assessed via the Kaufman Brief Intelligence Test (Kaufman and Kaufman, 2004). Children with chronic medical or mental conditions (e.g., congenital abnormalities, mental retardation, language disorders, mood, attention deficit hyperactivity disorder and motor disorders) were excluded from the study. Children whose mothers reported adverse pregnancy indicators (e.g., diabetes, hypertension) or complications at birth were also excluded from the study. All mothers had no history of smoking and alcohol-drinking habit before and during the pregnancy, except two mothers who self-reported one or two glasses of wine every couple of weeks.

Stockings of Cambridge (SOC)

The Cambridge Neuropsychological Test of Automated Battery (CANTAB) includes language-independent cognitive tests (Luciana and Nelson, 2002) administered on a computer fitted with a touch-sensitive screen and a 2-button response pad. Participants were first screened on two motor and learning tasks to verify the ability to follow simple instructions. Subsequently, participants performed Stockings of Cambridge (SOC). The CANTAB tests were conducted outside the MRI scanner.

SOC is an executive function task involving planning and execution of a series of actions. During the task, participants are shown two displays containing colored balls that can be perceived as stacks of colored balls in stockings or socks suspended from a beam. Participants are required to copy the pattern shown in the upper display by moving the balls in the lower display. Prior to the execution of ball moves, participants need to plan their moves. Participants are instructed to complete a trial with the minimum number of moves at increasing difficulty levels of 2-, 3-, 4- and 5-move problems. The balls can be moved one at a time by touching the required ball and then touching the target position. Two accuracy measurements are assessed for each difficulty level: the number of trials in which the minimum number of moves were used to solve the problem, and the mean number of moves across trials. Participants who performed the tasks with the minimum number of moves could solve the problems in the most efficient manner. Since we were interested in the early stage of planning in children, we used the mean number of moves across all the trials in each difficulty level to estimate overall planning efficiency in this study.

Subsequently, children were classified based on their SOC performance into good and poor performers using k-means clustering in MATLAB (Lee et al., 2016). To ensure stability of cluster allocation of individual children, cluster analysis was repeated for 1000 trials. For each trial, 80% of the children were randomly selected and k-means clustering was employed. The cluster probability of each subject, representing the chance that the subject was assigned to the same cluster over all 1000 trials, was computed. Subjects with a cluster probability greater than 0.8 were included in the following analysis.

MRI acquisition and preprocessing

MRI data from children were acquired on a 3T Siemens Magnetom Trio Tim scanner with a 32-channel head coil at Clinical Imaging Research Centre of the National University of Singapore. The image protocols were as follows: (i) high-resolution isotropic T_1-weighted MPRAGE sequence (190 slices, 1 mm thickness, field of view = 190×190 mm, matrix = 190×190, voxel size = $1 \times 1 \times 1$ mm^3, repetition time = 2000 ms, echo time = 2.08 ms, flip angle = 9°); (ii) isotropic axial resting-state fMRI protocol (single-shot echo-planar imaging; 42 slices with 3 mm thickness, no inter-slice gaps, field of view = 192×192 mm, matrix = 64×64, voxel size = 3×3x3 mm^3, repetition time = 2400 ms, echo time = 27 ms, flip angle = 90°, 150 vol, 6 min scanning time). The children were asked to close their eyes during the resting-state scan. The scan quality was verified immediately after the acquisition through visual inspection while the children were still in the scanner. If the MPRAGE showed no clear anatomical structure due to head motion, a repeat scan was conducted. The dataset was removed from the study if no acceptable scan was acquired after three repetitions. With successful MPRAGE acquisition, any checkerboard images caused by motion for the resting-state scan were removed before analyses.

Anatomical MRI Processing. FreeSurfer was used to segment the brain into cortical grey matter (GM), white matter (WM), cerebro-spinal fluid (CSF), subcortical regions, and cerebellum (Fischl et al., 2002). Large deformation diffeomorphic metric mapping (LDDMM) algorithm was used to align individual T_1-weighted MRI images to the John Hopkins University (JHU) T_1-weighted brain atlas (Du et al., 2011). We chose the adult brain as atlas since the brain of 6-year-old children is approximately 95% of adult brain size (Lenroot and Giedd, 2006) and shows adult-like gyrification (Armstrong et al., 1995). Aligning the brain of 6-year-old children to an adult's brain does not influence fMRI measures (Burgund et al., 2002; Kang et al., 2003).

Rs-fMRI Preprocessing. The rs-fMRI scans used in this study were with maximal translational motion less than 1 mm, rotational movement less than 2°, and framewise displacement (FD) < 0.5 mm (Power et al., 2012).

For independent component analysis (ICA), all rs-fMRI scans were preprocessed by the following pipeline using FSL (Smith et al., 2004): slice time correction, motion correction, and skull stripping. Within subjects the mean functional volume was aligned to the corresponding anatomical image via rigid body alignment. Subsequently, intensity normalization was applied. For the group analysis, the functional data were transformed to the atlas space via LDDMM obtained based on the anatomical data. Spatially normalized rs-fMRI data from children were kept at a voxel size of $3 \times 3 \times 3$ mm^3.

For the subsequent rs-fMRI functional connectivity analysis, nuisance signals, including six motion parameters as obtained during motion correction and mean WM and CSF signals were regressed from the rs-fMRI data. A temporal band-pass filter (0.01–0.08 Hz) was then applied.

Cerebellum-only and cerebrum-only group-ICA

We illustrate the schematic of the functional connectivity analysis in Fig. 1. We employed multivariate MELODIC group-ICA (Smith et al., 2004) to identify cerebellar and cerebral functional subdivisions in children (Fig. 1). The cerebellar and cerebral masks were created using FreeSurfer (Fischl et al., 2002). ICA was applied separately to the functional data in the cerebellum since it has been shown to be more suitable for parcellating the cerebellum into its functional units as compared to applying ICA to the whole-brain functional data (Dobromyslin et al., 2012). Whole-brain ICA might result in non-apparent cerebellar components due to reduced sensitivity (Dobromyslin et al., 2012). Subsequently, ICA was performed separately on the cerebrum to identify cortico-cortical networks. Component dimensionality was kept as a free-choice parameter to assure robust, but noise-reduced functional networks. The spatial mixture model of ICA (0.99–1) was used to construct cerebellar and cerebral functional networks in children.

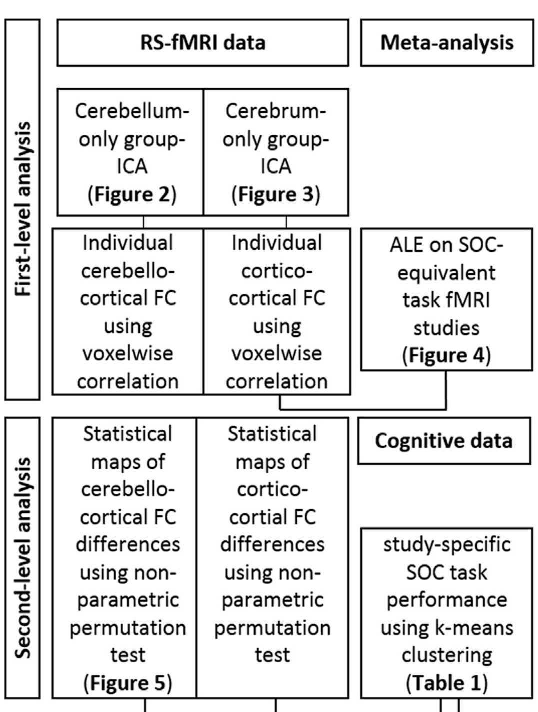

Fig. 1. Schematic for the method used in this study.

Meta-analysis for cortical regions related to planning and cortico-cortical functional network

As illustrated in Fig. 1, meta-analysis was conducted on whole-brain fMRI studies to identify brain regions related to planning as anatomical references in this study. BrainMap Sleuth 2.4 (Fox et al., 2005; Laird et al., 2005) was used to search fMRI studies utilizing the Tower of London task, equivalent to SOC (Shallice, 1982), on healthy individuals, with a sample size greater than 8, publication date after year 2000 and with only positive activations. Only 5 fMRI studies on adults fulfilled the above searching criteria and are listed in the Supplementary Table S1. Peak coordinates of identified experiments were extracted from the database and analyzed using activation likelihood estimation (ALE) in GingerALE 2.3.6 (Eickhoff et al., 2012; Turkeltaub et al., 2012) to detect brain regions consistently activated during the Tower of London task. The ALE map was thresholded at a cluster-corrected $p < 0.05$ (voxelwise uncorrected threshold of $p < 0.001$) (Balsters et al., 2014). The ALE map showed the brain regions relevant to cognitive planning.

Cortico-cortical and cerebello-cortical functional connectivity analysis

We illustrated our examination of the cortico-cortical and cerebello-cortical functional connectivity analysis in Fig. 1. At the first-level analysis, within individual subjects, the time series averaged over individual cerebellar ICs or cerebral ICs identified above were extracted and correlated with each voxel in the cerebral cortex. Correlation maps were then normalized using Fisher's z-transformation. Spatial smoothing with an isotropic Gaussian kernel with a 6 mm full-width-at-half-maximum was performed on Fisher's z-transformed correlation maps. This procedure yielded individual cerebello-cortical and cortico-cortical functional connectivity maps. We selected the cortico-cortical functional connectivity maps that are relevant to cognitive planning when these maps were spatially overlapped with the ALE maps defined above. These functional maps were further used in the second level analysis described below.

Statistical analysis

In the second-level analysis (Fig. 1), non-parametric two-sample t-tests as implemented in FSL (command 'randomise') were used to examine differences in the cerebello-cortical and cortico-cortical functional connectivity between good and poor planning performers (Winkler et al., 2014). The t-distribution was empirically generated using 10000 permutations to overcome the imbalanced sample sizes of the two cognitive groups. The correction for multiple comparisons was achieved through cluster-based thresholding (cluster-corrected $p < 0.05$) using the null distribution of the max cluster size over the image, where the cluster size was computed based on voxelwise $p < 0.005$.

Results

Good and poor performers in SOC

Among 76 children, 69 children performed all 4 levels of the SOC task. All children completed at least half of the trials of 2-move problems (mean moves = 2.07, standard deviation (SD) = 0.24, range of moves = 2–3), while only 23% of children completed at least half of the trials of 5-move problems (mean moves = 8.37, SD = 1.59, range of moves = 5–12),

Table 1
Demographics in poor and good performers.

	Age in Years (SD)	Mean FD (SD)	IQ (SD)	Mean moves of 3-move-problems (SD)	Mean moves of 4-move-problems (SD)
Poor performers (n = 16)	6.42 (0.24)	0.045 (0.024)	31.13 (9.89)	5.19 (0.60)	6.66 (1.04)
Good performers (n = 36)	6.43 (0.31)	0.05 (0.028)	32.22 (8.58)	3.47 (0.48)	5.20 (0.64)
Poor > good	$p = 0.874$	$p = 0.551$	$p = 0.686$	$p < 0.001$	$p < 0.001$
	$t_{(50)} = -0.76$	$t_{(50)} = -0.6$	$t_{(50)} = -0.41$	$t_{(50)} = 11.02$	$t_{(50)} = 6.19$

SD — standard deviation.

suggesting that 2-move problems were easy and 5-move problems were demanding for 6-year-old children (Luciana and Nelson, 2002). In contrast, 82% and 67% children completed at least half of the trials of 3-move problems (mean moves = 3.88, $SD = 0.88$, range of moves = 3–7) and 4-move problems (mean moves = 5.95, $SD = 1.09$, range of moves = 4–9), respectively, suggesting that children aged 6 years had achieved an intermediate, however non-adultlike, level of cognitive planning. Hence, the performance of 3- and 4-move problems was included in the k-means clustering. The cluster analysis identified two groups of children, who were repeatedly clustered into the same group with a probability of >0.80: group 1 (n = 16) with poor performance, and group 2 (n = 36) with good performance in planning. Table 1 lists the demographics for each group. By design, group 1 performed worse in both mean moves of the 3- and 4-move problems than group 2 ($p < 0.001$). However, no group differences were found in age, IQ and mean FD ($p > 0.55$).

Cerebellar and cerebral functional networks in children

The FastICA algorithm in MELODIC (Hyvärinen and Oja, 1997) estimated 50 independent components (ICs) for the cerebellum and 28 for the cerebrum. Thirteen cerebellar ICs (Fig. 2) and 19 cerebral ICs (Fig. 3) were selected since they were functionally relevant, mostly bilateral or homologous unilateral components in the gray matter. Functional relevance of spatial maps was identified with the help of network descriptions in the literature for the cerebellum (Dobromyslin et al., 2012; Kipping et al., 2017) and cerebrum (de Bie et al., 2012; Smith et al., 2009). Discarded ICs were along cerebellar or cerebral gray matter and CSF borders, or along the supratentorial space, or within white matter.

As illustrated in Fig. 2 13 cerebellar functional networks were identified in the cerebellar regions I–III (IC 1), VI (IC 2), medial VIIa (IC 3 and IC 7), bilateral IX (IC 4), V/VIII (IC 11, IC 12, and IC 20), lateral VIIa (IC 13 and IC 24), medial VIIb (IC 17), lateral VIIa/b (IC 18) and lateral VIIb (IC 32).

Likewise, Fig. 3 shows 19 cerebral functional networks, namely the visual (IC 1, IC 3, IC 10, IC 19), somatomotor (IC 2, IC 4, IC 16, and IC 24), auditory (IC 17), dorsal attention (IC 5 and IC 6), ventral attention (IC 13), executive (IC 12 and IC 14), salience (IC 15), default mode (IC 7 and IC 8), language (IC 22), and limbic (IC 11) networks.

Meta-analysis on planning

Meta-analysis was conducted based on 5 fMRI studies on the Tower of London task (see Table S1 in the Supplementary Material). These 5 studies included 8 experiments, 72 subjects, and 89 brain locations. Fig. 4A illustrates the ALE map, suggesting that the frontal and parietal cortices were involved in the functional activation for planning. Among the cerebral functional networks shown in Figs. 3 and 4 overlapped with the ALE map to various degrees but above a cluster extent of 594 mm^3, namely the dorsal attention network, right and left executive networks, and salience network. Fig. 4B shows the spatial overlap between the cerebral functional networks and ALE map. All 4 cerebral functional networks were considered for the subsequent cortico-cortical functional connectivity analysis in relation with SOC.

Cerebello-cortical and cortical-cortical functional connectivity in good and poor performers

Figure S1 in the Supplementary Material shows 13 thresholded cerebello-cortical functional networks. Fig. 5A and B shows the cerebello-cortical functional connectivity maps for the cerebellar networks VI and lateral VIIa, respectively ($p < 0.05$, FWE corrected). The cerebellar network of the VI was functionally connected to the middle frontal, inferior temporal, inferior parietal, and anterior cingulate cortex, whereas the cerebellar network of the lateral VIIa showed functional connectivity with the anterior prefrontal, middle frontal, inferior temporal, and inferior parietal cortex. These connectivity patterns are in agreement with the previous findings on the cerebello-cortical functional organization seen in adults (Buckner et al., 2011; Kipping et al., 2013) and in children (Kipping et al., 2017; Wang et al., 2016).

Among the 13 cerebello-cortical functional networks, the cerebellar network of VI showed greater functional connectivity with the premotor cortex in poor task performers than in good task performers (voxelwise $p < 0.005$, cluster-corrected $p < 0.05$) (Fig. 5A, C). For the lateral VIIa-cortical network, greater functional connectivity with the anterior prefrontal cortex was found in poor performers than in good performers (voxelwise $p < 0.005$, cluster-corrected $p < 0.05$) (Fig. 5B and C). No group differences in the other 11 cerebello-cortical functional

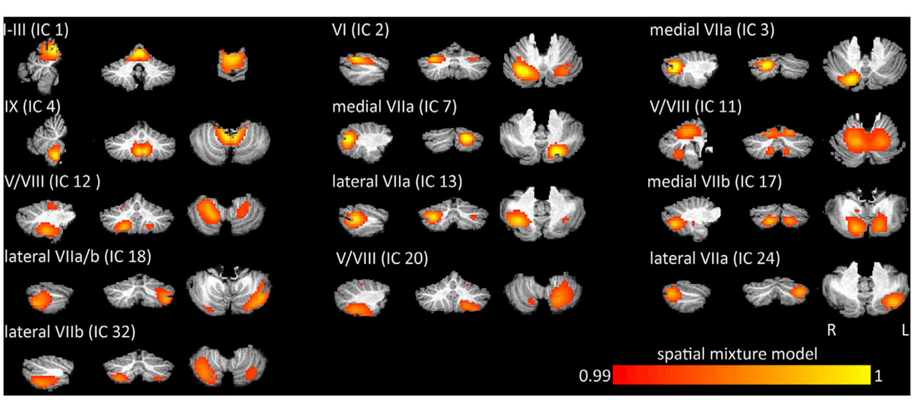

Fig. 2. Cerebellar functional networks in 6-year-old children. The networks were identified from resting-state fMRI datasets of 76 children using ICA. Color bar shows the spatial mixture model (0.99–1) used for thresholding spatial independent components. The description of the functional networks is guided by the anatomical cerebellar regions where peak values were detected.; Abbreviations: L, left; R, right; lat, lateral; med, medial.

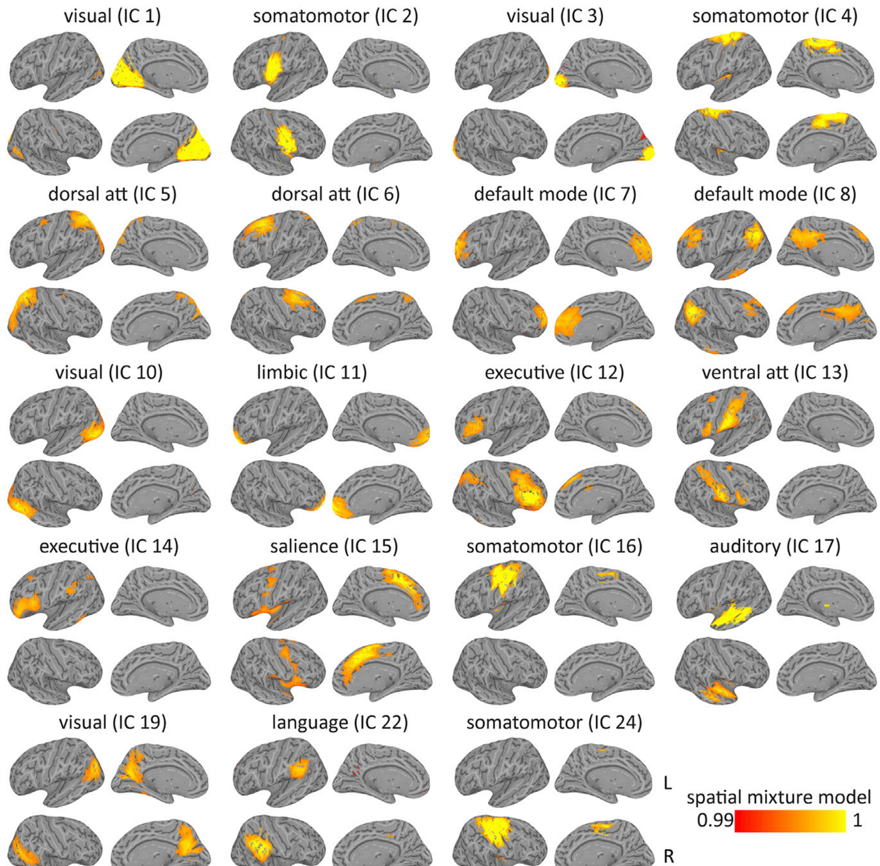

Fig. 3. Cerebral functional networks in 6-year-old children. The networks were identified from resting-state fMRI datasets of 76 children using ICA. Color bar shows the spatial mixture model (0.99–1) used for thresholding the independent components.; Abbreviations: L, left; R, right; att, attention.

connectivity maps were found. Moreover, there were no group differences in the cortico-cortical functional connectivity maps between good and poor task performers.

Discussion

Our results suggest that brain adaptation to planning acquisition in early life is associated with cerebello-cortical rather than with cortico-cortical functional networks during this specific developmental window. Using data-driven ICA and ALE meta-analysis, we identified cerebello-cortical and cortico-cortical networks, and associated them with differences in planning skills in a group of 6 year-old children. Functional connectivity of two cerebellar networks (VI and lateral VIIa) with the prefrontal and premotor cortex was found to be greater in children with poorer planning ability. In contrast, the cortico-cortical association networks, identified through a meta-analysis of brain activation patterns during the Tower of London task, were not associated with the performance of planning in children. These results highlight the involvement of the lateral cerebello-frontal networks, but not of the cortico-cortical association networks, in regulating planning ability in 6-year-old children.

Our findings suggest that the lateral cerebello-frontal networks represent crucial components in the acquisition of planning skills in 6-year-old children. Cerebellar functions have been discussed based on the concept of internal process optimization on motor or cognitive planning (Bellebaum and Daum, 2007). Findings from task-based fMRI and lesion studies suggest that a series of individual movements (Ito, 2008) and individual thoughts (Schmahmann et al., 2007) are processed by the lateral cerebellum. Functional activation of the lateral cerebellum is increased during the early stage of sequence learning (Doyon et al., 2002) and require high demands for the manipulation of information (Marvel and Desmond, 2012). Difficulties in the sequential ordering of actions and thoughts have been shown in children with neurodevelopmental problems (Bauer et al., 2009; Stoodley, 2016; Stoodley and Stein, 2013). Children suffering from early-life maltreatment-related post-traumatic stress disorder showed a reduced volume in the lateral cerebellum, as well as poor performance in planning and memory in early adolescence (Bauer et al., 2009). Likewise in adults, damage to the cerebellum, specifically the lateral regions, showed deficiency in planning skills (Grafman et al., 1992; Schmahmann, 2004). Moreover, adults showed functional activations in the prefrontal, parietal, striatal and cerebellar regions during early performance of the Tower of London (Beauchamp et al., 2003). Additionally, the cerebello-cortical system features distinct reciprocal connections of the lateral cerebellum with the prefrontal and premotor cortex, and are respectively engaged in the adjustment of contextual changes and the control of movements (Imamizu and Kawato, 2012).

The functional organization of the cerebellum with the premotor and prefrontal cortex may compensate for the immature cortico-cortical association networks in order to cope with cognitive demands in childhood (Koziol and Lutz, 2013). In healthy adults, the energy efficiency of global cerebellar connectivity is higher than that of the whole-brain average (Tomasi et al., 2013). Similar to the findings in our study, an increase in global cerebellar connectivity was suggested to function as a compensatory mechanism at higher energy costs to master cognitive demands in aging and in neurodegenerative research (Schaefer et al., 2014; Tomasi et al., 2013). The present study did not reveal any contribution of the cortico-cortical association networks, including the dorsal attention network, bilateral executive networks, and the salience network, to high- and low levels of planning performance in children. In contrast, a positive

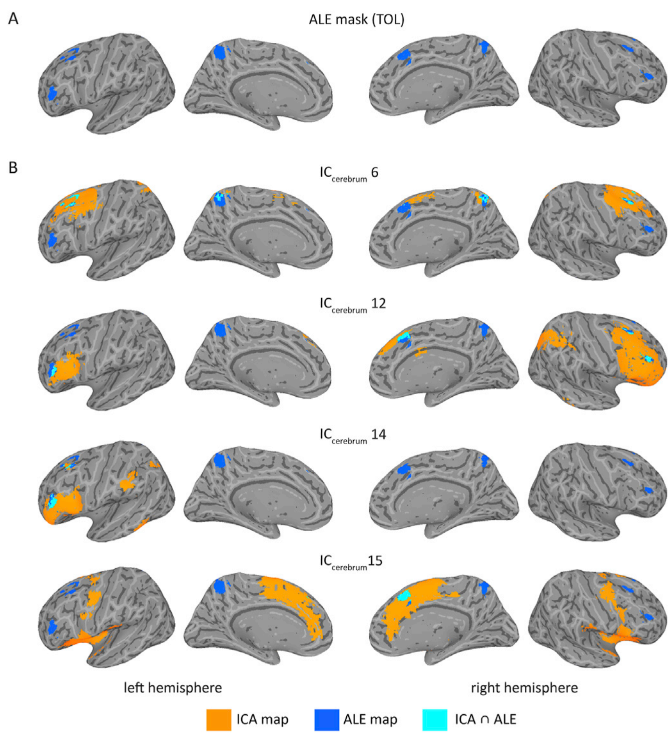

Fig. 4. Cerebral activation maps relevant to planning. Panel (A) shows cerebral activation likelihood estimation (ALE) map derived from meta-analysis on Tower of London fMRI studies. Panel (B) shows cerebral functional networks of Fig. 3 that have overlap with the ALE map shown in Panel (A). Blue color indicates the cerebral regions for the ALE map, while cyan color indicates overlapping regions between the ALE map and four cerebral functional networks.

association of planning performance in the SOC and resting-state graph measures of the prefrontal cortex was reported in an adult functional near infrared spectroscopy study (Zhao et al., 2016). The functional relevance of cortical networks in adults are supported by task fMRI (meta-analysis) and PET studies which show greater activation of the prefrontal and parietal cortex (Nitschke et al., 2017; van den Heuvel et al., 2005; Wagner et al., 2006), and additional cerebellar regions as the difficulty level of planning increased in the Tower of London task (Newman et al., 2003; Nitschke et al., 2017; Schall et al., 2003). This discrepancy between children and adults may be due to the development of cerebello-cortical and cortico-cortical functional networks. Indeed, high-level cortico-cortical functional networks are less connected (Kipping et al., 2017) and more fragmented into subnetworks (de Bie et al., 2012) during childhood as compared to adulthood. The development of distributed cerebello-cortical functional organization can be seen very early on in fetuses (van den Heuvel et al., 2018), newborns (Herzmann et al., 2018) and 6-months old infants (Kipping et al., 2017). Cerebellar-cortical functional organization reaches a peak of connectivity strength during the middle of childhood (age 6 years) as compared to children age 4 and 10 years and adults (Kipping et al., 2017). In parallel, during adolescence and young adulthood, the functional connectivity of the lateral cerebellum (Crus I and II) continues to decrease, which is correlated with increases in white matter structural integrity in the corresponding cerebello-thalamo-cortical white matter tracts (Bernard et al., 2016). Our findings of the negative association of planning with the lateral cerebello-frontal functional connectivity in children, but not on associations with the high-level cortico-cortical functional connectivity, integrate these independent findings on developmental trajectories of cognitive planning (Munakata et al., 2012) and brain functional organization (Kipping et al., 2017; Muetzel et al., 2016). Hence, these findings suggest that lateral cerebello-frontal functional networks provide an important neural basis for planning in 6-year-old children.

Findings of the contralateral functional connectivity between the cerebellum and cortex are in line with anatomical pathways and reflect lateralized processes regarding planning. Differences between good and poor performers in the functional connectivity of two right-cerebellar regions (VI and lateral VIIa) were found in the left cortical hemisphere. The primate and human brains show connection of the right cerebellum with the left cortex, and vice versa, using tract tracing and diffusion MRI techniques respectively (Ramnani et al., 2006; Salmi et al., 2010). This across-hemispherical cerebello-cortical functional organization is also supported by rs-fMRI studies (Buckner et al., 2011; Dobromyslin et al., 2012; Kipping et al., 2017; Krienen and Buckner, 2009). The right-left cerebellar asymmetry is supported by an early, and slow development of myelin content in the right cerebellum and left cerebral white matter which has been observed in infants (Deoni et al., 2011). Functionally, the right lateral cerebellum is more involved in timing (Van Mier and Petersen, 2002) and planning (Bauer et al., 2009; Schall et al., 2003) as compared to the left hemisphere. Likewise, the left prefrontal cortex is involved in control processes associated with executing a plan (Newman et al., 2003, 2009) and task complexity (Newman et al., 2003; Owen et al., 1996; Schall et al., 2003; Wagner et al., 2006).

This study included children in a restricted age range, which allowed for examining the neural mechanisms of planning without compromising age effects. However, children at 6 years of age may show a rudimentary form of executive functioning, as children could not solve the complex 5-move problems in the SOC task. **Nevertheless,** future longitudinal designs that include late childhood and adolescence are needed to better understand the developmental trajectories of the brain-cognition relationship with planning ability (Anderson et al., 2001; Luciana et al., 2009; Welsh et al., 1991). Future studies that include cerebellar-relevant executive functions, such as inhibition and attention shifting (Bellebaum

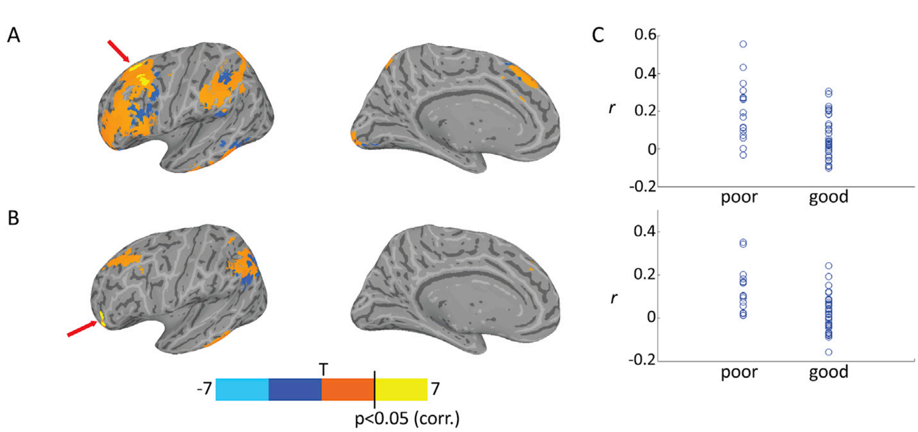

Fig. 5. Relation of cerebellar network VI and lateral VIIa-cortical functional networks in children with the performance of Stockings of Cambridge task. Panels (A, B) respectively show group differences in VI-frontal and lateral VIIa-frontal functional connectivity between poor and good task performers. Overlaid on the anatomical surface, group differences in functional connectivity of VI-frontal and VIIa-frontal functional networks are shown (orange/blue). Regions with significant group differences in functional connectivity are colored in yellow (cluster-corrected $p < 0.05$). Panel C shows scatter plots representing Fisher's z-to-r transformed values averaged in the cortical region colored in yellow in poor and good task performers (see red arrows).

et al., 2012), will also be helpful to further specify our understanding of cerebellar contribution to broad aspects of executive functions in children. Last but not least, our study employed the adult atlas where the children's brains were mapped. Even though the brain size of 6-year-old children is approximately 95% of the adult's brain size, statistical power of this study could be further improved by adopting an age-appropriate brain atlas.

Conclusion

Our study examined neural mechanisms for planning abilities in young children. Our findings support the notion that brain adaptation to planning acquisition in early life is achieved through more engagement of the lateral cerebello-cortical functional networks during this specific developmental time window and might function as a reference for future investigation of typical and atypical cognition-related cerebellar development.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.neuroimage.2018.04.067.

Disclosure of potential conflicts of interest

The authors declare that they have no conflict of interest.

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