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ORIGINAL RESEARCH

Development of spatial orientation skills: an fMRI study

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Abstract

The ability to orient and navigate in spatial surroundings is a cognitive process that undergoes a prolonged maturation with progression of skills, strategies and proficiency over much of childhood. In the present study, we used functional Magnetic Resonance Imaging (fMRI) to investigate the neurological mechanisms underlying the ability to orient in a virtual interior environment in children aged 10 to 12 years of age, a developmental stage in which children start using effective spatial orientation strategies in large-scale surroundings. We found that, in comparison to young adults, children were not as proficient at the spatial orientation task, and revealed increased neural activity in areas of the brain associated with visuospatial processing and navigation (left cuneus and mid occipital area, left inferior parietal region and precuneus, right inferior parietal cortex, right precentral gyrus, cerebellar vermis and bilateral medial cerebellar lobes). When functional connectivity analyses of resting state fMRI data were performed, using seed areas that were associated with performance, increased connectivity was seen in the adults from the right hippocampal/parahippocampal gyrus to the contralateral caudate, the insular cortex, and the posterior supramarginal gyrus; children had increased connectivity from the right paracentral lobule to the right superior frontal gyrus as compared to adults. These findings support the hypothesis that, as children are maturing in their navigation abilities, they are refining and increasing the proficiency of visuospatial skills with a complimentary increase in connectivity of longer-range distributed networks allowing for flexible use of efficient and effective spatial orientation strategies.

Keywords Children · Cognitive · Hippocampus · Memory · Navigation

Introduction

Successfully locating yourself and objects within an environment is an important adaptive behavior that begins developing from an early age. Children as young as three months old display memory for location of events (Hayne et al. 1991), and toddlers as young as 18–24 months use the geometry of an enclosure to find hidden objects (Hermer and Spelke 1994; Huttenlocher and Vasilyeva 2003). Toddlers also start to orient in an enclosure using landmarks when they are very distinctive and salient (Learmonth et al. 2008; Nardini et al. 2008). By the age of four years, children begin to use multiple sources of spatial information, including more distal landmarks (Waismeyer and Jacobs 2013), and start to ascribe increased weight to the use of large, stable landmarks for orientation (Newcombe et al. 2010). These findings suggest that the sophistication and accuracy of orientation has a prolonged maturation across childhood.

Studies investigating spatial orientation and navigation in young children take place in small-scale environments or enclosures. As children gain mobility and independence they are increasingly exposed to new and larger surroundings, which provide the opportunity to apply and practice their orientation skills in large-scale environments. In such surroundings, Siegel and White suggested that children first use landmarks to navigate, then construct routes between landmarks, and finally integrate routes in an overall framework (or spatial representation) that link smaller portions of the environment into a cohesive internal model for navigation (Siegel and White 1975).

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With further development and experience, children develop the cognitive flexibility to choose the most appropriate or efficient strategy, as well as improved ability to access landmark-based strategies for orientation.

The space surrounding an individual can be internally represented relative to an individual's body position (egocentric coding) or relative to landmarks independent of their current position (allocentric coding) (Dudchenko 2010). Both egocentric and allocentric frames of reference can be used during orientation and navigation in a large-scale environment. Evidence suggests that the capacity for using allocentric reference frames (in room sized enclosures) may be present in children as young as two years old, but increases in proficiency as the child develops (Ribordy et al. 2013; van den Brink and Janzen 2013) with a preference for allocentric navigation developing over early school age (Bullens et al. 2010). In many instances an allocentric strategy is advantageous because it allows for accurate and flexible routing from multiple points; however, there are instances when other strategies may be more efficient. Bohbot and colleagues (Bohbot et al. 2012) studied navigation across a range of ages using a virtual arm-radial maze. In this task a stimulus response strategy, which involved learning a set of specific movements from a given starting point or landmark location, resulted in improved performance in all ages and was favored after increased repetition. It was found that 83.3% of children (ages 8 to 18 years) used an allocentric strategy, whereas 46.6% of young adults (ages 19 to 40 years) and 39.3% of older adults (> 40 years old) spontaneously favored a stimulus response strategy. Together, these findings suggest that mature and efficient spatial orientation involves flexible use of different strategies in response to the particular task.

Previous neuroimaging studies in adults have demonstrated that allocentric spatial memories and navigation heavily involve the hippocampus and the parahippocampal gyrus (Bohbot et al. 2007; Burgess et al. 2002; Iaria et al. 2003; van Asselen et al. 2006). Whereas, the caudate nucleus, in conjunction with posterior parietal and frontal lobes, has previously been implicated in navigation that employs a response, or egocentric navigation strategy (Iaria et al. 2003). Differences in the blood-oxygen-level dependent (BOLD) signal on functional magnetic resonance imaging (fMRI) from these different cortical areas may indicate a dependence on different spatial strategies for completion of a navigation task across development.

The cognitive evolution observed in the development of spatial orientation skills is potentially mediated through the maturation of extended neural networks that connect cortical areas known to be involved in effective spatial navigation and orientation in adults (Ekstrom et al. 2014), in addition to increased proficiency of the cortical processing in those areas (Schedlbauer et al. 2014). This is congruent with a frequently observed trend in cognitive neuroimaging studies that indicate local, regional cortical interactions in children evolve into longer-distance (also referred to as global or random) interactions in young adults as the brain matures (Dosenbach et al. 2010; Vogel et al. 2010).

Only a handful of previous studies have specifically investigated neural-anatomical correlates of navigation in a developing population. Previous investigations have found that many of the same cortical areas are implicated in navigation for children as for adults (such as the medial temporal, retrosplenial, superior parietal, dorsolateral prefrontal, premotor, and thalamic areas (Saluja et al. 2015). However, when compared to adults, developmental differences in neural activity have been reported. Pine and colleagues demonstrated that adolescents (age 12 to 16 years old) could navigate as proficiently as adults in a virtual environment but did not have the ability to recreate the map environment afterwards, indicating they were not as proficient as adults in allocentric spatial strategies. During navigation, adolescents demonstrated increased BOLD signal change in the left temporoparietal cortex (supramarginal gyrus), right posterior parietal cortex (angular gyrus), left medial frontal cortex, areas of the left cerebellum, brain stem, and bilateral thalami, compared to adults (Pine et al. 2002). van Ekert and colleagues completed a fMRI study of children age 8–18 in an investigation of fMRI correlates during a landmark recognition task. They found age-related increases in BOLD signal change in the parahippocampal region and the anterior cingulate cortex for landmarks that were associated with a spatial context (but not for ambiguous landmarks) (van Ekert et al. 2015).

Here, we hypothesize that children will use similar cortical areas for spatial navigation as adults but may have increased neural activity in some areas reflecting increased effort compared to adults. Improved adult performance will depend on an increase of functional connectivity between navigation areas in adults. We tested this hypothesis by investigating the neural correlate of spatial orientation and navigation in early adolescents using a virtual navigation task that can be completed in an MRI scanner. We recruited 10 to 12 year-olds participants because this is an age at which children can make reliable use of spatial orientation skills but not with the proficiency of adults (Bullens et al. 2010; Pine et al. 2002), and are able to comply with task instructions within a MRI scanner. Children performed a virtual navigation task while undergoing fMRI, and their navigation abilities and neural correlates were compared with a group of young adults.

Methods and materials

Participants

The study included 15 healthy children (9 females, age range = 10 years and 2 months to 12 years, mean age = 11.25 years, $SD = 0.627$ years) and 18 young adults (9 females, age range = 19 to 34 years, mean age = 24.7 years, *SD* = 4.2 years). All participants were right-handed with no history of neurologic disease, chronic medical illness, or injury. Participants were required to have sufficient English literacy to understand written instructions in the game and normal, or corrected to normal, vision. Braces or other implanted metal devices were exclusion criteria for imaging. Children were recruited from the Healthy Infants and Children's Clinical Research Program (HICCUP) database at the Alberta Children's Hospital and by word of mouth. Young adult participants were recruited through the University of Calgary Department of Psychology Online Research Participation System. The study was approved by the research ethics board of the University of Calgary. Written, informed consent was obtained from the adult participants; assent was obtained from children, with written consent provided by their guardians.

Virtual environments

The virtual environments used to perform the experimental tasks were created using the 2007 Source Engine software development kit and Hammer map editor version 4.1 (Valve Software). We created two virtual environments, one for the experimental task and the other for the practice and control tasks. The experimental environment contained four doorless rooms connected via a hallway network such that no room was visible from any other room. Rooms had unique names and contents, thus serving as landmarks for the task. The rooms in the experimental environment consisted of the Lockers, Computer Lab, Office, and Cafeteria (Fig. 1). The practice and control tasks had floor, wall, and ceiling textures that were perceptually distinct from those used in the experimental environment. The control environment consisted of one single path without landmarks or navigational choices.

In all virtual environments, the participants navigated from the first-person perspective (Fig. 1). Their unseen avatar within the game had a maximum speed of 150 map units per second (corresponding to 2.86 m/s) within 500 ms of initiating movement, and a turning rate of 60° per second. The viewpoint of the avatar was situated 64 map units from the ground (corresponding to a height of 1.2 m), with a horizontal field of view of 75°. The task was executed on a personal computer with the Windows 8 operating system, recording the position of the participants' avatar within the game as x and y coordinates, as well as heading direction and velocity, every 250 ms. This information was used for scoring participants' performance and running behavioral data analyses.

Experimental procedure

Prior to entering the MRI scanner, all participants were given a detailed description of the study and instructions for how to make appropriate motor responses using a Lumina 4-button response pad (Cedrus Corporation) to control their forward, left and right movement within the virtual environment. Within the MRI scanner, a projector was used to display the navigation task on a screen positioned at the far end of the bore, which was viewed via a mirror positioned in front of the participant's head while supine. As a standard procedure, we used foam padding to stabilize the participant's head inside the head coil to minimize head movement.

While in the scanner, participants first completed a practice task to become familiar with the motor controls (Fig. 1a). In this task participants were required to perform a series of trials in which they were asked to navigate through a single winding hallway. They were asked to get to the end of the designated pathway as quickly and as smoothly as possible, turning corners and steering through the hallway without stopping or bumping into walls. The participant's objective was to follow the path to the end, at which point they walked into an elevator terminating the task. Participants performed as many trials as needed until they could follow the hallway without stopping.

When the practice task was completed, participants were instructed to perform the learning task in the experimental environment. During the learning task, participants maneuvered themselves through a tour of the experimental environment; visiting all four rooms by following a predetermined path marked by arrows (Fig. 1b). They were explicitly asked to follow the predetermined path and pay attention to the pathways to learn the locations of the four different rooms. Room names were presented upon entry of each location, and invisible barriers prevented participants from deviating from the pathway. Participants completed the path only once during the learning task, and were not allowed to explore any hallways that were not part of the pathway. All participants therefore received identical exposure to the experimental environment. The amount of time that the participants required to complete the practice and learning tasks was not recorded.

After touring the experimental environment, participants performed the retrieval task, which consisted of 12 unique trials, and neuroimaging data were acquired while the task was performed. Elements of the task was separated from the next by a white overlay with a central black fixation cross presented for 10 s. Each trial of the retrieval task started in one room and, after a fixation period, participants were presented with written instructions indicating the target room to be reached. Participants were instructed to proceed to the target room as quickly as possible. After reaching the target room participants were notified they had completed the task, a fixation cross was presented again followed by instructions on the next target room to be reached, and the next trial began. At the end of each block of three trials, participants were required to perform a control task; the participant's objective in the control task was to follow a defined single path to the end, at which point they walked into an elevator terminating the task. Participants were automatically transported between

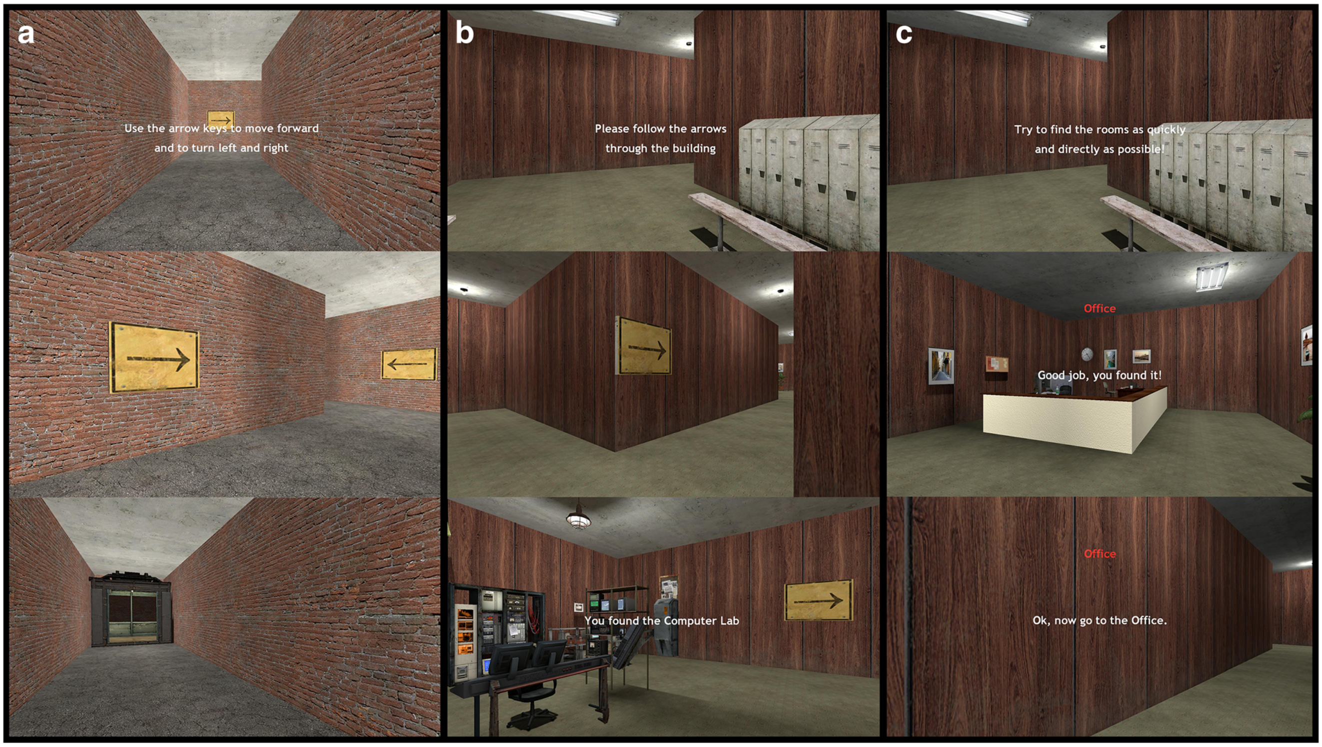

Fig. 1 **Behavioral Task. a** Task for practice using task controls. Control tasks took place in similar hallways with the same texture but without directing arrows. **b** Learning phase; tour of rooms in spatial orientation task. C. Retrieval trial of spatial orientation task

virtual environments for the retrieval and the control tasks. Lengths of retrieval trials were variable due to the self-paced nature of the task and individuals' skills. Cut-off times equal to the mean time plus one standard deviation for each trial were derived from separate pilot samples of adults and children; if a participant exceeded the cut-off time for a given trial they would be automatically transported to their destination. The average total amount of time that children spent completing the retrieval tasks was 621 s (SD = 189 s) and the total amount of time children spent completing the control tasks was 203 s (SD = 34.5 s). The total time for scanning (including both control tasks, retrieval tasks and time with fixation cross was an average of 1116s for children (SD = 91.9 s) and adults mean = 835 s (SD = 137 s).

To score performance, the shortest possible time on each trial was subtracted from the participant's time for that trial. This was averaged over all trials for each participant and referred to as the average delay time. Performance was compared between the adult and child groups using ANOVA and used as a covariate for between-group comparisons during task fMRI analyses.

Image acquisition and data analyses

Scanning was performed at the Alberta Children's Hospital on a 3 T GE Discovery MR750w MRI scanner (GE Healthcare, Waukesha, WI) with a 32-channel head coil. All participants underwent a high-resolution T1 weighted anatomical scan (3D acquisition type, ultrafast gradient echo with magnetization preparation (IR-FSPGR), field of view = 25.6 cm, voxel size 1 mm isotropic, flip angle = 11°; T1 = 600 ms) followed by a T2-weighted sequence (2D acquisition type axial orientation, 38 slices, field of view = 23.0 cm; slice thickness = 3.6 mm, repetition time (TR) = 3800 ms, echo time (TE) = 80 ms, flip angle = 111°). Functional scans were T2*-weighted, gradient echo, echo-planar images (GRE-EPI). Participants also underwent a resting state functional MRI scan (rs-fMRI) consisting of 240 whole brain volumes with 38 axial slices acquired in a sequential bottom-up pattern (TR = 2000 ms, TE = 30 ms, flip angle = 77°, field of view = 23.0 cm; slice thickness 3.6 mm). For the rs-fMRI acquisition, children were instructed to lie still, think about nothing in particular, and focus on a fixation cross projected on the screen.

Functional MR images were acquired during the retrieval tasks capturing whole brain volumes with 38 slices over 23.0 cm field of view. Images were acquired in a bottom-up interleave pattern (TR = 2000 ms, TE = 30 ms, flip angle = 77°, slice thickness 3.6 mm). The first five volumes of the functional run were discarded to allow for T1 equilibration. Functional MRI data were preprocessed and analyzed using SPM12 (Welcome Trust Centre for Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm/). The images were slice time corrected to reference slice 20. Volumes were smoothed using 5 mm full width at half maximum (FWHM) kernel, realigned to the mean of the fMRI volumes using a linear interpolation, and then coregistered to the individual's 3D SPGR anatomical scan. Images were segmented into grey matter, white matter and CSF spaces using tissue probability maps for ages 7.5yo to 13yo available from the NIH pediatric MRI database for the children. Standard tissue probability maps available in SPM were used for the adults. The fMRI volumes were then normalized to Montreal Neurological Institute (MNI) space using the individual deformation fields produced from segmentation and resampled to 2 mm isotropic volume. Images were smoothed with a 6 mm FWHM Gaussian kernel and high-pass filtered with a 128 s cutoff. The ART toolbox was used for both the kids and adults' fMRI volumes to check for outlier scans based on global intensity and movements >2 mm; 11 of 15 children and 1 of the 18 adults had outlier scans. Regressors comprised of the 6 motion correction parameters calculated during realignment and the outlier scans were used in the general linear model (GLM) in the first level analysis as nuisance regressors.

The data were modeled by decomposing the retrieval task into three distinct components, in addition to the control task, to better isolate the cognitive processes associated with the trial and how they may differ between the age groups. The components were identified as the time in which (i) the participant was at or approaching a decision point, (ii) the participant was in a hallway, and (iii) the participant was in a target room. Separate regressors were constructed for each component and for the control task, and convolved with a single gamma canonical hemodynamic response function (HRF). The instruction and fixation periods between trials were not modelled and were therefore part of the implicit baseline. Participant-specific parameter estimates were calculated for each regressor corresponding to an element of the task (decision points, hallways, rooms) contrasting with the control task.

Random-effects analyses were conducted by entering contrasts for all individuals (separately for the child and adult groups) into one-sample *t*-tests at the group level. Two sample t-tests of the first level contrasts were also done comparing the children and adult groups. During comparison between groups, the average delay for each participant was entered as a covariate to determine if differences in Blood Oxygenated Level Dependent (BOLD) signal were mediated by performance. The resulting images were thresholded using a voxel height threshold of $p < 0.001$ and a family-wise error (FWE) corrected cluster threshold of $p\text{FWE} < 0.05$.

Resting state functional data were processed in the CONN toolbox (v14.p; http://www.nitrc.org/projects/conn), modeling head motion, slice time correcting, outlier scan detection and scrubbing, segmenting and normalizing to MNI space and smoothed using a 6 mm FWHM kernel. Data from white matter and CSF were regressed out and the scans were temporally bandpass filtered between 0.008 Hz and 0.09 Hz. Seeds for resting state functional data analysis were generated from the task fMRI analysis by exporting the significant clusters from the decision vs control tasks, children vs adult covaried for average delay (i.e. brain regions where BOLD signal was more associated with performance for children than adults). Differential functional connectivity of brain regions was compared between adults and children by calculating the difference in seed-to-region of interest (ROI) temporal correlation coefficients for all ROIs included in the CONN default atlas. Only changes in resting state functional connectivity that were significant at two-sided $p\text{-}_{\text{FDR}} < 0.05$ for all analyses were reported.

Results

Behavioral data

The analysis revealed a statistically significant difference in the average delay time between children ($M = 32.24$, $SD = 10.06$) and adults ($M = 21.14$, $SD = 10.82$; $F(1,31) = 9.174$, $p = 0.005$; Fig. 2a) in performing the retrieval task; these findings confirmed that children took longer than young adults in performing the retrieval task. The young adults did not reach the target before cut off times between 0 and 7 times with an average success rate for reaching the target of 83.8%. The children failed to the reach the target between 1 and 8 of the 12 trials with an average success rate of 72.6%. Importantly, however, no differences were found in the average time taken by children and adults to complete the control tasks (children $M = 53.3$, $SD = 3.27$; adults $M = 54.30$, $SD = 5.49$; $F(1,31) = 0.379$, $p = 0.542$; Fig. 2b) indicating that the difference in performance was not due to manual dexterity or ability to manipulate task controls.

In the children's group, the females (average delay $M = 27.5$ s; $SD = 9.18$ s) performed significantly better than the males (average delay $M = 39.39$ s; $SD = 6.82$ s; $F(1,13) = 7.329$, $p = 0.018$). In the adult group the opposite was true: average delay for adult females was 28.5 s ($SD = 8.33$ s) and for males was 13.8 s ($SD = 7.62$ s; $F(1, 16) = 15.2$, $p = 0.001$).

Task-based fMRI

In the children's group, several areas in the brain were identified in which the BOLD signal was significantly increased during the three components of the retrieval task over and above that of the control task. See Table 1 for a list of all significant clusters across reported fMRI analyses. When comparing decision points to the control task in the children group only, we found a significant increased BOLD signal change in the left inferior occipital and fusiform gyri (735 voxels, peak $Z = 4.58$, $x = -32$, $y = -76$, $z = -2$), the left precuneus extending into the right superior parietal region

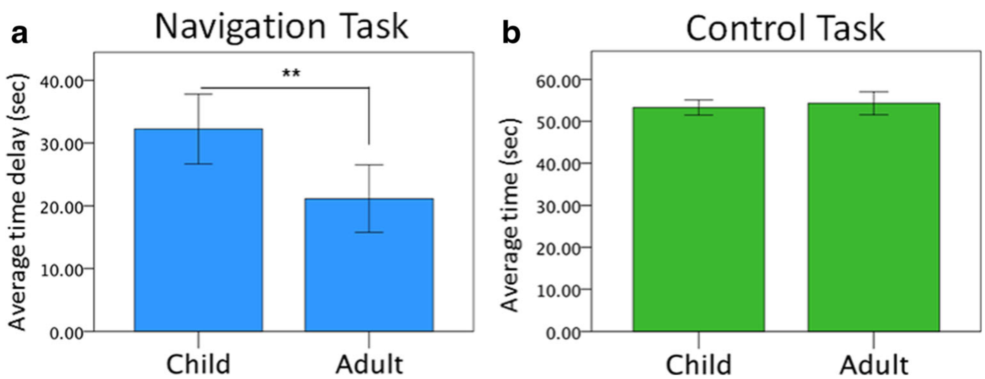

Fig. 2 **Behavioral performance. a** Comparison of average time delay in reaching the target room revealed that the children's group took significantly longer than the adult group (** indicates $p < 0.001$). **b** There was no significant difference in the length of time that children took to complete the control tasks as compared to the adults, indicating that increased time to the target rooms during retrieval was not due to difficulty with manual control

and calcarine sulcus (1243 voxels, peak Z = 4.49, x = 8, y = −60, z = 50), and the bilateral medial superior frontal lobe (205 voxels, peak Z = 4.17, x = 8, y = 14, z = 46). In the contrast comparing rooms to control task in the children group, two significant clusters were found: a large one over the left inferior temporal, inferior occipital and fusiform and lingual gyri (1034 voxels, peak Z = 4.49, x = −30, y = −54, z = −14), and a contralateral cluster in the right precuneus and cuneus (165 voxels, peak Z = 4.40, x = 8, y = −66, z = 20). The comparison of hallways to control in the children group revealed significant clusters in the left precuneus extending to the right superior parietal and mid-occipital lobe (similar in location to

Table 1 Significant clusters of metabolic activation during orientation task in Children and as compared to Adult group. Peak Z-statistics and Montreal Neurological Institute coordinates (mm) are provided for the peak voxel in each cluster. Labels are based on cluster area covering AAL atlas area

Anatomic region	Size	Cluster $p_{\text{-FWE}}$	Peak Z	MNI x,y,z (mm)
Child: Decisions > control				
Left inferior occipital and fusiform gyrus	735	<0.001	4.58	−32, −76, −2
Left precuneus, right superior parietal and calcarine gyrus	1243	<0.001	4.49	8, −60, 50
Right and Left medial superior frontal lobe	205	0.013	4.17	8, 14, 46
Child: Rooms > control				
Left inferior temporal, inferior occipital, fusiform and lingual gyri	1034	<0.001	4.49	−30, −54, −14
Right precuneus and cuneus gyri	165	0.037	4.40	8, −66, 20
Child: Hallways > control				
Left precuneus, right superior parietal and mid-occipital lobe	1129	<0.001	4.78	34, −74, 32
Left angular gyrus	182	0.021	4.32	−30, −54, 44
Right medial superior frontal lobe and mid-cingulum	189	0.018	4.31	8, 18, 44
Left precuneus and calcarine gyri	368	<0.001	3.93	−30, −72, 28
Child > Adult:				
Decisions > control				
Left cuneus and mid occipital	177	0.036	5.06	−20, −82, 14
Right inferior parietal	353	0.001	4.97	16, −64, 58
Right precentral gyrus	256	0.008	4.64	26, −14, 54
Cerebellar vermis and bilateral medial lobes	487	<0.001	4.44	12, −76, −20
Left inferior parietal and precuneus	346	0.002	3.96	−22, −62, 54
Child > Adult (covaried for delay):				
Decisions > control				
Right hippocampus and parahippocampal gyrus	308	0.003	5.04	32, −42, 0
Left posterior medial temporal	282	0.005	4.78	−32, −54, 6
Right paracentral lobule	191	0.028	4.45	14, −34, 54

a cluster found in the decisions >control task) (1129 voxels, peak Z = 4.78, x = 34, y = −74, z = 32), in the left precuneus and calcarine sulcus (368 voxels, peak Z = 3.93, x = −30, y = −72, z = 28), the right angular gyrus (182 voxels, peak Z = 4.32, x = −30, y = −54, z = 44), and the right medial superior frontal lobe and mid cingulum (189 voxels, peak Z = 4.31, x = 8, y = 18, z = 44).

When comparing the task-dependent signal (i.e. decision, room, or hallway vs control) between children and adults, a number of areas indicated increased BOLD signal change in the children over the adults during the decisions. These areas included a cluster in the left cuneus and mid occipital area (171 voxels, peak Z = 5.06, x = −20, y = −82, z = 14), a cluster in the left inferior parietal region and precuneus (346 voxels, peak Z = 3.96, x = −22, y = −62, z = 54), a cluster in the right inferior parietal cortex (353 voxels, peak Z = 4.97, x = 16, y = −64, z = 58), another in the right precentral gyrus (256 voxels, peak Z = 4.64, x = 26, y = −14, z = 54), and one in the cerebellar vermis and bilateral medial cerebellar lobes (487 voxels, peak Z = 4.44, x = 12, y = −76, z = −20) (Fig. 3). No significant differences were found between the children and adults when comparing the BOLD signal change in rooms vs control and in hallways vs control. This would imply that, if there was a difference in BOLD signal that would be associated with the difference in task performance between children and adults, it was most likely occurring in the time near decisions points. Therefore, the decision vs control contrast was covaried with the average delay time for each individual, and compared between the children and adult groups. This yielded three significant clusters: one in the right hippocampus and parahippocampal gyrus (308 voxels, peak Z = 5.04, x = 32, y = −42, z = 0), one in the right paracentral lobule (191 voxels, peak Z = 4.45, x = 14, y = −34, z = 54), and one in the left posterior cingulum (282 voxels, peak Z = 4.78, x = −32, y = −54, z = 6) (Fig. 4). These clusters were then used as the seed regions for analyses of functional connectivity in the resting state fMRI data. Because of the difference in performance between boys and girls in the children's group, a contrast was also performed between BOLD signal in boys and girls at decision points. No peaks survived FWE cluster correction

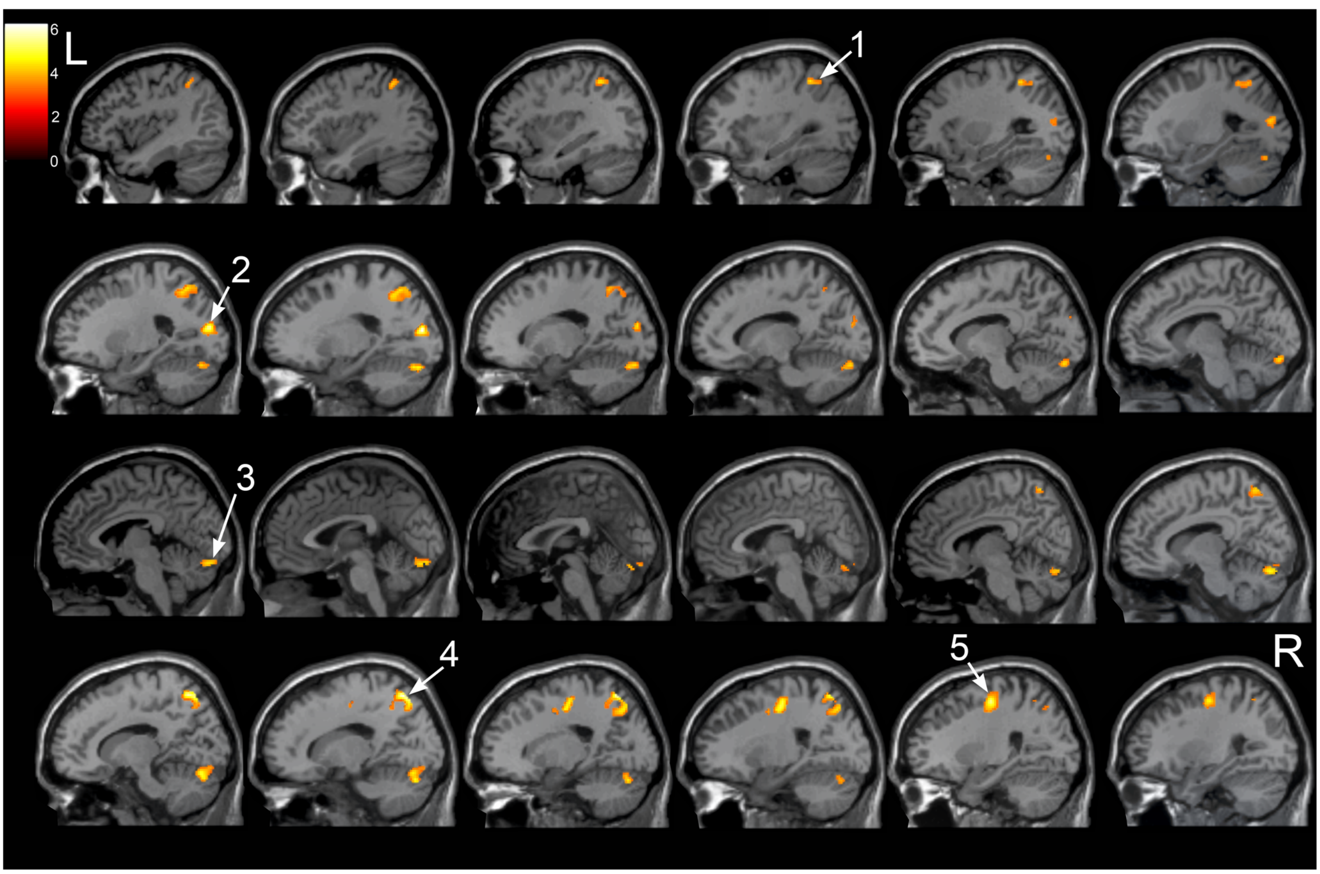

Fig. 3 Differences in task based neural activity at decision points between children and adults. The fMRI BOLD signal during decision points was first contrasted with the control task for both children and adults to give the activation that was associated with navigation during the behavioral task. This was then contrasted for children > adults yielding 5 clusters that showed increased activation in children compared to adults. 1. Left inferior parietal and precuneus, 2. Left mid occipital and cuneus, 3. Cerebellar vermis and medial lobes, 4. Right inferior parietal, 5. Right precentral gyrus

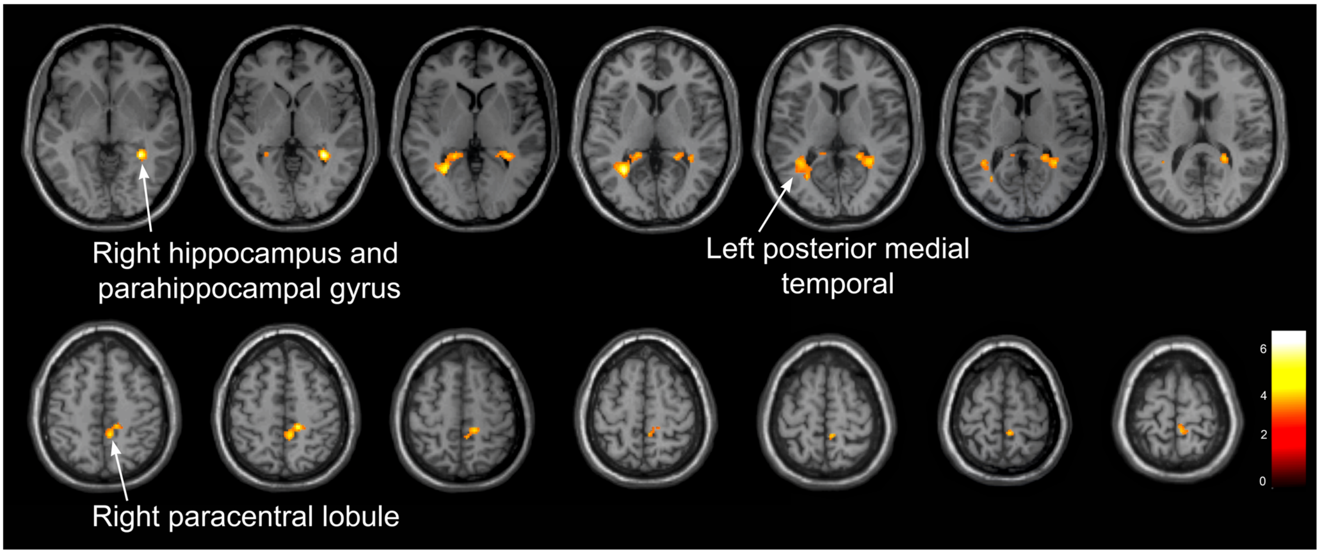

Fig. 4 Areas that had differences in task-based neural activity with navigation performance in children compared to adults. These areas were used as ROI for resting state connectivity analysis (see Fig. 5)

in either the females vs males, or the males vs females contrasts. However, this may be due to the lack of power due to the low number of participants (females = 9, males = 6).

Functional connectivity in resting state fMRI

The comparison between adults and children's resting state functional connectivity for the task-derived ROIs to all areas in the CONN atlas revealed no areas that significantly differed in connectivity between groups for the left posterior cingulum ROI. For the right hippocampus and parahippocampal gyrus ROI we found a significant increased connectivity for adults over children in the left insular cortex ($T_{31} = 4.35$, $p\text{-}_{FDR} = 0.0149$), the left posterior supramarginal gyrus (pSMG) ($T_{31} = 4.06$, $p\text{-}_{FDR} = 0.0149$), and the left caudate nucleus ($T_{31} = 4.05$, $p\text{-}_{FDR} = 0.0149$) (Fig. 5a). The analysis on the right paracentral lobule ROI revealed a significant increased connectivity with the right superior frontal gyrus for children over adults ($T_{31} = 4.34$, $p\text{-}_{FDR} = 0.0195$) (Fig. 5b).

Discussion

In this study, we investigated the behavioral and neurological mechanisms underlying the development of spatial orientation and navigation skills in children. We found that children aged 10 to 12 years-old are not as proficient as young adults on a virtual navigation task, with a longer delay time to complete the task. This demonstrates that, while children in early adolescence have developed many of the cognitive skills required for successful spatial orientation and navigation (Bullens et al. 2010; Negen and Nardini 2015), they are not yet as successful in implementation compared to young adults (an age that is most proficient in navigation abilities) (Liu et al. 2011). In addition, girls in the children's group, who reach adolescence earlier than boys and would be closer to maturity at this age, had delay times similar to adult females, confirming that this is indeed an age of active maturation of navigation skills. This is in agreement with Nazareth and colleagues who demonstrated that, when children across a range of ages were asked to orient within a virtual environment, performance reached adult levels at approximately 12 years of age (Nazareth et al. 2018).

Analysis of fMRI BOLD signal collected during active navigation implicated several cortical areas in children that have been associated with visuospatial tasks or navigation in adults in previous studies. In hallways and at decision points, there were areas of increased BOLD signal change (above what was seen in the control task) observed in the left precuneus and the right superior parietal cortex extending into the occipital lobe, and was seen more limited to the right precuneus and cuneus in the rooms condition. This is an area of the dorsal (or "where') visual processing stream (Goodale and Milner 1992) that has been implicated in visuospatial imagery and memory in 3D space (Seydell-Greenwald et al. 2017; Stock et al. 2009). The precuneus has also been demonstrated to be a "hub" of high functional connectivity, along with the hippocampus, prefrontal cortex, and visual cortex, during successful spatial memory retrieval (Schedlbauer et al. 2014). At both rooms and decision points there were also clusters of increased BOLD signal change in the inferior occipital and temporal lobes, areas of the ventral (or "what") visual processing stream that is connected to visual memory for recognition of objects (Goodale and Milner 1992). The fusiform gyrus in particular has been linked to landmark recognition (Takahashi and Kawamura 2002). It is not unexpected that broad involvement of the visual processing pathways

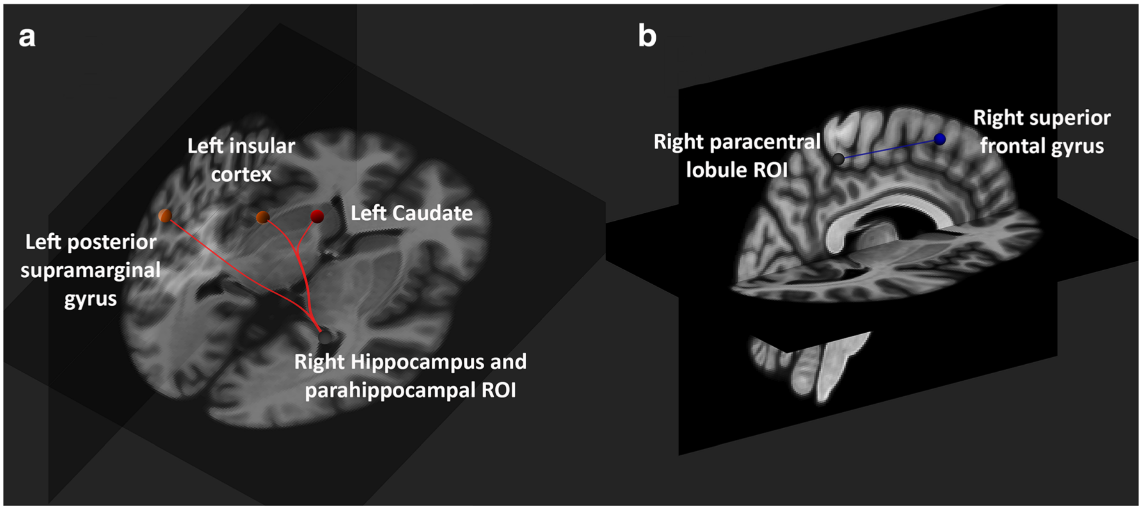

Fig. 5 **Resting state connectivity**. Temporal functional connectivity was compared between children and adults from ROI defined by the task based fMRI to all areas in the CONN atlas in the children and adult rs-fMRI. **a** From the right hippocampal/parahippocampal gyrus ROI there was increased functional connectivity to the left caudate, the left insular cortex, and the left posterior supramarginal gyrus (pSMG) in the adult group. **b** From the right paracentral lobule ROI, there was increased functional connectivity to the right superior frontal gyrus in the children as compared to the adults

would be involved during most portions of the navigation task as all periods of movement would require processing and updating of visual-spatial information. In contrast, the medial superior frontal lobe, that has been associated with decision making and error response (Zhang et al. 2012) demonstrated involvement only at decision points and in the hallways, which were periods during the task that the participant would be actively attending to their position and making decisions in navigation. In addition, the left angular gyrus was implicated only during the hallway portions of the task. The left angular gyrus is associated with directing attention toward salient environmental features and may control shifts in visuospatial attention (Chen et al. 2012), in addition to distinguishing left from right (Hirnstein et al. 2011).

We found increased neural activity in children compared to young adults at decision points during the navigation task, but not during portions of the task in the hallways or rooms. Significant clusters included many areas already implicated in navigation in children (within the left and right parietal lobes and left occipital), which may represent increased effort in the children group during visuospatial processing. In addition, a cluster of increased signal was found at the cerebellar vermis and bilateral medial cerebellar lobes of children. The cerebellum is associated with both motor and memory aspects of spatial navigation with evidence that it is involved in goal-directed navigation through construction of hippocampal-dependent cognitive maps (Rochefort et al. 2013).

Compared to Pine et al. 2002, we found a similar general pattern of increased neural activity in the children compared to the adults across broad areas of the brain and including the cerebellum; however, the specific cortical areas of increased signal were not the same. The explanation for this may be that our study involved children at an earlier age that was not yet as proficient at the task. We also attempted to isolate the cognitive processes at different stages of the task by subdividing navigation into decision points, hallways and in rooms and demonstrated that the difference in neural activity is seen at the decision points during navigation.

To further investigate the functional connectivity of areas associated with individual differences in performance, the average time delay was used as a covariate in the decision contrast and compared between groups to produce seed areas for functional connectivity analysis. The right hippocampus and parahippocampal gyrus, the right paracentral lobule, and left posterior medial temporal cortex were found to have a significantly higher association with performance in children compared to adults. The hippocampus and parahippocampal gyrus are well-known to be implicated in the formation of spatial memory and use of allocentric spatial strategies (Bohbot et al. 2007; Burgess et al. 2002; Iaria et al. 2003; van Asselen et al. 2006). Using resting state functional connectivity, stronger temporal correlations between the right hippocampal region and contralateral caudate, insular cortex and pSMG where seen in adults compared to children. This is consistent with recent analysis of rs-fMRI connectivity in which most of the major components of hippocampal networks seen in adults were also present in children (age 4–10 years), but with a strength of connectivity with regions of lateral temporal lobes and the anterior cingulate increased throughout the studied age range (Blankenship et al. 2017). Our data is also reflected in van Ekert and colleagues study in children which found that there was an age-related increase in BOLD signal change in the parahippocampal region and the anterior cingulate cortex during a landmark recognition (van Ekert et al. 2015). We found that the parahippocampal region was important for improved performance on the navigation task and was functionally more connected in adults than children.

We subsequently demonstrated in the adult group that the right hippocampal region had increased connectivity to contralateral cortical areas (left caudate, the left insular cortex, and the left pSMG) in rs-fMRI compared to the children. These areas have previously been shown to have relevance in spatial navigation. The caudate nucleus, in conjunction with posterior parietal and frontal lobes, has been implicated in navigation that employs an egocentric navigation strategy (Iaria et al. 2003). The insular region has been associated with a number of different cognitive functions, including high-level cognitive control and spatial attentional processes and is part of the salience network that regulates attention for the most relevant stimuli in goal-oriented behavior (Menon and Uddin 2010). The supramarginal gyrus is associated with sensory processing including somatosensory and visuospatial integration, mental imagery (Ptak et al. 2017) and is part of the frontoparietal attentional control network (Ptak 2012). Specifically, increased BOLD signal change has been seen in the left SMG while moving a virtual avatar (Floegel and Kell 2017).

From the right paracentral lobule, we found increased functional connectivity with the right superior frontal gyrus in the children as compared to the adults. This correlation to the frontal lobe may relate to motor and attention skills that children depend on more heavily while performing tasks than adults, due to their lack of proficiency in specific cognitive processes. However, further research investigating compensatory strategies in children is required.

Our findings (of increased contralateral connectivity in adults, and increased ipsilateral connectivity in children) are in agreement with previous functional neuroimaging studies that reflect a general developmental trend away from local geographic connections with strengthening of global interactions as networks mature (Dosenbach et al. 2010; Vogel et al. 2010). Altogether, these data are supportive of a pattern in adults of decreased neural activity in areas of visuospatial processing and an increase in functional connectivity in areas that are associated with both allocentric and egocentric spatial navigation. This supports the hypothesis that an increase in navigation abilities is due to maturation of networks that allow for flexible use of different spatial strategies.

A number of other areas of spatial development are not addressed by the current study. By scanning a narrow age range we captured a time of developing navigation sophistication but this study does not address the evolution or progression of different navigation skills over time. By investigating at earlier ages and potentially following children over time, a great deal could be learned about how cognitive processes and the neural correlates develop over time. Furthermore, this task could be performed either with cognitive map strategy or a response strategy. Imaging using tasks that varied, with different portions that would favor cognitive maps vs response strategies may be helpful in assessing the relative maturity of the different strategies as well as the ability to switch between strategies. This analysis presupposes a difference in cognitive processes during retrieval but factors during learning or encoding, including attention and visuospatial processing, could also play a role in the differences seen between adults and children navigation skills.

Conclusion

The findings reported in this study support the hypothesis that spatial orientation and navigation undergoes a prolonged maturation with emergence, refinement and then mastery of a different cognitive skills and strategies throughout childhood. Decreased navigation proficiency within a virtual environment in children was reflected in different neural activity as observed with fMRI at the decision points during navigation. The increased areas of activity largely related to areas of visuospatial integration and utilization of visuospatial information (Ptak 2012), possibly indicating increased effort to process incoming spatial information. In the adult participants there was a significant increase in functional connectivity from the right hippocampus and parahippocampal region, a well-established locus of spatial mapping and memory (Aguirre et al. 1996; Muller et al. 1996; O'Keefe and Nadel 1978), to other brain areas associated with egocentric navigation strategies and areas that control attention. This is congruent with previous work that has shown a preference for refinement of long-range functional networks over shorter, less efficiency networks as the brain matures (Fair et al. 2009).

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Compliance with ethical standards All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, and the applicable revisions at the time of the investigation.

Disclosures Kara Murias, Edward Slone, Sana Tariq, and Giuseppe Iaria declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all patients for being included in the study.

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