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Visuospatial working memory and cortical structural development in early childhood

Syventävien opintojen kirjallinen työ

Syyslukukausi 2024

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Psykiatrian laitos

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Lääketieteellinen tiedekunta

LILJA, ANNA: Visuospatial working memory and cortical structural development in early childhood

Syventävien opintojen kirjallinen työ, 19 s.

Psykiatria

Joulukuu 2024

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We explored associations between VSWM (using Spin the pots task) in 2.5-year-olds as well as 5-year-olds and cortical metrics from T1-weighted magnetic resonance images (MRIs) of 157 typically developing 5-year-olds (mean age 5.41, SD 0.13; 83 males). MRIs were processed using FreeSurfer.

We found that in 5-year-olds cortical volume and surface area were positively correlated in the right middle temporal region with Spin the pots scores. There were no associations between 2.5-year-olds Spin the pots scores and structural brain metrics.

This study presents a brain region possibly significant for cognitive development in early childhood and is somewhat supported by previous studies with adult participants. Studies like ours focusing on parallels between brain maturation and neuropsychological development could broaden the understanding of the typical development of brain in early childhood, which is an interesting standpoint and offers a background for the research of abnormal and pathological development.

Keywords: MRI, cortical development, visuospatial working memory

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Abstract

Visuospatial working memory (VSWM) is essential in multiple areas of life including academic abilities and emotional development. Studies focusing on early childhood and cortical structural development are scarce. We explored associations between VSWM (using Spin the pots task) in 2.5-year-olds as well as 5-year-olds and cortical metrics from T1-weighted magnetic resonance images (MRIs) of 157 typically developing 5-year-olds (mean age 5.41, SD 0.13; 83 males). MRIs were processed using FreeSurfer. We found that in 5-year-olds cortical volume and surface area were positively correlated in the right middle temporal region with Spin the pots scores. There were no associations between 2.5-year-olds Spin the pots scores and structural brain metrics. This study presents a brain region possibly significant for cognitive development in early childhood and is somewhat supported by previous studies with adult participants. Studies like ours focusing on parallels between brain maturation and neuropsychological development could broaden the understanding of the typical development of brain in early childhood, which is an interesting standpoint and offers a background for the research of abnormal and pathological development.

Introduction

Working memory (WM) is one of the core executive functions (Miyake et al., 2000) and can be defined as the cognitive system that temporarily stores information that is needed for completing complex cognitive tasks, such as language comprehension, learning and reasoning (Baddeley, 1992). WM skills improve remarkably in early childhood and this development continues well into adolescence (Best & Miller, 2010; Garon et al., 2008). Performance on tasks measuring the three components of WM, including visuospatial working memory (VSWM), have been shown to increase linearly from age 4 to early adolescence (Gathercole et al., 2004). WM and its development is essential to many skills in life and there is an understanding that the development of WM is a reflection of the structural and functional brain maturation supporting this ability (Casey et al., 2000; Kharitonova et al., 2013; Klingberg, 2006; Tamnes et al., 2013).

VSWM supports many skills in life, such as academics and emotional development. A recent systematic review concluded that mathematics performance is positively associated with VSWM in school-aged children (Allen et al., 2019). WM measures may also predict future development of academic abilities (Alloway & Alloway, 2010; Bull et al., 2008; Dumontheil & Klingberg, 2012). For instance, one study showed that children's WM skills at 5 years of age were even more powerful predictors of literacy and numeracy skills 6 years later than intelligence quotient (Alloway & Alloway, 2010). Beyond academics, WM has been associated with social and emotional development (de Wilde et al., 2016; Moriya, 2018), peer and teacher relationships (de Wilde et al., 2016), social anxiety (Moriya, 2018) and compromised WM is seen in numerous neurodevelopmental disorders such as attention deficit and hyperactivity disorder (Martinussen et al., 2005), language impairment (Archibald & Gathercole, 2006), dyscalculia (Szucs et al., 2013) and dyslexia (Reiter et al., 2005; Smith-Spark & Fisk, 2007).

It is crucial to understand typical development of structural brain metrics in order to assess the relationship between WM performance and brain structure in early childhood. The brain structure undergoes significant non-linear and region-specific maturational changes in childhood (Phan et al., 2018). A recent article created brain growth charts for the human life span across more than 100 primary studies, including 123,984 MRI brain scans (Bethlehem et al., 2022) and concluded that by age 3 the brain reaches approximately 80% of its maximum size and total cerebral colume peaks approximately at 11–12 years of age. Cortical volume (CV) increases from birth to early childhood, reaching its maximum around 6 years of age, and then decreases almost linearly into adulthood (Bethlehem et al., 2022). It was noted that among the total brain tissue volumes, CV peaks the earliest. Maturation of the brain structure is region-specific, as stated before, and the maturation of the gray matter (GM) seems to finish latest in the insular and parahippocampal regions as defined by Desikan–Killiany parcellation (Bethlehem et al., 2022; Desikan et al., 2006). According to Bethlehem et al. (2022) cortical surface area (SA) peaks later than CV, around 11 years of age. Bethlehem et al. (2022) concluded that cortical thickness (CT) peaks remarkably early at 1.7 years of age. In conclusion at the age of five, CT has already reached its peak and CV as well as SA are still increasing. In order to assess the parallels between cortical structural development and brain structural maturation and VSWM in early childhood we need understanding of whether better performance in tasks is reflected as faster or slower cortical maturation.

There are some studies that investigate the relationships between WM and structural brain metrics in children. Previous studies have found frontal and parietal GM volumes to be negatively correlated with participant's WM capacity (Mahone et al., 2009; Rossi et al., 2013). More specifically, CV has been negatively correlated with WM in 10-year-olds, and these correlations occurred in different regions depending on the task (backward or forward span) (Rossi et al., 2013). One study found that the cumulative early life stress was associated with worse visuospatial WM and smaller prefrontal cortex (PFC) volumes in children aged around 12 years (Hanson et al., 2012). Associations between CT reductions and age related improvements in WM tasks have been reported in 5–10-year-old children (Kharitonova et al., 2013). Results from another study suggest that thinner cortex is associated with better WM performance (verbal digit span task) in frontoparietal regions in children aged 4–8 years (Botdorf & Riggins, 2018). A recent study found a negative correlation between WM and right inferior parietal as well as precuneus thickness in term born children aged between 7 and 12 years of age (Mürner-Lavanchy et al., 2018). Based on previous studies there is no clear knowledge of parallels between cortical development and VSWM. Some studies suggest that there is a negative correlation between CV and WM while some show associations between lower CV and WM (Hanson et al., 2012; Rossi et al., 2013). Several studies suggest that there is an association between thinner cortex and better WM performance (Botdorf & Riggins, 2018; Mürner-Lavanchy et al., 2018). However, in mentioned studies findings have been in various brain regions, therefore, there is no clear understanding of what to expect at the age of five.

Many studies have focused on functional magnetic resonance imaged (fMRI) to examine WM and associated brain regions. Although it is known that the locations of structural and functional correlates do not always align (Basten et al., 2015), these studies provide useful information on possibly significant brain regions for WM. For instance, one fMRI study showed that children recruited core WM regions (dorsal lateral PFC and parietal regions) as well as ventromedial regions (caudate nucleus and anterior insula) during a VSWM task (Scherf et al., 2006). Some studies show even more widespread bilateral activation (Ciesielski et al., 2006). In several fMRI studies children show similar activation in visuospatial tasks than adults (Nelson et al., 2000; Thomas et al., 1999).

In conclusion, while there are some studies on WM and brain metrics in children, the children are often older. Age groups 5 years and younger are underrepresented, which is a problem especially since in early childhood the brain is undergoing rapid development and the relevant areas for VSWM may not be the same as in older children and adults. Furthermore, many of these studies focus on functional imaging, and the functional correlates of a cognitive task may not reflect the same areas where structural changes are seen (Basten et al., 2015).

In this study, we explored associations between a VSWM (Spin the pots task) in 2.5-year-olds as well as 5-year-olds and cortical metrics from T1-weighted magnetic resonance images (MRIs) of typically developing 5-year-olds vertex-wise using Query, Design, Estimate, Contrast (QDEC) from the FreeSurfer software suite (Fischl, 2012).

Methods and materials

This study was conducted in accordance with the Declaration of Helsinki, and it was approved by the Joint Ethics Committee of the University of Turku and the Hospital District of Southwest Finland: (1)

ETMK: 26/1801/2015 for the neuropsychological measurements, and (2) ETMK: 31/180/2011 for the neuroimaging.

Participants

The participants are a part of the FinnBrain Birth Cohort Study (www.finnbrain.fi), which prospectively examines the influence of genetic and environmental factors on child development and later health outcomes (Karlsson et al., 2018). In this study, we included typically developing children that attended neuropsychological and neuroimaging visits as part of the 5–year data collection.

We originally aimed to scan all subjects between the ages 5 years 3 months and 5 years 5 months; however, there was a pause in visits due to the start of the COVID–19 pandemic, and subsequently many of the participants were older than planned when they were scanned. Mean age for all 203 participants was 5.40 (SD 0.13) years ranging from 5.08 to 5.79 years. Of all 203 participants, 113 (55.7 %) were boys and 90 (44.3 %) girls. The exclusion criteria for the neuroimaging study were: 1) born before gestational week 35 (before gestational week 32 for those with exposure to maternal prenatal synthetic glucocorticoid treatment), 2) developmental anomaly or abnormalities in senses or communication, 3) known long–term medical diagnosis, 4) ongoing medical examinations or clinical follow up in a hospital, 5) child use of continuous, daily medication (including per oral medications, topical creams and inhalants. One exception to this was desmopressin (®Minirin) medication, which was allowed), 6) history of head trauma (defined as concussion necessitating clinical follow up in a health care setting or worse), 7) metallic (golden) ear tubes (to assure good–quality scans), and routine MRI contraindications.

In 5-year-olds out of 203 participants, 173 were included after MRI quality control. Out of these 173 participants, 157 had Spin the pots task results and were included in the final sample of 5-year-olds. For participant demographics and maternal background variables for the final 157 participants, see Table 1 and Table 2. Out of the 157 participants 97 had Spin the pots task data at 2.5-year-olds and. In continuous variables one value from maternal pre-pregnancy body mass index (BMI) was missing. In categorical variables nine of prenatal alcohol exposure values were missing and one pregnancy complications value was missing.

Table 1

Continuous participant and maternal background variables. Number of participants = 157.

Continuous variables	Mean	SD	Min	Max
Age at scan (years)	5.41	0.13	5.23	5.79
Maternal age at term (years)	31.04	4.71	19.10	41.95
Ponderal index	14.08	1.17	11.85	17.63
Gestational age at birth (weeks)	39.81	1.55	33.86	42.29
Maternal pre-pregnancy BMI	24.14	4.17	17.48	36.93

Table 2

Categorical participant and maternal background variables. Number of participants = 157.

Categorical variables	Number (n)	Percent (%)
Sex	**157**	
Male	83	52.9
Female	74	47.1
Maternal education level	**157**	
University degree	82	52.2
Lower than university degree	75	47.8
Prenatal alcohol exposure	**148**	
Yes	13	8.8
No	135	91.2
Prenatal tobacco exposure	**157**	
Yes	11	7.0
No	146	93.0
Pregnancy complications	**156**	
Yes	22	14.1
No	134	85.9

Neuropsychological Assessments

Spin the pots task

Spin the pots task was measured at 2.5 years of age as well as at 5 years of age. Median result for 2.5-year-olds was 13 (3.7 SD). Median result for 5-year-olds was 9 (SD 3.1).

Normality assumptions were checked visually e.g. using normal quantile plot, box plot, skewness and kurtosis evaluation as well as Kolmogorov-Smirnov test of normality using IBM SPSS Statistics (Version 27). Spin the pots task data at 5 years of age did not follow normal distribution.

Spin the pots task used in this study is a modified version of its original version (Hughes & Ensor, 2005), where it was described as a measure of EFs. In the modified Spin the Pots task for 5-year-olds, the child was encouraged to watch as ten stickers were hidden in boxes that were fixed to a rotating tray. The boxes were differently shaped and colored, and all boxes had lids so that their content could only be seen when lifting the lid. There were in total twelve boxes fixed to the tray, ten in which stickers were hidden and two that were left empty. For 2.5-year-olds six stickers were hidden under eight visually distinct jars and two were left empty.

In each trial, the children were encouraged to choose one box in which they thought there was a sticker. Following the child's selection, the lid was lifted. Stickers found in the boxes were handed to the child, who then put the sticker aside prior to the next trial. After each trial, the tray was covered by an opaque scarf and was rotated 180°. The task terminated when the children had found all 10 (5–year olds) or 6 (2.5–year olds) hidden stickers or when the maximum number of 20 (5–year olds) or 16 (2.5–year olds) spins was reached. The final score was calculated as the maximum number of trials (20 or 16) minus the number of unsuccessful attempts to find a sticker, the maximum score being 20 for 5–year olds and 16 for 2.5–year olds. A higher score indicated better working memory performance.

While Spin the pots task is a multifaceted, complex task, it does have a WM component and has been used as a proxy for a WM measure before (Blakey et al., 2016; Zimmermann et al., 2021).

MRI Study Visits

MRI scans were performed by the research staff (one research nurse, four Ph.D. students, two MR technologist) for research purposes. The image acquisition process was thoroughly introduced to the parents through home familiarization methods as well as practice session using a mock scanner and a toy. The participants were scanned awake or during natural sleep. The participants were able to watch and listen to a movie or a TV show through the whole scan. Foam padding was applied to help the head stay still. If the research staff noticed movement, the participants were reminded to stay still by touching their foot, as previously agreed. All images were viewed by one neuroradiologist Riitta Parkkola who, when necessary, consulted a pediatric neurologist Tuire Lähdesmäki. Four out of 146 (2.7 %) cases with an incidental finding that required consultation. For more detailed information of study visits please see (Pulli et al., 2022).

MRI Data Acquisition

Participants were scanned using a Siemens Magnetom Skyra fit 3T with a 20-element head/neck matrix coil. We used Generalized Autocalibrating Partially Parallel Acquisition (GRAPPA) technique to accelerate image acquisition (parallel acquisition technique [PAT] factor of 2 was used). The max. 60-minute scan protocol included a high resolution T1 magnetization prepared rapid gradient echo (MPRAGE), a T2 turbo spin echo (TSE), a 7-minute resting state functional MRI, and a 96-direction single shell (b = 1000 s/mm^2) diffusion tensor imaging (DTI) sequence (Merisaari et al., 2019) as well as a 31-direction with b = 650 s/mm^2 and a 80-direction with b = 2000 s/mm^2. For the purposes of the current study, we acquired high resolution T1-weighted images with the following sequence parameters: TR = 1900 ms, TE = 3.26 ms, TI = 900 ms, flip angle = 9 degrees, voxel size = 1.0 x 1.0 x 1.0 mm^3, FOV 256 x 256 mm^2. The scans were planned as per recommendations of the FreeSurfer developers (https://surfer.nmr.mgh.harvard.edu/fswiki/FreeSurferWiki?action=AttachFile&do=get&target=FreeSurfer_Suggested_Morphometry_Protocols.pdf, at the time of writing).

MRI Data Processing

Cortical reconstruction and volumetric segmentation were performed using FreeSurfer software version 6.0 which is freely available for download online (https://surfer.nmr.mgh.harvard.edu/). The technical details of these procedures have been described in previous studies (Anders M. Dale et al., 1999; Fischl et al., 1999a; Fischl & Dale, 2000). FreeSurfer's morphometric procedures have been demonstrated to show good test–retest reliability across scanner manufacturers and across field strengths (Han et al., 2006). FreeSurfer has been successfully used in studies of children as young as age four (Ghosh et al., 2010). An automatic ”recon–all” processing stream command was applied. This process includes motion correction and averaging (Reuter et al., 2010), removal of non-brain tissue (F. Ségonne et al., 2004), automated Talairach transformation, segmentation of white and GM (Fischl et al., 2002; Fischl, et al., 2004), intensity normalization (Sled et al., 1998), tessellation of the Gray–white matter boundary, topology correction (Fischl et al., 2001; Ségonne et al., 2007), surface deformation (Dale & Sereno, 1993; Dale et al., 1999; Fischl & Dale, 2000), cortical parcellation (Desikan et al., 2006; Fischl, et al., 2004), surface inflation (Fischl et al., 1999b), registration to spherical atlas (Fischl et al., 1999b) and thickness calculation (Fischl & Dale, 2000). Additionally, a visual inspection was conducted for quality control and manual corrections were performed including skull fragment and artery removal as well as corrections to the gray–white matter border. The editing and quality control protocol is described in detail in our previous work (Pulli et al., 2022).

Statistical methods

Participant demographics and maternal background variables (Table 1, Table 2) were calculated using IBM SPSS Statistics (Version 27).

Relationships between VSWM performance and GM measures were examined using Freesurfer's QDEC application. QDEC is a graphical interface for a statistics engine that runs a vertex-by-vertex general linear model (GLM). It was applied to identify associations between age-corrected Spin the pots scores and cortical volume, surface area and cortical thickness. A Monte Carlo Null–Z simulation was run with a threshold of 1.3, corresponding to a corrected p-value of < 0.05 (Hagler et al., 2006). Participant sex, maternal education level (newest available information, two classes: 1) university degree, and 2) lower than university degree), maternal age at term, participant ponderal index (mass in kilograms divided by height in meters cubed) at scan, and participant age at scan were controlled as confounders in QDEC analyses (Silver et al., 2022). Participants' age at scan was squared in order to perform QDEC–analysis successfully. Spin the pots scores were corrected for age at measurement. Clusters of regions significantly related to the predictor were mapped onto a predefined naming scheme based on the Desikan–Killiany atlas (Desikan et al., 2006; Fischl, Van Der Kouwe, et al., 2004).

Regions of interest (ROI) analyses were performed using IBM SPSS Statistics (Version 27) partial correlations tool correcting for sex, maternal education level, age at scan (days), maternal age at term and ponderal index. P-values of the results were corrected for multiple comparisons using the Bonferroni method. Bonferroni correction was conducted by dividing the p-value of 0.05 by the number of comparisons (210), resulting in p = 0.000238.

Spearman's correlations were analyzed between Spin the pots results and continuous maternal background variables (age at term, ponderal index, gestational age at birth, BMI). Differences in categorical maternal background variables (education level, prenatal alcohol exposure, prenatal tobacco exposure, pregnancy complications) and Spin the pots results were analyzed using Mann–Whitney U–test.

Results

No significant correlations were found between Spin the pots results in 5-year-olds and continuous maternal background variables. No significant correlations were found between Spin the pots results in 2.5-year-olds and continuous maternal background variables. No significant differences were found between Spin the pots results in 5-year-olds and categorical maternal background variables.

No significant differences were found between Spin the pots results in 5-year-olds and categorical maternal background variables.

Descriptive statistics

Correlation coefficients (Spearman's)

	Spin the pots in 5-year-olds (correlation coefficient, significance 2-tailed)	Spin the pots in 2.5-year-olds (correlation coefficient, significance 2-tailed)
Age at scan (years)	-0.027 (0.74)	0.117 (0.26)
Maternal age at term (years)	-0.129 (0.11)	-0.020 (0.85)
Ponderal index	0.041 (0.61)	-0.170 (0.10)
Gestational age at birth (weeks)	-0.120 (0.13)	0.020 (0.85)
Maternal pre-pregnancy BMI	0.117 (0.14)	-0.111 (0.29)

** Correlation is significant at the 0.01 level (2-tailed)

Cortical volume and working memory in 5-year-olds

For Spin the pots and CV, a significant cluster was found in the right middle temporal region (peak p = 0.0138, size = 1023.73 mm^2, peak coordinates 61.5, -34.9, -14.2). This cluster can be seen in Figure 1.

Surface area and working memory in 5-year-olds

For Spin the pots and SA, a significant cluster was found in the right middle temporal region (peak p = 0.0025, size = 1032.63 mm^2, peak coordinates 61.5, -34.9, -14.2). This cluster can be seen in Figure 1.

Cortical thickness and working memory in 5-year-olds

No significant clusters were found for CT and Spin the pots scores.

Cortical measures and working memory in 2.5-year-olds

No significant clusters were found in CV, SA or CT and Spin the pots scores.

ROI analyses

None of the ROI-analyses results survived the Bonferroni correction for multiple comparisons (p = 0.000238). Brain regions that were significant at alpha level $p < 0.05$ are presented in Table 3.

Table 3

	Working memory in 5-year-olds (partial correlation, p-value)	**Working memory in 2.5-year-olds (partial correlation, p-value)**
Left hemisphere		
Cortical volume	Pericalcarine cortex (0.201, 0.039)	Parahippocampal gyrus, precuneus cortex (0.214, 0.042)
Surface area	Fusiform gyrus (0.168, 0.041)	Entorhinal cortex, temporal pole (0.235, 0.024)
Cortical thickness	Insula (0.189, 0.037)	
Right hemisphere		
Cortical volume	Middle temporal gyrus (0.214, 0.042), frontal pole (0.166, 0.041)	
Surface area	Parahippocampal gyrus (-0.201, 0.013), paracentral lobule (0.220, 0.008)	
Cortical thickness	Inferior parietal cortex (-0.221, 0.014)	Caudal middle frontal gyrus (0.231, 0.031), pars triangularis (0.229, 0.030), superior temporal gyrus (0.257, 0.038)

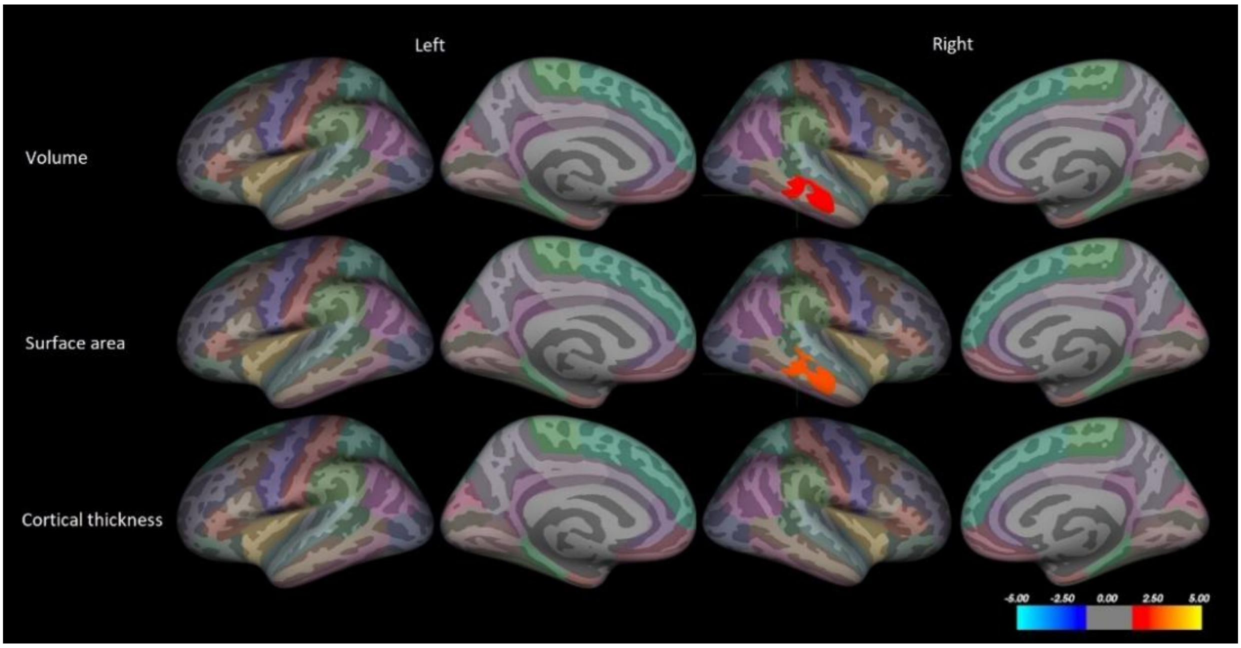

Figure 1

Positive associations between Spin the pots and cortical volume as well as Spin the pots and surface area. Results corrected for multiple comparisons using Monte Carlo Null-Z simulation. Color indicates significance as -$\log_{10}(p)$). Color coding of regions according to the Desikan–Killiany atlas.

Discussion

In this study, we investigated the associations between VSWM and cortical morphometry in typically developing 5-year-olds and 2.5-year-olds. Significant relationships were observed between two of the brain cortical measures (CV, SA) and VSWM in 5-year-olds. We did not find any statistically significant associations between WM and structural cortical development in 2.5-year-olds, which may have resulted from the smaller sample size.

Better VSWM function was associated with larger GM volume and SA in the right middle temporal region. There is limited research on the structural correlates of WM in typically developing children. However, our findings converge with adult studies that find the right hemisphere important for VSWM (Baddeley, 2003; Reuter-Lorenz et al., 2000; Smith & Jonides, 1998). Furthermore, there is evidence that the right temporal region, specifically, is important to WM function in adults. For instance, it has been shown that patients with unilateral right temporal lobectomy perform more poorly on a measure of VSWM (Morris et al., 1997). One study reported conservation in GM thickness and SA in several regions (including the right temporal cortex) in a group that completed a challenging adaptive cognitive training programme based on visual and auditory n–back tasks (Román et al., 2016). In another study executive function deficits correlated to reduced SA in frontal and temporal cortices in very low birth weight late teenagers aged 19–20 years old, who seemed to have specific difficulties with WM and processing speed (Østgård et al., 2016). In functional studies, the right superior temporal gyrus has been reported to be critical for WM maintenance (Park et al., 2012). There is evidence that this region is involved also in children performing WM tasks. For instance, children aged six years old showed pattern of activation which included the right superior temporal cortex while performing a visual categorical n–back task (Ciesielski et al., 2006).

A recent article created brain growth charts for the human life span, and it was concluded that CV and SA are still increasing at the age of five (Bethlehem et al., 2022). Additionally, it seems that cortical surface expansion is completed at a younger age in children with higher cognitive ability (Schnack et al., 2015). Therefore, at age 5 faster GM development is might be reflected by increase in GM volume and SA. Assuming that higher neuropsychological test scores indicate faster GM development, it is reasonable that we found a positive association between CV, SA and WM function. Nevertheless, longitudinal studies are needed to more accurately study the developmental aspect of neuropsychological development parallel with cortical structural development.

This study has some limitations. Cross-sectional design is one limitation of our study when trying to understand parallels between VSWM development and brain maturation. However, this study provides valuable information on the associations between structural brain metrics and WM in a developmentally crucial and underrepresented age group in typically developing children. Predictive role of structural and functional brain maturation and future WM capacity has been studied before (Ullman et al., 2014). In future studies, longitudinal approach could be used to study the predictive role of structural brain maturation and future WM or vice versa, as well as parallels between brain maturation and neuropsychological development. It would be insightful to explore the VSWM even more extensively with additional tasks and take other areas of working memory into consideration in further studies.

Conclusion

In this study we explored cortical structural development in relation to VSWM ability in typically developing 5-year-olds. We found that better scores in a visuospatial working memory task were associated with greater CV as well as surface area in right middle temporal region. We did not find any significant associations in the 2.5-year-olds, possibly due to smaller sample size. There is limited research on the structural correlates of working memory in typically developing children, however our findings converge with adult studies that find the right hemisphere important for VSWM (Baddeley, 2003; Reuter-Lorenz et al., 2000; Smith & Jonides, 1998). More research, especially longitudinal studies, is needed to further explore the parallels between brain maturation and neuropsychological development.

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