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Relations between gross motor skills, cardiovascular fitness and visuospatial working memory-related brain activation in 8-10-year-old children

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\textsuperscript{1}This chapter has shared first authorship with A.G.M. de Bruijn. Both authors have equally contributed to this chapter
Abstract

Relations of gross motor skills and cardiovascular fitness with visuospatial working memory in children are hypothesized to be mediated by underlying functional brain mechanisms. As there is little experimental evidence supporting this mechanism, the present study aimed to investigate relations of gross motor skills and cardiovascular fitness with visuospatial working memory-related brain activation in 8-10-year-old children. Functional Magnetic Resonance Imaging data obtained during a visuospatial working memory task were analyzed for 80 children from grades 3 (47.5%) and 4, of 21 primary schools in the Netherlands (51.3% girls). Gross motor skills (Körper Koordinationstest für Kinder and Bruininks-Oseretsky Test of Motor Proficiency - 2nd Edition) and cardiovascular fitness (20-meter Shuttle Run Test) were assessed. Visuospatial working memory-related brain activation was found in a network involving the angular gyrus, the superior parietal cortex and the thalamus; deactivation was found in the inferior and middle temporal gyri. Although behavioral results showed that gross motor skills and cardiovascular fitness were significantly related to visuospatial working memory performance, they were not related to visuospatial working memory-related brain activation. Therefore, we could not confirm the hypothesis that brain activation underlies the relation of gross motor skills and cardiovascular fitness with visuospatial working memory performance. Either our results suggest that effects of physical activity on cognition do not necessarily go via changes in gross motor skills and/or cardiovascular fitness; or that brain activation patterns as measured with the blood oxygen level-dependent signal may not be the mechanism underlying the relations of gross motor skills and cardiovascular fitness with visuospatial working memory.
Introduction

Gross motor skills represent the involvement of large body muscles in balance, limb, and trunk movements (Corbin, Pangrazi, & Franks, 2000). Gross motor skills that children acquire during childhood enable further development of complex movement and sport-specific skills (Clark & Metcalfe, 2002). Well-developed gross motor skills go hand in hand with higher levels of physical activity, which are important for developing higher levels of cardiovascular fitness (Clark & Metcalfe, 2002). Cardiovascular fitness refers to the ability of the circulatory and respiratory systems to supply oxygen during sustained physical activity (Corbin et al., 2000). Low cardiovascular fitness levels have shown to be related to cardiovascular disease risk factors, increased body fatness, and hypertension (Ortega, Ruiz, Castillo, & Sjöström, 2008). Therefore, gross motor skills and cardiovascular fitness are important aspects of children’s physical development (Ortega et al., 2008; Robinson et al., 2015; Stodden et al., 2008).

There is accumulating evidence that gross motor skills and cardiovascular fitness are related to executive functioning in children (Haapala, 2013; van der Fels et al., 2015). Executive functioning refers to a subset of interrelated processes that are involved in purposeful, goal-directed behavior, and includes inhibition, working memory, and cognitive flexibility (Miyake et al., 2000; Banich, 2009; Diamond, 2013). Executive functions are important for success throughout life and play a critical role in the development of academic skills (Best, Miller, & Jones, 2009; Best, Miller, & Naglieri, 2011; Bull, Espy, & Wiebe, 2008). Underlying functional brain mechanisms are thought to be responsible for the relations of gross motor skills and cardiovascular fitness with executive functions. However, there is little direct evidence supporting these underlying mechanisms. Therefore, this study aims to get a better insight into the brain mechanisms underlying relations between physical variables and executive functions.

Gross motor skills and visuospatial working memory

Behavioral studies have shown that gross motor skills are related to the executive functions that are most directly involved in gross motor tasks in children, such as visuospatial working memory (Rigoli, Piek, Kane, & Oosterlaan, 2012a; Chapter 3). Visuospatial working memory refers to the ability to maintain and manipulate visuospatial information over brief periods of time (Baddeley & Hitch, 1994). Visuospatial working memory is an important executive function, as it is a prerequisite for several cognitive processes such as logical reasoning, problem-solving, and academic performance (e.g. Baddeley & Hitch, 1974; Baddeley & Hitch, 1994; Diamond, 2013).

In children and adults, functional neuroimaging studies have shown visuospatial working memory-related brain activity in frontal areas (van Ewijk et al., 2015; Kwon, Reiss, & Menon, 2002; Nelson et al., 2000), parietal areas (Kwon et al., 2002; van Ewijk et al., 2015; Nelson et al., 2000), the occipital cortex (Nelson et al., 2000; van Ewijk et al., 2015) the premotor cortex (Kwon et al., 2002), and in the cerebellum, the thalamus, and the insula (van Ewijk et al., 2015; Figure 1). Therefore, visuospatial working memory seems to be facilitated by a complex network of brain activity. It is hypothesized that the neural network involved in visuospatial working memory tasks is also important for the planning, execution, and control of movements, thereby explaining the relations
between gross motor skills and visuospatial working memory (Goldberg, 1985; Diamond, 2000; Dum & Strick, 1991; Künzle, 1978; Tanji, 1994; Wiesendanger, 1981). Although this makes it likely that brain mechanisms can explain the link between gross motor skills and visuospatial working memory, we are not aware of studies that directly examine relations between gross motor skills and visuospatial working memory-related brain activation. It is important to investigate this relation, as interventions focusing on gross motor skills can stimulate visuospatial working memory development as well, by recruiting brain networks that are also critical for visuospatial working memory.

Figure 1. Overview of Brodmann Areas in red that have been shown to be related to visuospatial working memory (Figure based on Gray, 1918). Blue boxes represent all other Brodmann Areas, which have not been related to visuospatial working memory. Medial (left) and lateral (right) surfaces are shown.

Cardiovascular fitness and visuospatial working memory

Not only gross motor skills, but also cardiovascular fitness has shown to be related to visuospatial working memory (de Bruijn, Hartman, Kostons, Visscher, & Bosker, 2018; Scudder et al., 2014). To explain the relation between cardiovascular fitness and visuospatial working memory, the cardiovascular fitness hypothesis has been brought forth. Participation in physical activity is assumed to lead to changes in the cardiovascular system (physical fitness), which go hand in hand with changes in the brain, such as increased cerebral blood flow and the up-regulation of neurotransmitters, which in the long term leads to neurogenesis and angiogenesis, in turn resulting in better cognitive performance on, amongst others, executive function tasks (Cotman, Berchtold, & Christie, 2007; Dishman et al., 2006; Sibley & Etnier, 2003).

There is some support for this hypothesis from neuroimaging studies, showing that cardiovascular fitness is related to neural networks supporting executive functioning. However, this evidence is mainly provided for inhibition. Chaddock et al. (2012) and Voss et al. (2011) have shown that children with higher cardiovascular fitness show less frontal, parietal and temporal inhibition-related brain activity and this was related to higher levels of accuracy on the inhibition task. We are not aware of studies investigating relations between cardiovascular fitness and visuospatial working memory-related brain functioning. It is important to investigate this relation, because visuospatial working memory is important for several cognitive processes and academic performance. Therefore, interventions aiming to improve cardiovascular fitness may bring...
about functional changes in the brain that are important for visuospatial working memory, subsequently also resulting in positive effects on several other cognitive processes as well as academic achievement.

The present study
The main aim of the present study is to investigate relations of gross motor skills and cardiovascular fitness with visuospatial working memory-related brain activation in 8-10-year-old typically developing children. First, the pattern of visuospatial working memory-related brain activation will be examined. Subsequently, gross motor skills and cardiovascular fitness will be related to the observed visuospatial working memory-related activity patterns. To clarify the hypothesis that brain activity is the mechanism underlying the relations of gross motor skills and cardiovascular fitness with visuospatial working memory, the relation of both gross motor skills and cardiovascular fitness with behavioral visuospatial working memory performance during scanning is also reported. It is hypothesized that both gross motor skills and cardiovascular fitness will be associated with visuospatial working memory performance and visuospatial working memory-related brain activation. The results of this study will contribute to our understanding of the mechanisms underlying relations between physical capacities and visuospatial working memory, which will help in the development of physical activity interventions that can also stimulate brain development important for executive functioning.

Materials and methods

Participants
A total of 92 children from 21 schools in the Netherlands were included in this study (47 girls, 51.1%). Participating children were in grade 3 (n = 46, 50.0%) or grade 4, and were 8-10 years old (9.14 ± 0.63 years). This study was part of a large cluster randomized controlled trial (RCT; “Learning by Moving”) assessing the effects of two types of physical activity on cardiovascular fitness, gross motor skills, cognitive functions, and academic performance. Children who participated in the cluster RCT were invited to participate in this magnetic resonance imaging (MRI) sub-study. Only children aged over 8 years that had no contraindications for MRI were included. Written informed consent was provided by children’s parents or legal guardians. This study was approved by the ethical board of the Vrije Universiteit Amsterdam (VCWE-S-15-00197) and registered in the Netherlands Trial Register (NL5194).

Tasks

Visuospatial working memory
An adapted version of a spatial span task developed by Klingberg, Forssberg, & Westerberg (2002) was used to assess visuospatial working memory (van Ewijk et al., 2014; van Ewijk et al., 2015). The task was created in E-prime (version 2.0.10.356; Psychology Software Tools). A 4 x 4 grid was presented on a screen behind the MRI scanner that was visible for the child via a mirror attached to the head coil. In the grid, a sequence of either three (low working memory load) or five (high
working memory load), either yellow (working memory condition) or red (control condition) circles was presented, 500 ms per circle, with an inter-stimulus interval of 500 ms (Figure 2). Next, a probe was presented in one of the 16 possible locations in the grid, consisting of a number, referring to one of the presented stimuli, followed by a question mark. In the working memory conditions, children were instructed to remember the order in which the circles (three or five) were presented. When the probe was shown, the child had to indicate with a right (‘yes’) or left (‘no’) button press whether the probe location matched the location of the stimulus that was indicated by the probe number (see example in Figure 2). Children were asked to respond within a 2000 ms response window. In the control conditions, the circles (three or five) were shown in a predictable manner in the four corners of the grid, and were always followed by a probe with the number 8. Children were instructed to look at the circles, but not to remember the order, and to always press ‘no’ when the probe appeared. Feedback was provided in both conditions by presenting a green (correct response) or red (incorrect response) coloured bar underneath the probe. The task was administered in four blocks, each containing 24 trials, with a short break in between blocks, resulting in a total task duration of approximately 16 minutes. The percentage of the correct working memory trials (for the low and high working memory load trials separately, and for the low and high working memory load trials combined) were used as outcome measures for behavioral performance. Figure 2 shows a schematic overview of the spatial span task.

Figure 2. Schematic overview of a low working memory load trial of the spatial span task (van Ewijk et al., 2015). In this example trial, a sequence of three (low load) yellow (working memory) circles was presented (500 ms per circle, with a 500 ms inter-stimulus interval; stimulus presentation). Next, a probe appeared, in this example prompting whether the second circle appeared in that position in the grid. Children were instructed to respond within a 2000 ms response window, in this case responding with ‘yes’ (i.e. the second circle was in that position). The response was followed by feedback (a red or green bar underneath the probe) which was presented for the remainder of the response window (response and feedback). In this example, a correct response (‘yes’) was given and a green bar appeared below the probe as feedback.

Gross motor skills
Gross motor skills were evaluated using three subtests (jumping sideways, moving sideways, and backwards balancing) of the Korper Koordinationstest für Kinder (KTK; Kiphard & Schilling, 2007). The KTK originally consists of four subtests, but a recent study has shown substantial agreement...
between the test battery consisting of three subtests and the original test battery consisting of four subtests (Novak et al., 2017). Additionally, one item of the Bruininks-Oseretsky Test of Motor Proficiency, Second Edition (BOT-2; Bruininks & Bruininks, 2005) was used to measure ball skills. Both test batteries have shown to be reliable and valid for primary school children (Bruininks, 2005; Bruininks & Bruininks, 2005; Kiphard & Schilling, 2007; Novak et al., 2017).

Jumping sideways (KTK)
Children jumped laterally as quickly as possible over a small wooden slat (60 x 4 x 2 cm) for 15 s. The total number of jumps in two trials was used as the score for jumping sideways.

Moving sideways (KTK)
Children moved across the floor as quickly as possible in 20 s by stepping on and transferring two plates (25 x 25 x 5.7 cm). Children stepped from the first plate to the next, subsequently lifting and transferring the first plate alongside the second and stepping on it. Each successful transfer from one plate to the next resulted in two points: one for shifting the plate and one for stepping on the next plate. The total number of points on two trials was used as a score for moving sideways.

Backwards balancing (KTK)
Children made as many steps backwards as possible on three wooden beams with lengths of 3 m, but decreasing in width (resp. 6 cm, 4.5 cm, and 3 cm). For each beam, children performed three trials. A maximum of eight steps per trial was counted, resulting in a maximum score of 72.

Ball skills (BOT-2)
The ball skills subtest consisted of seven activities executed with a tennis ball. Activities were catching, throwing and dribbling a ball with one or both hands and throwing a ball at a target. Five trials were performed for catching a tossed ball (with one and two hands), dropping and catching a ball (with one and two hands), and throwing a ball at a target. For each correct trial, a child received one point. For dribbling a ball (with one hand and with alternating hands), children had two attempts to dribble 10 times. Based on the highest number of dribbles of the two attempts, a child received a maximum of 7 points. The maximum score for ball skills was 39 points.

Cardiovascular fitness
Cardiovascular fitness was administered with the 20-meter Shuttle Run Test (20-m SRT, in number of completed stages; Adam, Klissouras, Ravazzolo, Renson, & Tuxworth, 1988). In the 20-m SRT, children run back and forth over a distance of 20 meters, indicated by lines on the floor. An audio signal sounds at the moment in time that children must have covered the distance on the track by touching the line with one of their feet. The required average speed to cover the track is initially set at 8 km/h and increases every minute by 0.5 km/h. The test was terminated for a child when he/she failed to reach the other end of the track in time on two consecutive occasions. The validity and reliability of the SRT have shown to be adequate in children (Leger, Mercier, Gadoury, & Lambert, 1988).
**Procedure**

Visuospatial working memory was assessed during a functional MRI scan, carried out as part of a scanning protocol that was performed at the Vrije Universiteit Medical Centre in Amsterdam (n = 47), or the University Medical Center in Groningen (n = 45). Children were familiarized with the scanning procedure using a mock scanner and with the task in a half-hour session prior to data collection. Children responded to the task using a button-box (Current designs Inc., Philadelphia, USA). Head movements were minimized by inserting small, wedge-formed pillows between the head coil and the child’s head. Children received a small present and a copy of their structural T1-weighted scan.

Cardiovascular fitness and gross motor skills were assessed by trained research assistants using standardized protocols, at the children's own school, within a timeframe of two weeks around the scanning procedure. Cardiovascular fitness was assessed during a physical education lesson in groups of up to 15 children. Gross motor skills were individually assessed during one or two (depending on the class size) physical education lessons, in circuit form, with tests administered in a random order.

**Image acquisition**

The imaging protocol was carried out at two different sites (Amsterdam and Groningen) on either a 3 Tesla whole-body unit (Discovery MR750, GE Healthcare, Milwaukee, Wisconsin; Amsterdam) or a 3 Tesla Philips Intera scanner (Philips Medical Systems, Best, the Netherlands; Groningen), using a 32-channel head coil and closely-matched acquisition parameters. Blood oxygen level-dependent (BOLD) contrasts with T2*-weighted functional gradient echo-planar images (EPI) were obtained using the following parameters: repetition time (TR) = 2000 ms, echo time (TE) = 35 ms, flip angle (FA) = 80°, field of view (FOV) = 211 mm, slice thickness = 3.0 mm, interslice distance = 0.3 mm, 135 dynamics, and 64 x 64 grid (Amsterdam protocol), or 64 x 60 grid (Groningen protocol), voxel size = 3.3 x 3.3 x 3.3 mm. Four runs were obtained. Two spin echo EPI scans with opposing polarities of the phase-encode blips were acquired (TR = 6000 ms, TE = 60 ms, all other parameters remained the same) which would later be applied to correct for distortions in the functional images caused by the susceptibility distribution of the subjects head (Andersson & Sotiropoulos, 2016; Smith et al., 2004). Additionally, high resolution, whole-brain T1-weighted sagittal brain images were acquired at the beginning of the scan protocol (TR = 400 ms, TE = min full, FA = 111°, FOV = 250 mm, slice thickness = 3.0 mm, interslice distance = 0.3 mm, and 256 x 192 grid, voxel size = 1 x 1 x 1 mm).

**Image analyses**

**First level analysis**

For each subject, data were preprocessed using FLS feat (FMRI Expert Analysis Tool; FMRIB Analysis group, Oxford, UK; available from the FMRIB Software Library at www.fmrib.ox.ac.uk/fsl). The first steps (until the data were combined into a single 4D dataset) were performed separately for all the four experimental blocks. Blocks were only included if (1) there was at least one correct
response for each of the four conditions (working memory and control conditions, high and low memory load), and (2) the block was complete, i.e., the scan was not aborted before the end of the block. In total, 91.3% of the blocks was included in the analyses. Functional images were corrected for head motion using rigid body transformations (MCFLIRT, FSL; Jenkinson, Bannister, Brady, & Smith, 2002), followed by a correction for the susceptibility distribution of the subjects' head (TOPUP tool in FSL; Andersson & Sotiropoulos, 2016; Smith et al., 2004). To remove non-brain tissue from the functional scans and the T1-weighted structural images, the Brain Extraction Tool (BET; Smith, 2002) was applied. Subsequently, spatial smoothing was applied to the functional data using a 5-mm Full Width Half Maximum (FWHM) Gaussian Kernel. Smoothing was applied to improve the signal-to-noise ratio by replacing the value of a single voxel by a weighted average of neighboring voxels. Finally, the experimental blocks were combined into a single 4D dataset per subject which could be used for further analyses.

In order to remove artefacts from the subject's data, an independent-component analysis (ICA) was conducted using Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC; Beckmann & Smith, 2005) for each subject's 4D dataset. MELODIC is a method by which a 4D dataset can be decomposed into spatial and temporal components. This way, activation and artefactual components can be distinguished, as they have unique spatial patterns (Kelly et al., 2010; Thomas, Harshman, & Menon, 2002). By using ICA, the data were represented by a multiplication of two matrices (see Box 1):

\[ Y = T \times M; \]  

(1)

in which Y represents the time course spatial maps (dimension time by voxel), T represents the component time course (dimension time by component) and M the component spatial maps (component by voxel). Based on the recommendation to use about one-fourth to one-fifth of the total of time points in the scans (Greicius, Srivastava, Reiss, & Menon, 2004), and previously widely adopted settings of 20-30 components for ICA (Smith et al., 2009), a fixed number of 30 components was extracted per subject. The spatial component maps were visually inspected for artefacts, and components representing artefacts were removed. The remaining components (T', M') were used to generate contrast images (i.e. a representation of differences in brain activation between different task conditions), using the following procedure:

1. A model representing the expected BOLD response was created for each of the task-conditions (X: dimension time by condition) using Statistical Parameter Mapping 12.0 (SPM 12.0 v6470, running in MATLAB 2017b). The task-conditions are presented in Table 1. Only correct trials were included to minimize variability in brain activation between different conditions, because differences in brain activation were expected during incorrect and omission trials as compared to correct trials. The model was created by convolving a stick function with a canonical Hemodynamic Response Function (HRF). Additionally, a constant was added to this model to capture an offset.
Table 1. Overview of all task-conditions in the visuospatial working memory task. Conditions used for this study (only correct trials) are shown in italics.

<table>
<thead>
<tr>
<th>Working memory trials</th>
<th>Control trials</th>
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</thead>
<tbody>
<tr>
<td>Low load</td>
<td>High load</td>
</tr>
<tr>
<td>Correct response</td>
<td>Con1</td>
</tr>
<tr>
<td>Incorrect response</td>
<td>Con2</td>
</tr>
<tr>
<td>Omission error</td>
<td>Con3</td>
</tr>
</tbody>
</table>

Note. Con = condition.

2. The time course of each of the remaining components $T'$ was regressed against the model created in step 1 using Ordinary Least Square (OLS), resulting in an effect size per condition ($B$: dimension condition by component):

$$T' = X \cdot B \quad (2)$$

3. Two contrast vectors ($c_1$, $c_2$) were defined in order to reconstruct a contrast effect size map per subject (CM: dimension contrast effect size by voxel), representing differences in brain activation when comparing different conditions:
   a. A working memory contrast ($c_1$): successful working memory trials (Con1 and Con4) versus successful control trials (Con7 and Con10);
   b. A load difference contrast ($c_2$): successful high working memory load trials (Con4) versus successful low working memory load trials (Con1).

For each voxel in CM, the contrast effect size was reconstructed by summing the contrast effect size per component ($c \cdot B$) across components, weighted by the corresponding value in $M$. This way, components with larger effect sizes had a higher weight in reconstruction of the maps:

$$CM = c \cdot B \cdot M \quad (3)$$

This resulted in a contrast image representing the activation differences between the conditions for each voxel per subject. A difference between the two sites was found in the scaling of the contrast images, as the intensity scale of the images acquired in Groningen was five times larger than that of those acquired in Amsterdam. The images were therefore rescaled by dividing their intensity scale by its respective standard deviation.
4. The contrast image CM was coregistered to the subject’s own 3D anatomical space and normalized to standard space by registration to an MNI-152 template. Normalization was used in order to match anatomical brain locations across subjects. This allows averaging brain activation patterns across subjects, which can therefore be used for further second level (group) analysis. The contrast CM images were spatially smoothed with an 8-mm FWHM Gaussian Kernel. The smoothing, co-registration and normalization steps were performed in SPM.

Children were excluded from the analysis if (1) more than 15 components were manually removed from the data (n = 3); (2) normalization had failed (n = 7), or (3) children were absent on testing days at school, and therefore had no score for visuospatial working memory, cardiovascular fitness, or motor skills (n = 1). The final sample consisted of 80 children (87.0% of the total number of children that was scanned; 41 girls [51.3%]; 38 grade 3 children [47.5%]). An overview of the number of children that participated (separated by site, grade, and sex), and the final number of children that was included for the data analyses is presented in Appendix 4.1.
Box 1. Independent Component Analysis (ICA) and reconstruction of the contrast effect size maps

\[ Y: 4D \text{ dataset time course spatial maps for a subject represented by the component time course (T) and the component spatial maps (M).} \]

\[ T': \text{ the component time course of the remaining components (after removing components with artefacts), represented by the condition time course (X) and the effect size per condition for each of the remaining components (B).} \]

\[ CM: \text{ contrast effect size map per contrast, represented by sum of the contrast effect size per component (c * B) and the component spatial maps for the remaining components (M').} \]

\[ c: \text{ contrast vector, either for the working memory contrast or for the load difference contrast:} \]

\[ c_1 = \text{ working memory contrast: successful working memory trials (Con1 and Con4) versus successful control trials (Con7 and Con10).} \]

\[ c_2 = \text{ load difference contrast: successful high working memory load trials (Con4) versus successful low working memory load trials (Con1).} \]
Analyses

Behavioral data
A principal component analysis on the standardized scores of the gross motor skill tests was performed to calculate a Bartlett factor score. This analysis was performed on the total sample of 891 children in the ‘Learning by Moving’ project (see data analysis in Chapter 3.). The four gross motor skill components loaded highly onto one factor (> 0.6) and explained 48.2% of the total variance. This factor was used in the analysis as a measure of gross motor skills.

IBM SPSS Statistics version 25 was used to calculate Pearson correlations between the physical task scores (gross motor skills and cardiovascular fitness) and behavioral visuospatial working memory task scores (low working memory load trials, high working memory load trials, and low and high working memory trials together) for the children who participated in this fMRI study. Level of significance was set at p < 0.05.

Second level fMRI analysis
The fMRI data were analyzed in SPM12.0 (v6470, running in Matlab 2017b). In a first step, two General Linear Models (GLM) were created (one for each contrast) to capture the overall BOLD response. The contrast images (CM in box 1) from the first level analysis were added as dependent variables in the models. Additionally, scan site (Amsterdam or Groningen), sex, age and socioeconomic status (SES) were included in the model as covariates of no interest. In a second step, a GLM was created for both contrasts with the factor score for gross motor skills as covariate of interest. Finally, a GLM was created for both contrasts with cardiovascular fitness as covariate of interest. If the covariates of no interest included in step 1 were significant, they were included in the models created in steps 2 and 3 as well. Figures will represent activation maps thresholded at significance level of p < 0.01 (uncorrected). The table and the text will represent results that survived the cluster level significance of p < 0.05, family wise error (FWE) corrected, initial threshold p < 0.001.

Results

Behavioral results
Demographics and scores on cardiovascular fitness, gross motor skills and visuospatial working memory are shown in Table 2. Pearson correlations showed that gross motor skills were positively related to task performance on low working memory load trials, r = 0.364, p = 0.001, to high working memory load trials, r = 0.236, p = 0.035, and to all working memory trials, r = 0.268, p = 0.016. Cardiovascular fitness was positively related to task performance on low working memory load trials, r = 0.279, p = 0.012, to high working memory load trials, r = 0.221, p = 0.049, and to all working memory trials, r = 0.268, p = 0.016.
### Table 2. Pearson correlations between the study variables, and descriptive statistics and test scores (means and standard deviations) of the total sample (n = 80)

<table>
<thead>
<tr>
<th></th>
<th>Age (years)</th>
<th>Sex (% girls)</th>
<th>SES</th>
<th>Grade (% grade 3)</th>
<th>Low visuospatial working memory load trials (% correct)</th>
<th>High visuospatial working memory load trials (% correct)</th>
<th>All visuospatial working memory trials (% correct)</th>
<th>Gross motor skills (factor score)</th>
<th>Cardiovascular fitness (stages)</th>
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<tbody>
<tr>
<td>Age (years)</td>
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<tr>
<td>Grade (% grade 3)</td>
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<td>0.093</td>
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<tr>
<td>working memory load</td>
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</tr>
<tr>
<td>trials (% correct)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>All visuospatial</td>
<td>0.008</td>
<td>-0.020</td>
<td>0.23*</td>
<td>0.136</td>
<td>0.937**</td>
<td>0.934**</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>working memory load</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>trials (% correct)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Gross motor skills</td>
<td>0.268*</td>
<td>-0.057</td>
<td>0.020</td>
<td>0.306**</td>
<td>0.364**</td>
<td>0.236**</td>
<td>0.322**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(factor score)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular fitness</td>
<td>0.198</td>
<td>-0.257*</td>
<td>0.154</td>
<td>0.279**</td>
<td>0.221**</td>
<td>0.268**</td>
<td>0.494**</td>
<td></td>
<td></td>
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<tr>
<td>(stages)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD or percentage</td>
<td>9.17 ±</td>
<td>51.30b</td>
<td>4.58 ±</td>
<td>47.50b</td>
<td>70.70 ±</td>
<td>66.00 ±</td>
<td>68.35 ±</td>
<td>0.18 ±</td>
<td>4.74 ±</td>
</tr>
<tr>
<td></td>
<td>0.62a</td>
<td>1.06a</td>
<td>15.97a</td>
<td>15.54a</td>
<td>14.74a</td>
<td>1.01a</td>
<td>1.91a</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. Performance on low and high working memory significantly differed as measured with a paired sample t-test, \( t (80) = 4.245, p < 0.001 \); SES = socioeconomic status, obtained by a parental questionnaire. Level of parental education of both parents was requested and varied from 0 (no education) to 7 (postdoctoral education; Schaart, Mies, & Westerman, 2008). Average education level of both parents was used as a measure of SES. If the level of parental education was specified for only one of the parents, this level was used as a measure of SES for the child; aMean ± SD; bPercentage; * \( p < 0.05 \); ** \( p < 0.01 \).
fMRI results

**Working memory contrast**
Brain activation during working memory trials compared to control trials, while controlling for the covariates of no interest that were included in step 1 (i.e. scan site, sex, age, and SES) are shown in Figure 3. Table 3 shows the MNI coordinates of the significant clusters of brain activation. Significant clusters were located right in the angular gyrus and bilateral in the superior parietal cortex, the inferior temporal gyrus and the middle temporal gyrus ($p < 0.05$), indicating task-related increases in activation in the angular and superior parietal areas, and task-related decreases in the inferior and middle temporal areas. Results on the covariates (scan site, age, sex and SES) are presented in Appendix 4.2. Only scan site was a significant covariate and was therefore included as a covariate of no interest in all subsequent analyses.

![Sagittal view](image1)

**Sagittal view**
- $x = -58$
- $x = -20$
- $x = 2$
- $x = 32$
- $x = 48$

![Coronal view](image2)

**Coronal view**
- $y = -72$
- $y = -54$
- $y = -20$
- $y = -4$
- $y = 4$

![Axial view](image3)

**Axial view**
- $z = -32$
- $z = -28$
- $z = 10$
- $z = 46$
- $z = 52$

**T-value**
- $-3.2$
- $-3.6$
- $-4.0$
- $-4.4$
- $-4.8$

![Colour scale](image4)
- $-3.2$
- $3.6$
- $4.0$
- $4.4$
- $4.8$

**Figure 3.** Brain activation for the working memory contrast. Sagittal (upper), coronal (middle) and axial (lower) view. Warm colours indicate activation in working memory trials as compared to control trials. Cool colours indicate deactivation in working memory trials as compared to control trials. MNI coordinates (x, y, and z) represent the location of the maximum intensity voxel.
Table 3. Significant clusters of brain activation associated with visuospatial working memory, controlling for scan site, age, sex and SES

<table>
<thead>
<tr>
<th>Cluster #</th>
<th>Anatomical label(s)</th>
<th>Hemisphere</th>
<th>N voxels</th>
<th>MNI coordinates&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Activation&lt;sup&gt;b&lt;/sup&gt; Angular gyrus, superior parietal gyrus</td>
<td>Right</td>
<td>3900</td>
<td>32  -54  46</td>
</tr>
<tr>
<td>2</td>
<td>Superior parietal gyrus</td>
<td>Left</td>
<td>1562</td>
<td>-20 -72  52</td>
</tr>
<tr>
<td>3</td>
<td>Thalamus</td>
<td>Bilateral</td>
<td>503</td>
<td>2   -20  10</td>
</tr>
<tr>
<td>4</td>
<td>Deactivation&lt;sup&gt;c&lt;/sup&gt; Inferior temporal gyrus, middle temporal gyrus</td>
<td>Left</td>
<td>6940</td>
<td>-58 -4  -28</td>
</tr>
<tr>
<td>5</td>
<td>Inferior temporal gyrus, middle temporal gyrus</td>
<td>Right</td>
<td>1498</td>
<td>48   4    -32</td>
</tr>
</tbody>
</table>

Note. Activation for the working memory contrast that survived the cluster level significance of p < 0.05, family wise error (FWE) corrected, initial threshold p < 0.001; SES = socioeconomic status; N voxels: number of voxels involved in the significant cluster (total brain volume consisted of 153138 voxels); <sup>a</sup>Brain coordinates defined by the Montreal Neurological Institute (MNI), based on which the location of (de)activated clusters of voxels can be identified. MNI coordinates represent the location of the maximum intensity voxel; <sup>b</sup>Brain areas indicating activation in working memory trials as compared to control trials; <sup>c</sup>Brain areas indicating deactivation in working memory trials as compared to control trials.

Load difference contrast

Although the percentage of correct trials was higher for low working memory load (70.7%) than for high working memory load (66.0%; p < 0.01), analysis on the load difference contrast revealed no significant differences in brain activation between high and low working memory load (all p > 0.05). Therefore, this contrast was not further examined.

Gross motor skills and cardiovascular fitness

The results regarding gross motor skills and cardiovascular fitness revealed no significant relations of gross motor skills and cardiovascular fitness with visuospatial working memory-related brain activation (p > 0.05), indicating that both gross motor skills and cardiovascular fitness were not related to visuospatial working memory-related brain activation.
Discussion
The main aim of this study was to investigate relations of gross motor skills and cardiovascular fitness with visuospatial working memory-related brain activation in 8-10-year-old typically developing children. Visuospatial working memory-related brain activation was found in a neural network involving the angular gyrus (right hemisphere), the superior parietal cortex (bilateral), and the thalamus (bilateral). In addition, visuospatial working memory-related deactivation was found in the inferior and middle temporal gyri (bilateral). Although there were significant relations of gross motor skills and cardiovascular fitness with behavioral visuospatial working memory performance, gross motor skills and cardiovascular fitness were not associated with visuospatial working memory-related brain activation. Therefore, we could not confirm the hypothesis that functional brain mechanisms underlie the relations of gross motor skills and cardiovascular fitness with visuospatial working memory in 8-10-year-old children.

Visuospatial working memory-related brain activation
The brain regions that were found to be involved in visuospatial working memory are partly in accordance with brain regions found to be associated with visuospatial working memory in the literature. As summarized in a meta-analysis by Wager & Smith (2003), spatial storage tasks most frequently activate the superior parietal cortex, which was also found in our study. Furthermore, it has been shown that during visuospatial working memory tasks, the prefrontal cortex is interconnected with posterior parietal and temporal cortices, and with subcortical areas such as the thalamus (van Ewijk et al., 2015; Klingberg et al., 2002; Selemon & Goldman-Rakic, 2011), an area where we found visuospatial working memory-related activation as well. However, contradicting these previous findings, we found deactivation in the inferior and middle temporal gyrus and there was no difference in activation in prefrontal areas. It is difficult to explain these findings, as previous studies in children have consistently found increased activation in working memory trials as compared to control trials in temporal and prefrontal areas, based on which it is expected that working memory trials require more brain activation in these areas than control trials (e.g. van Ewijk et al., 2015; Klingberg et al., 2002).

There were no differences in brain activation between the high working memory load trials and the low working memory load trials, although children performed significantly better on low working memory load trials than on high working memory load trials. This was unexpected based on a previous study by van Ewijk et al. (2015) in which the same task was used. In their study, participants also performed better on low working memory load trials (75% correct) than on high working memory load trials (80% correct), but this was related to differences in brain activation in frontal, temporal, occipital and parietal regions. In the current study, participants performed worse on both high working memory load trials (66% correct) and low working memory load trials (71% correct) than the participants in the study by van Ewijk et al. (2015). Possibly, performance levels of the children in the current study on both high and low working memory load trials were not stable enough and therefore, there were no differences in brain activity between the high and low working memory load trials. Furthermore, the power in our study might have been too low to detect differences in brain activation, as compared to the study by van Ewijk et al. (2015) who included a much larger sample (n = 212).
Relations with gross motor skills and cardiovascular fitness

Neither gross motor skills nor cardiovascular fitness was related to the neural network supporting visuospatial working memory. Although both gross motor skills and cardiovascular fitness were significantly related to behavioral visuospatial working memory performance, we could not confirm the hypothesis that the neural network supporting visuospatial working memory underlies the relations of gross motor skills and cardiovascular fitness with visuospatial working memory. Our results are contradictory to the studies by Chaddock et al. (2012) and Voss et al. (2011), where associations between cardiovascular fitness and brain activation were found. In those studies, cardiovascular fitness was measured by estimating the VO2 max of children during a running test on a treadmill, whereas in the current study, cardiovascular fitness was assessed with the 20-m SRT. The estimation of the VO2 max in the studies by Chaddock et al. (2012) and Voss et al. (2011) was possibly more sensitive in measuring differences in cardiovascular fitness level than the 20-m SRT, which might have been a reason that we did not find associations between cardiovascular fitness and visuospatial working memory-related brain activity. Further, it should be noted that Chaddock et al. (2012) and Voss et al. (2011) measured brain activation during an inhibition task. A review by Haapala (2013) revealed that physical fitness and gross motor skills were differently related to specific cognitive functions. Possibly then, relations of cardiovascular fitness and gross motor skills with executive functioning related brain activity differ depending on the specific executive function being examined (i.e. inhibition, working memory, or cognitive flexibility). For future studies, it would be interesting to compare relations of gross motor skills and cardiovascular fitness with brain activity patterns underlying the different executive functions.

Strengths, limitations, and future directions

Strengths of this study include the large sample of typically developing children that was examined. This enabled us to get a detailed and reliable insight into brain activation during a visuospatial working memory task. Additionally, by including both gross motor skills and cardiovascular fitness it was possible to examine underlying brain mechanisms in the relations of gross motor skills and cardiovascular fitness with visuospatial working memory performance.

However, this study also showed that it is difficult to perform an fMRI study in young children, as participating children had difficulties with laying still throughout the scanning protocol. The total acquisition protocol had a total scan time of approximately one hour. The active state scan used for this study was the last part of the protocol, which explains why it was difficult for children to remain still, resulting in movement artefacts in the fMRI data. By applying extensive preprocessing steps, we tried to minimize the effect of these movement artefacts. Still, subtle changes in brain activity related to gross motor skills and/or cardiovascular fitness might have been filtered out by the preprocessing steps that we applied.

Furthermore, our results might be limited by the way that we represented children’s gross motor skills. The total factor score that we calculated explained only 48.2% of the variance of the gross motor skill scores. Therefore, we could have missed aspects of gross motor skills that might have been related to visuospatial working memory-related brain activity. Furthermore, the review
by van der Fels et al. (2015) showed that the strongest relations are found between complex
motor skills (e.g. fine motor skills or bilateral body coordination) and executive functions. At
the neuropsychological level, it can be argued that these complex motor skills require greater
involvement of executive functions than relatively simple motor skills (Best, 2010; van der Fels et
al., 2015). This implies that complex forms of motor skills share more overlapping neural networks
with executive functions than gross motor skills. For future studies, it would be interesting to use
tests that measure more complex forms of motor skills than the BOT-2 and KTK do.

The results of our study suggest that the effects of physical activity on visuospatial working
memory and underlying brain functioning are not brought about via changes in gross motor skills
or cardiovascular fitness per se. Yet, several studies have shown that physical activity interventions
can result in changes in brain structure and function, going hand in hand with improvements
in cognitive functioning (e.g. Davis et al., 2011a; Hillman et al., 2014; Krafft et al., 2014; also see
Gunnell et al., 2019). Following this, it can be argued that physical activity has more direct effects
on the brain (either by neurophysiological mechanisms or by the cognitive demands inherent
in the physical activity), instead of indirect effects via changes in cardiovascular fitness or motor
skills. It is of interest for future research to examine the effects of physical activity interventions on
visuospatial working memory-related brain activity as well, to see whether this hypothesis holds.

Furthermore, the current study examined whether functional brain activity patterns measured
with the BOLD signal underlie the relations of gross motor skills and cardiovascular fitness
with visuospatial working memory. We did not find support for this hypothesis. It is therefore
questionable whether brain activation patterns measured with the BOLD signal are the best way
to investigate the mechanisms underlying the relations of gross motor skills and cardiovascular
fitness with visuospatial working memory. Possibly, imaging techniques that measure structural
connectivity of white matter or functional connectivity may give a better insight into the neural
networks underlying the relations of gross motor skills and cardiovascular fitness with visuospatial
working memory.

**Conclusion**

In conclusion, regions in the parietal and temporal cortices and the thalamus were found to be
important for visuospatial working memory performance in 8-10-year-old children. Activation
patterns did not differ between high and low working memory load trials. Although gross motor
skills and cardiovascular fitness were both related to visuospatial working memory performance,
they were not related to visuospatial working memory-related brain activation. Based on these
results, we could not confirm the hypothesis that brain activation patterns underlie the relation
of gross motor skills and cardiovascular fitness with visuospatial working memory performance.
Therefore, our results suggest that effects of physical activity on brain functioning do not
necessarily need to go via changes in gross motor skills and/or cardiovascular fitness, but further
research is needed to investigate the effects of physical activity on visuospatial working memory-
related brain functioning.
Furthermore, our results suggest that brain activation patterns as measured with the BOLD signal may not be the best way to examine the mechanism underlying the relations of gross motor skills and cardiovascular fitness with visuospatial working memory. Further research should use imaging techniques that measure structural and functional connectivity to further investigate the mechanisms underlying the relations of gross motor skills and cardiovascular fitness with visuospatial working memory.
Appendix 4.1

Inclusion Table showing the number of children per grade/sex/scan site that were planned to be scanned, that were actually scanned and that were used for analyses

<table>
<thead>
<tr>
<th></th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Boys</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Planned</td>
<td>23</td>
<td>22</td>
<td>45</td>
</tr>
<tr>
<td>Scanned</td>
<td>24</td>
<td>21</td>
<td>45</td>
</tr>
<tr>
<td>Analyzed</td>
<td>20</td>
<td>19</td>
<td>39</td>
</tr>
<tr>
<td>Amsterdam planned</td>
<td>12</td>
<td>10</td>
<td>22</td>
</tr>
<tr>
<td>Amsterdam scanned</td>
<td>13</td>
<td>10</td>
<td>23</td>
</tr>
<tr>
<td>Amsterdam analyzed</td>
<td>11</td>
<td>10</td>
<td>21</td>
</tr>
<tr>
<td>Groningen planned</td>
<td>11</td>
<td>12</td>
<td>23</td>
</tr>
<tr>
<td>Groningen scanned</td>
<td>11</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>Groningen analyzed</td>
<td>9</td>
<td>9</td>
<td>18</td>
</tr>
</tbody>
</table>

|                |         |         |       |
| **Girls**      |         |         |       |
| Planned        | 22      | 23      | 45    |
| Scanned        | 22      | 25      | 47    |
| Analyzed       | 18      | 23      | 41    |
| Amsterdam planned | 12  | 11      | 23    |
| Amsterdam scanned | 12  | 12      | 24    |
| Amsterdam analyzed | 11 | 12      | 23    |
| Groningen planned | 10  | 12      | 22    |
| Groningen scanned | 10  | 13      | 23    |
| Groningen analyzed | 7   | 11      | 18    |

|                |         |         |       |
| **Total**      |         |         |       |
| Planned        | 45      | 45      | 90    |
| Scanned        | 46      | 46      | 92    |
| Analyzed       | 38      | 42      | 80    |
| Amsterdam planned | 24  | 21      | 45    |
| Amsterdam scanned | 25  | 22      | 47    |
| Amsterdam analyzed | 22 | 22      | 44    |
| Groningen planned | 21  | 24      | 45    |
| Groningen scanned | 21  | 24      | 45    |
| Groningen analyzed | 16  | 20      | 36    |
Appendix 4.2

Results of the contribution of the covariates to visuospatial working memory-related brain activation

Age, sex and SES did not contribute significantly to visuospatial working memory-related brain activation ($p > 0.05$). However, there was a significant difference between brain activation of children scanned in Amsterdam and those who were scanned in Groningen (Figure 4.2.1), located bilateral in superior parietal gyrus and the anterior prefrontal gyrus, bilateral in the premotor and supplementary motor cortex, and left in the angular gyrus and the inferior frontal gyrus. Scan site was therefore included as covariate in all subsequent analyses.

Figure 4.2.1. Difference in brain activation between children scanned in Amsterdam and in Groningen. Sagittal (upper), coronal (middle) and axial view (lower). Threshold is set at $p < 0.001$ (uncorrected). Warm colours indicate activation in children scanned in Amsterdam as compared children scanned in Groningen. Cool colours indicate deactivation in children scanned in Amsterdam as compared to children scanned in Groningen. MNI coordinates ($x$, $y$, $z$) represent the location of the maximum intensity voxel.
Table 4.2.1. Significant clusters of brain activation associated with scan site for the working memory contrast.

<table>
<thead>
<tr>
<th>Cluster #</th>
<th>Anatomical label(s)</th>
<th>Hemisphere</th>
<th>N voxels</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Superior parietal gyrus, angular gyrus</td>
<td>Left</td>
<td>739</td>
<td>-20</td>
<td>-70</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>Superior parietal gyrus</td>
<td>Right</td>
<td>1907</td>
<td>16</td>
<td>-76</td>
<td>54</td>
</tr>
<tr>
<td>3</td>
<td>Premotor cortex, supplementary motor cortex</td>
<td>Right</td>
<td>725</td>
<td>32</td>
<td>2</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>Premotor cortex, supplementary motor cortex</td>
<td>Left</td>
<td>601</td>
<td>-28</td>
<td>-10</td>
<td>52</td>
</tr>
<tr>
<td>5</td>
<td>Inferior frontal gyrus and anterior frontal gyrus</td>
<td>Left</td>
<td>829</td>
<td>-50</td>
<td>38</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>Anterior prefrontal gyrus</td>
<td>Right</td>
<td>1429</td>
<td>8</td>
<td>58</td>
<td>10</td>
</tr>
</tbody>
</table>

Note. Activation for the working memory contrast that survived the cluster level significance of $p < 0.05$, family wise error (FWE) corrected, initial threshold $p < 0.001$; N voxels: number of voxels involved in the significant cluster (total brain volume consisted of 153138 voxels); aBrain coordinates defined by the Montreal Neurological Institute (MNI), based on which the location of (de)activated clusters of voxels can be identified. MNI coordinates represent the location of the maximum intensity voxel; bBrain areas indicating deactivation in children scanned in Amsterdam as compared to children scanned in Groningen; cBrain areas indicating activation in children scanned in Amsterdam as compared to children scanned in Groningen.