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EMPIRICAL ARTICLE

CHILD DEVELOPMENT

Resting state networks mediate the association between both cardiovascular fitness and gross motor skills with neurocognitive functioning

Anna Meijer[1] | **Marsh Königs**[2] | **Petra J.W. Pouwels**[3] | **Joanne Smith**[4] |
Chris Visscher[4] | **Roel J. Bosker**[5] | **Esther Hartman**[4] | **Jaap Oosterlaan**[1,2]

[1]Clinical Neuropsychology Section, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands

[2]Emma Children's Hospital, Amsterdam UMC, Emma Neuroscience Group, Department of Pediatrics, Amsterdam Reproduction & Development, University of Amsterdam, Amsterdam, The Netherlands

[3]Department of Radiology and Nuclear Medicine, Amsterdam UMC, Vrije Universiteit, Amsterdam Neuroscience, Amsterdam, The Netherlands

[4]Center for Human Movement Sciences, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

[5]Groningen Institute for Educational Research, University of Groningen, Groningen, The Netherlands

Correspondence
Anna Meijer, Clinical Neuropsychology Section, Vrije Universiteit Amsterdam MF-B535, Van der Boechorststraat 7-9, 1081 HV Amsterdam, The Netherlands.
Email: a.meijer@fsw.leidenuniv.nl

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Abstract

Recent evidence suggests that cardiovascular fitness and gross motor skill performance are related to neurocognitive functioning by influencing brain structure and functioning. This study investigates the role of resting-state networks (RSNs) in the relation of cardiovascular fitness and gross motor skills with neurocognitive functioning in healthy 8- to 11-year-old children (n = 90, 45 girls, 10% migration background). Cardiovascular fitness and gross motor skills were related to brain activity in RSNs. Furthermore, brain activity in RSNs mediated the relation of both cardiovascular fitness (Frontoparietal network and Somatomotor network) and gross motor skills (Somatomotor network) with neurocognitive functioning. The results indicate that brain functioning may contribute to the relation between both cardiovascular fitness and gross motor skills with neurocognitive functioning.

KEYWORDS
brain functioning, cognition, Children, physical fitness, resting-state fMRI

INTRODUCTION

Engagement in physical activity is thought to stimulate neurocognitive functioning in children (de Greeff et al., 2018; Singh et al., 2018), possibly through changes in brain structure and function. Recent neuroimaging studies have shown that physical activity in children indeed can impact both structural brain properties and brain function (Meijer, Königs, Vermeulen et al., 2020; Valkenborghs et al., 2019). Despite an increasing number of studies reporting about physical activity-induced effects on neurocognitive functioning and brain properties

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Abbreviations: FMRIB, functional MRI of the brain; NOI, networks of interest; ROI, regions of interest; RSNs, resting-state networks; SES, sex, age, socio-economic status; TFCE, threshold-free cluster enhancement; WISC-III, wechsler intelligence scale for children III.

in children, the underlying mechanisms responsible for these effects are not clear.

Physical activity exposure is considered as an important determinant of cardiovascular fitness levels and motor skill development during childhood and adolescence (Aires et al., 2010; Stodden et al., 2008) that play an important role in both structural brain properties and brain function. Cardiovascular fitness is defined as the ability of the circulatory and respiratory systems to supply oxygen during sustained physical activity (Corbin et al., 2000) and is considerably influenced by exposure to long-term physical activity at moderate to high intensity (Rowland, 2007). Such long-term physical activity is associated with increased release of neurotrophic factors (e.g., brain-derived neurotrophic factor and neural growth factor), blood vessel formation, and neurogenesis (Colcombe et al., 2006; Dishman et al., 2006). These neural responses are known to promote plasticity in the structure and function of brain areas that support neurocognitive functioning (Vaynman & Gomez-Pinilla, 2006). An alternative or complementary pathway for physical activity-induced changes in the brain is represented by gross motor skill development (Voss, 2016). Gross motor skills refer to the proficiency in fundamental movement skills (e.g., throwing, catching, running) which require control over large body muscles involved in balance, limb, and trunk movements, but simultaneously tax a number of neurocognitive abilities such as information processing abilities and concentration. This combination is thought to enhance axonal arborization in white matter structures (Jones et al., 1999) as well as enhanced functional connectivity between brain regions involved in both motor and neurocognitive functioning (Diamond, 2000).

The existing literature supports the idea that both cardiovascular fitness and gross motor skills may relate to structural brain properties in children (Chaddock-Heyman et al., 2018; Erickson et al., 2014; Schaeffer et al., 2014; Valkenborghs et al., 2019) as well as brain function during neurocognitive tasks (task-based functional MRI; Meijer, Königs, Vermeulen et al., 2020). However, the relation of both cardiovascular fitness and gross motor skill with brain function during rest in children remains largely unexplored. Resting-state brain activity reflects the organization of functional brain activity during rest. Co-activated brain regions have been reliably identified as resting-state networks (RSNs) in both adults and children (Gordon et al., 2011; Thomason et al., 2011; Yeo et al., 2011), while RSNs in children are more diffuse than in adults and become more specialized with maturation (Jolles et al., 2010; Stevens et al., 2009). RSNs have shown to be related to neurocognitive functioning in both adults and children (Cabral et al., 2017; Laird et al., 2011; Rubia, 2013) and have shown a powerful model of brain function with proven sensitivity to developmental changes (Fan et al., 2021). Taken together, RSNs may represent an important target of the investigation to understand how physical activity promotes neurocognitive functioning.

Only a few studies have investigated the relation between cardiovascular fitness and brain activity in RSNs, while the relation between motor skills and brain activity in RSNs received hardly any attention. Cross-sectional studies in adults have shown that higher levels of cardiovascular fitness are related to increased activity in specific RSNs (Boraxbekk et al., 2016; Voss et al., 2010) and that brain activity in specific RSNs mediates the association between cardiovascular fitness and executive function performance in older adults (Voss et al., 2010). There is one intervention study that indicated beneficial effects of aerobic exercise on brain activity in RSNs in children with obesity (Krafft et al., 2014), but the relation with neurocognitive functioning was not studied. The few existing studies that focused on motor skills and brain activity in RSNs were all performed in adults and showed that motor learning tasks (e.g., finger sequence task, whole-body balance task) induced increased activity in motor regions (Ma et al., 2011; Vahdat et al., 2011) and brain activity in RSNs (Ma et al., 2011; Taubert et al., 2011). These studies did not investigate the relation with neurocognitive functioning. Although the available literature suggests that changes in brain activity in RSNs may mediate the relation of cardiovascular fitness and motor skills with neurocognitive functioning, there is no evidence available to support this link in typically developing children.

The present study aims to investigate the relations of both cardiovascular fitness and gross motor skills with (1) neurocognitive functioning, (2) RSNs with relevance for neurocognitive functioning, and (3) whether brain activity in RSNs mediates the relation of both cardiovascular fitness and gross motor skills with neurocognitive functioning. Based on the existing literature, we hypothesized that higher levels of cardiovascular fitness and better gross motor skills would be associated with enhanced neurocognitive functioning. Furthermore, we expected that brain activity in RSNs would significantly relate to neurocognitive functioning and that resting-state brain activity would significantly mediate the relation of both cardiovascular fitness and gross motor skills with neurocognitive functioning.

METHOD

Participants

Children were recruited from 22 primary schools in the Netherlands. A sample of 93 children was included in the current study (mean age = 9.13, SD = .62, 50.5% girls). Parents or guardians gave written consent for the participation of their children. Ten percent of the children had a migration background (defined as someone who has at least one parent born abroad), which approaches to recent figures observed in the Dutch pediatric population (~18%; CBS, 2021). Origins were Middle East (55%), Europe (35%), Netherlands Antilles (10%). Inclusion was guided by an inclusion protocol in order to balance the representation of sex, school grade (grade 3 or 4), and scanning site (Amsterdam and Groningen, the Netherlands) in the study sample (see Table A1 of the Appendix for the inclusion protocol).

Measures

Cardiovascular fitness

Cardiovascular fitness was assessed with the 20m Shuttle Run Test (20m SRT; Adam et al., 1987). During this test, children run back and forth on a 20m track, and need to reach the other side of the track at or before an auditory signal. The timing of the auditory signal was initially set at a required average speed of 8 km/h, and was increased each minute by 0.5 km/h. The test was terminated when a child failed to reach the required distance in time on two consecutive crossings of the track. From the last trajectory that was completed, the maximal oxygen uptake (VO2max in ml $kg^{-1}min^{-1}$) was estimated by using the following formula: $31.025 + (3.238 \times \text{velocity}) - (3.248 \times \text{age}) + (0.1536 \times \text{age} \times \text{velocity}$; Leger et al., 1988).

Gross motor skills

Gross motor skills were assessed using three subtests (Jumping Sideways, Moving Sideways, and Backwards Balancing) of the Körper Koordinationstest für Kinder (KTK; Kiphard & Schilling, 2007). Additionally, one item of the Bruininks–Oseretsky Test of Motor Proficiency, Second Edition (BOT-2) was used to include a measure for ball skills (Bruininks, 2005). Both motor skill test batteries have shown to be reliable and valid for primary school children (Bruininks, 2005; Deitz et al., 2007; Kiphard & Schilling, 2007).

Neurocognitive functioning measures

A set of neurocognitive functioning measures tapping into core domains of executive function (i.e., working memory, motor inhibition, and interference control) and lower-level neurocognitive functions (information processing and attention) was used (Table1). In addition, full-scale IQ was estimated using a two-subtest short form (Information and Block Design) of the Wechsler Intelligence Scale for Children III (WISC-III; Wechsler, 1991). All measures are comprehensively described in previous work (Meijer et al., 2020). Additional information was collected by parent questionnaires to assess demographic information (sex, age, socio-economic status [SES]), and information on participation in sports. SES was defined as the average level of parental education ranging from 0 (no education) to 7 (post-doctoral education; Statistics Netherlands, 2006).

MRI acquisition

MRI was performed on two 3 Tesla whole-body units, a GE Discovery 3T (location Amsterdam UMC, VU Medical Center Amsterdam) and a Philips Intera 3T (location University Medical Center Groningen), using a 32-channel head-coil. The MRI scanning protocol was part of a larger protocol which comprises structural and functional sequences in the following order: T1, DTI, resting-state fMRI, and active-state fMRI. Resting-state data were acquired using a T2*-weighted echo-planar functional scan with 202 volumes, 38 ascending slices with slice thickness of 3 and 0.3 mm gap, matrix size of 64 × 64, TR = 2000 ms, TE = 35 ms, flip angle of 80 degrees and field of view = 211 mm. All scans were acquired with reversed phase-encode blips which resulted in pairs of images with distortions presenting in opposite directions. From these pairs, the susceptibility-induced off-resonance field was estimated which was used to correct the susceptibility-induced distortions in the data (Smith et al., 2004).

Preprocessing

Behavioral data

Preprocessing steps and statistical analysis of the behavioral data were performed using IBM SPSS Statistics version 25.0 (SPSS IBM) and R for Statistical Computing (R Foundation for Statistical Computing). Outliers ($z \leq -3.29$ or ≥ 3.29) were winsorized, that is replaced with a value one unit greater than the neighboring non-outlier value. All neurocognitive functioning measures were recoded with higher scores indicating better performance. To reduce the number of measures and the potential risk of Type 1 errors and to enhance their reliability, principal component analyses were performed on all raw gross motor skills measures and neurocognitive functioning measures derived from the total group of children included in the cluster-randomized controlled trial “Learning by Moving” ($n = 814$). Data were subjected to principal component analysis with varimax rotation using the psych-package in R (Revelle, 2018 psych). For more information of this procedure and results for the total sample see Meijer et al. (2020).

TABLE 1 Description and operationalization of neurocognitive functioning measures

	Task	Measures	Description	Dependent variable
ANT	Computerized task in which target stimuli consisting of an arrow pointing left or right are presented on a computer screen. Children are instructed to respond as quickly as possible to the direction of a target stimulus by pressing the corresponding button. The ex-Gaussian model was used to extract the influence of extreme slow responses (tau) on information processing speed (Fan et al., 2002; Lacouture & Cousineau, 2008; Rueda et al., 2004).	Information processing	The speed of responding to target appearance	Mean reaction time (ms) on neutral trials.
		Tau	Lapses of attention	The average of the exponential component of the fitted ex-Gaussian curve, reflecting the influence of extremely slow responses (lapses of attention) on information processing.
		Alerting attention	The speed of achieving an alert state	The difference in mean reaction time (ms) between central cue trials and no cue trials.
			The accuracy of achieving an alert state	The difference in percentage of correct responses on central cue trials and no cue trials.
		Spatial attention	The speed of spatially orienting to information	The difference in mean reaction time (ms) between spatial cue trials and central cue trials.
			The accuracy of spatially orienting to information	The difference in the percentage of correct responses on central cue trials and spatial cue trials.
		Interference control	The speed of suppressing irrelevant information	The difference in mean reaction time (ms) between incongruent trials and congruent trials.
			The accuracy of suppressing irrelevant information	The difference in the percentage of correct responses on incongruent trials and congruent trials.
DS	Children are required to repeat a sequence of numbers presented auditorily in the order of presentation (forward condition) or reversed order (backward condition (WISC-III; Wechsler, 1991))	Verbal short-term memory	The ability to hold verbal information in short-term memory	The product of the number of correct responses and the highest span reached in the forward condition (Kessels et al., 2000).
		Verbal working memory	The ability to manipulate verbal information in working memory	The product of the number of correct responses and the highest span reached in the backward condition (Kessels et al., 2000).
GT	A sequence of yellow dots is presented on a four-by-four digital grid. Children are required to repeat the sequence in the order of presentation (forward) or reversed order (backward) by clicking on the relevant locations in the grid (Nutley et al., 2009).	Visuospatial short-term memory	The ability to hold visuospatial information in short-term memory	The product of the number of correct responses and the highest span reached in the forward condition (Kessels et al., 2000).
		Visuospatial working memory	The ability to manipulate visuospatial information in working memory	The product of the number of correct responses and the highest span reached in the backward condition (Kessels et al., 2000).

(Continues)

TABLE 1 (Continued)

	Task	Measures	Description	Dependent variable
SST	A computerized task involved Go trials and Stop trials. Go trials consist of an airplane either pointing to the right or left side. Stop trials are identical to Go trials but with a stop signal superimposed on the airplane. Children are instructed to respond as quickly as possible to Go trials by pressing the corresponding button, and to inhibit the motor response when the stop signal is presented (Logan, 1994).	Motor inhibition efficiency	The latency of an inhibitory process	The mean reaction time (ms) calculated for correct responses on go trials subtracted by the average stop signal delay time (ms).

Abbreviations: ANT, attention network test; DS, digit span; GT, grid task; SST, stop signal.

Resting-state fMRI

All processing of MRI images was performed using the Functional MRI of the Brain Software Library version 5.0.11 (FMRIB FSL). The following steps were undertaken to reduce the influence of noise and motion on the fMRI data. In order to correct for motion of the head during MRI acquisition, the acquired volumes over time were realigned to the first volume with FSL MCFLIRT (Jenkinson et al., 2002) followed by a correction for the susceptibility distortion of the subject's head (FSL TOPUP; Andersson & Sotiropoulos, 2016; Smith et al., 2004). The data were then denoised by removing artefactual activation components in the data (e.g., caused by motion; ICA-AROMA Pruim et al., 2015). To this end, automatic dimensionality estimation was performed using FSL MELODIC (including spatial filtering at 5 mm and brain extraction), from which every resulting component was cross-correlated with 17 well-described RSNs (RSNs) from the atlas by Yeo et al. (2011) in subject space. Components with lower correlation values than .3 were filtered from the data. Lastly, nuisance regression was performed by correcting data using the general linear model for activation measured in white matter and cerebrospinal fluid. The motion-corrected, denoised, and nuisance regressed data were then again subjected to automatic component estimation, estimating 20 activation components of interest at the individual level.

In the absence of an open-source atlas for RSNs in children, while also expecting developmental effects on RSNs (Uddin et al., 2010), we constructed a study-specific atlas of RSNs in a representative subsample of the total study sample (based on age, sex, and scanning site $n = 10$, 11%). We performed group-based automatic dimensionality estimation in this subsample to derive activation components at the group level. To identify the networks of interest (NOI) in this study, these components were then cross-correlated with seven well-known major RSNs in an atlas based on adults by Yeo et al. (2011). Components that correlated ($r > .3$) with one of the seven networks in the atlas were selected as NOI in our RSN atlas. These NOIs were then used to generate subject-specific versions of the NOIs and associated timeseries in each subject in the total study sample using dual regression (Beckmann et al., 2009), which were used for statistical analysis.

Procedure

The current MRI study is part of a larger randomized controlled trial ("Learning by Moving," registered in the Netherlands Trial register under NTR5341) in which a total of 891 children aged between 8 and 12 years old participated (mean age = 9.2 ± 0.7 years old; De Bruijn et al., 2020; Meijer et al., 2020; van der Fels et al., 2020). This study describes the results in a balanced subsample of 93 children for which MRI was performed. All described assessments were collected within a period of 2 weeks. The 20-m SRT and gross motor skills were assessed during two physical education lessons and were administered by trained test leaders under the guidance of physical education teachers. The neurocognitive assessment was individually executed during two school days by trained examiners using standardized protocols. MRI scanning took place at the Amsterdam UMC, location VU University Medical Centre in Amsterdam ($n = 48$), or at the University Medical Center in Groningen ($n = 44$). Prior to the MRI scan, children were made familiar with the MRI procedure using a mock scanner. During the resting-state functional scans, children were instructed to close their eyes and lie still without falling asleep. Head movements were minimized by inserting small pillows between the head coil and the child's head. Children received a small present and a copy of their structural T1-weighted scan. This study was approved by the ethical board of the Vrije Universiteit Amsterdam (Faculty of Behavioural and Movement Sciences, approval number VCWE-S-15-00197) and was registered in the Netherlands Trial Register (NTR5341).

Statistical analysis

Statistical analysis on behavioral data was performed in IBM SPSS Statistics version 25.0 (SPSS IBM). First, we investigated the associations between cardiovascular fitness and the neurocognitive functioning components, and gross motor skills and the neurocognitive functioning components. These relations were examined using linear regression analyses in which the neurocognitive functioning components (resulting from the principal component analysis) were used as dependent variables and either cardiovascular fitness or gross motor skills were included as a predictor. Only the neurocognitive components that were significantly related to cardiovascular fitness and gross motor skills were selected for subsequent analysis.

Second, we performed whole-brain spatial regressions between the significant neurocognitive functioning components and the NOIs using one-sided permutation testing in FSL Randomise (Winkler et al., 2014). The set of clusters where a significant relation between resting-state brain activity and a neurocognitive component score was found, was denoted as regions of interest (ROI) and selected for subsequent analyses.

Third, we investigated the relations between cardiovascular fitness and gross motor skills with brain activity in NOIs that showed relevance for neurocognitive functioning. Therefore, we investigated the relation between cardiovascular fitness and gross motor skill measures and brain activity in the set of regions in each NOI with predetermined relations with neurocognitive functioning (the ROIs), by performing linear regression models. For significant clusters from this analysis, mean resting-state activity was extracted for mediation analysis.

Last, we investigated whether resting-state brain activity mediated the observed significant relations between cardiovascular fitness and the neurocognitive functioning components, and gross motor skills and the neurocognitive functioning components by using bootstrap mediation analysis (PROCESS SPSS macro; Hayes, 2017). We included cardiovascular fitness or gross motor skills as independent variables, ROIs that were related to cardiovascular fitness or gross motor skills as mediators and the selected neurocognitive component as dependent variables. Indirect effects were tested using 5000 bootstrap samples and bias-corrected bootstrap confidence intervals.

Before independent variables were added to regression models, demographic variables (Sex, Age, Grade [three or four], and SES) were initially included as covariates, after which only the significant covariates ($p < .05$) were included in the final model. Furthermore, to control for differences between scanning sites, Scanning Site was added as a covariate in all MRI models. For all spatial analyses on brain activity in RSNs, family-wise error correction using threshold-free cluster enhancement (TFCE) was applied to correct for multiple comparisons (Smith & Nichols, 2009). Significance testing was two-sided and the level of significance was set at .05.

RESULTS

Participants

Children were excluded if they did not attend the cardiovascular fitness measurement ($n = 1$) and in case of poor-quality MRI data (>3 mm translation, $n = 2$), leaving a total of 90 children for the analysis (Table 2). Children's head motion during scanning (frame displacement; Power et al., 2012) was correlated with BMI (r (90) = .36, $p < .001$) but was not significantly related to Sex, Age, Grade SES, cardiovascular fitness, or gross motor skills. Overweight and obesity were observed in 14% and 2% of the participants, respectively, which parallels recent figures observed in the Dutch pediatric population (Cole & Lobstein, 2012; Volksgezondheid en zorg, 2020).

Selection of networks of interest

First, we constructed the study-specific atlas by cross-correlation between group-based RSNs based on 11% of the baseline data ($n = 10$) and seven RSNs of the atlas of Yeo et al. (2011). The results revealed the following five RSNs in the data: (1) Visual Network, (2) Default Mode Network, (3) Frontoparietal Network, (4) Somatomotor Network, and (5) Dorsal Attention Network (See Figure A1, left panel, Appendix). These RSNs were selected as

TABLE 2 Sample characteristics

	Total sample (*n* = 90)
Number of Girls, *n* (%)	45 (50%)
Age in year, *M* (*SD*)	9.13 (.62)
BMI in kg/m^2, *M* (*SD*)	16.84 (2.26)
Normal weight, *n* (%)[a]	75 (84%)
Overweight, *n* (%)[a]	12 (14%)
Obesity, *n* (%)[a]	2 (2%)
IQ, *M* (*SD*)	101.13 (15.31)
SES, *M* (*SD*)[b]	4.60 (1.05)
Cardiovascular fitness (VO2max, ml·kg^{-1} min^{-1}), *M* (*SD*)	48.94 (4.41)
Gross motor skills (*SD*) [c]	.03 (.99)
Jumping sideways	50.39 (14.74)
Moving sideways	35.86 (9.12)
Backwards balancing	42.84 (13.93)
Ball skills	30.99 (5.00)
Frame displacement, *M* (*SD*)[d]	.25 (.31)

Abbreviations: BMI, body-mass index; *M*, mean; *SD*, standard deviation; SES, socio-economic status.

[a] According to the reference values by Cole & Lobstein, 2012.

[b] The average level of parental education ranged from 0 (no education) to 7 (post-doctoral education).

[c] *Z* scores derived from four motor skills subtests including: Jumping Sideways, Moving Sideways, Backwards Balancing and Ball Skills.

[d] Mean frame wise displacement for raw rs-fMRI data.

NOIs for further analysis. The five NOIs were then used to generate group-based NOIs in the total study sample (See Figure A1, right panel, Appendix).

Neurocognitive functioning measures

Principal component analysis of all the neurocognitive measures using data of the larger study group ($n = 814$) extracted a total of six components from the neurocognitive data, together explaining 70% of the total variance (see Appendix Table A2 for Eigenvalues and factor loadings). The neurocognitive functioning components were labeled as follows: (1) Information Processing and Control (information processing, lapses of attention, and motor inhibition), (2) Interference Control (speed of interference control and accuracy of interference control), (3) Attention Accuracy (accuracy of alerting attention and accuracy of spatial attention), (4) Visuospatial Working Memory (visuospatial working memory and visuospatial short-term memory), (5) Verbal Working Memory (verbal short-term memory and verbal working memory), and (6) Attention Efficiency (speed of alerting attention and speed of spatial attention).

Results of the analyses focusing on the associations of both cardiovascular fitness and gross motor skills with the neurocognitive functioning components are displayed in Table 3 (including an overview of significant covariates). The results revealed that both cardiovascular fitness and gross motor skills were significantly related to Information Processing and Control ($p = .006$, $p < .001$, respectively). No meaningful associations were found between cardiovascular fitness or gross motor skills and any of the other neurocognitive functioning components. Table A3 (Appendix) shows the results of the additional model linear regression analysis, assessing the relation between both cardiovascular fitness and gross motor skills and specific neurocognitive measures that build up the component Information Processing and Control. Higher cardiovascular fitness was significantly related to faster information processing ($p < .001$) and less lapses of attention ($p = .008$). Better performance for gross motor skills was significantly related to all neurocognitive measures within the component Information Processing and Control (faster information processing, $p < .001$; less lapses and attention, $p < .001$; and faster motor inhibition, $p = .002$).

Identification of ROIs

First, we determined the RSNs with relevance for the Information Processing and Control component. Brain activity in all five NOIs was significantly associated with Information Processing and Control. For brain activity in the Visual and Frontoparietal networks, results revealed significant negative associations with Information Processing and Control ($p < .05$). The Default Mode network was positively related to Information Processing and Control ($p < .05$). The Somatomotor network and the Dorsal Attention network had both positive and negative associations with Information Processing and Control ($p < .05$). Taken together, these analyses revealed seven sets of brain regions with relevance to neurocognitive functions (i.e., ROIs; see Figure 1 and Figure A2 of the Appendix) within the selected NOIs, including one ROI in the Visual network (negative), Default Mode network (positive), Frontoparietal network (negative) and two ROIs in both the Somatomotor network (positive and negative) and the Dorsal Attention network (positive and negative). These seven ROIs are displayed in Figure 1 (green and blue) in which the five NOIs (red clusters) are thresholded for visualization purposes. Please note that the analysis was performed whole-brain. Therefore, the ROIs could also manifest outside the visual representation of NOIs (i.e., outside the thresholded red clusters).

RSN ROIs

Subsequently, we investigated associations between both cardiovascular fitness and gross motor skills with brain activity within the seven RSN ROIs that were related to Information Processing and Control.

TABLE 3 Overview of results of linear regression analysis relating cardiovascular fitness and gross motor skills to neurocognitive functioning and spatial regressions relating RSN ROIs to cardiovascular fitness and gross motor skills

Neurocognitive functioning component	Cardiovascular fitness					Gross motor skills				
	Covariates[a]	*B* (*SD*)	95% CI	*p*-value	R^2	Covariates[a]	*B* (SD)	95% CI	*p*-value	R^2
Information processing and control	Grade	.644 (0.194)	.018 to 0.106	.006	.180	—	0.462 (0.097)	0.270 to 0.664	<.001	.206
Interference control		.029 (0.024)	−.019 to 0.077	.235	.016	—	0.115 (0.108)	−0.101 to 0.330	.293	.013
Attention accuracy	—	−.007 (0.022)	−.052 to 0.037	.747	.001	—	−0.064 (0.100)	−0.262 to 0.135	.526	.005
Visuospatial working memory	—	.044 (0.026)	−.008 to 0.096	.099	.031	—	0.221 (0.117)	−0.011 to 0.454	.062	.039
Verbal working memory	—	.017 (0.023)	−.029 to 0.063	.468	.074	SES	0.080 (0.101)	−0.121 to 0.282	.430	.075
Attention efficiency	SES	.033 (0.023)	−.012 to 0.077	.153	.023	—	0.106 (0.101)	−0.095 to 0.308	.297	.012
RSN ROI (Information Processing and Control)										
Visual network (negative)	Site, age	−.381 (.174)	−.728 to −.035	.032	.073	Site, age	−.920 (.858)	−2.625 to .785	.286	.034
Default Mode network (positive)	Site, age	.173 (.175)	−.176 to .522	.327	.101	Site, age	.815 (.845)	−.866 to 2.496	.338	.101
Frontoparietal network (negative)	Site, age	−.397 (.156)	−.707 to −.088	.012	.183	Site, age	−.624 (.775)	−2.164 to .917	.423	.128
Somatomotor network (positive)	Site	.328 (.156)	.017 to .639	.039	.059	Site	1.648 (.716)	.225 to 3.071	.024	.068
Somatomotor network (negative)	Site, age	−.266 (.166)	−.596 to .064	.112	.069	Site, age	−1.665 (.792)	−3.239 to −.092	.038	.088
Dorsal Attention network (positive)	Site	.125(.172)	−.217 to .466	.470	.196	Site	.673 (.790)	−.897 to 2.243	.397	.197
Dorsal Attention network (negative)	Site, age	−.867 (.547)	−1.955 to .221	.117	.117	Site, age	−2.671 (2.661)	−7.960 to 2.618	.319	.162

Abbreviation: SES, socioeconomic status.

[a] Covariates significantly related to the neurocognitive functioning component or the RSN ROI.

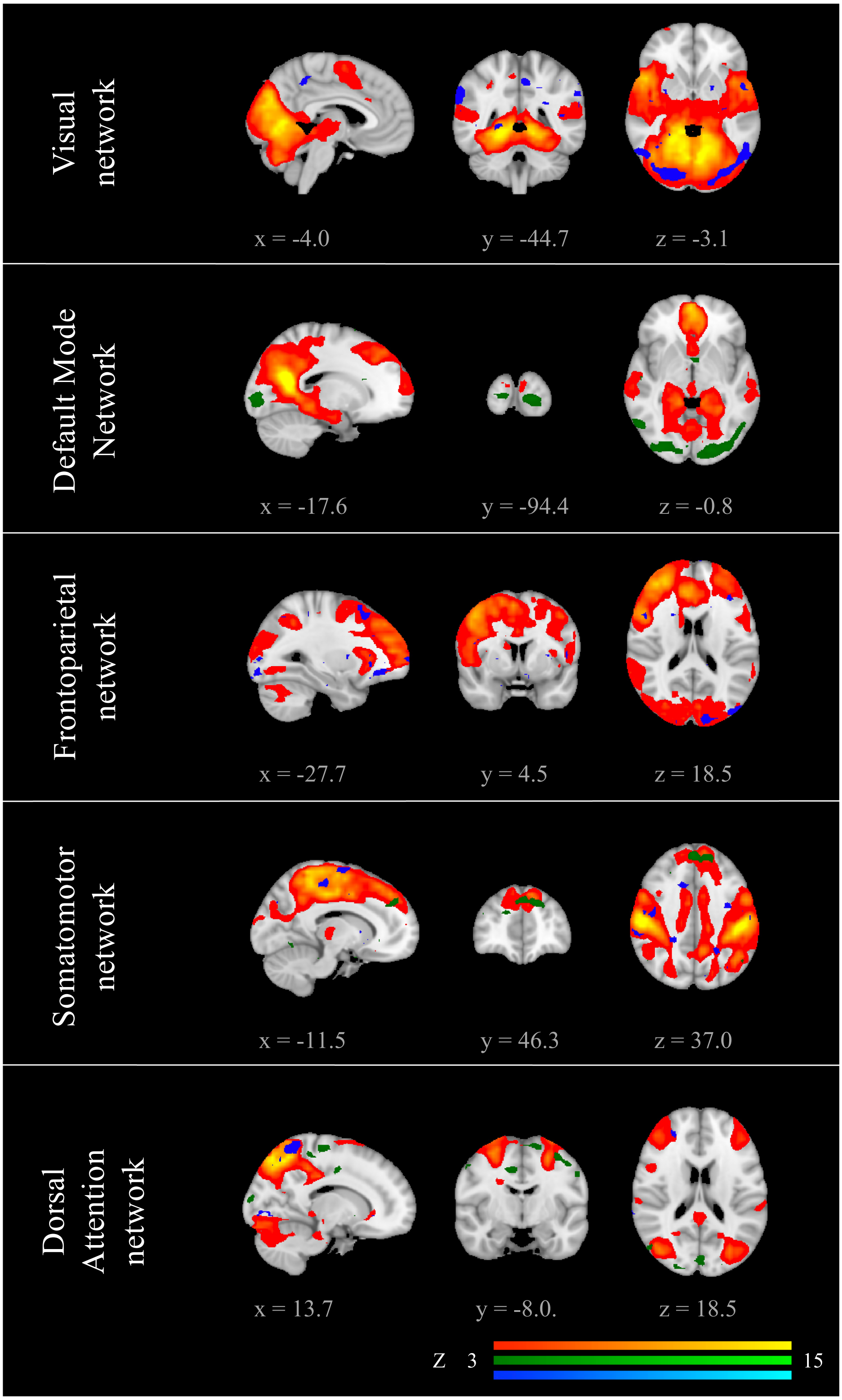

FIGURE 1 Sagittal, coronal, and axial slices of five RSNs of interest (NOIs in red) overlaid with regions of interest (ROIs) that are associated with the neurocognitive functioning component Information Processing and Control (positive relations in green, negative relations in blue). NOIs and ROIs overlaid onto the MNI152 standard brain. Images are shown in radiological convention. All networks are shown in color encoding using a $3 < z$-score < 15 threshold window

Results of the linear regression analyses are displayed in Table 3 (including an overview of significant covariates). The results revealed that higher cardiovascular fitness was significantly related to lower brain activity in the Visual network (negative) ROI ($R^2 = .073$, $p = .032$, Figure 2a), lower brain activity in the Frontoparietal network (negative) ROI (R^2 = .183, p = .012, Figure 2b) and higher brain activity in the Somatomotor network (positive) ROI (R^2 = .059, p = .032, Figure 2c). Likewise, gross motor skills were related to higher and lower brain activity in both Somatomotor network (positive and negative) ROIs (R^2 = .068, p = .024, Figure 2d R^2 = .088, p = .038, Figure 2e, respectively). No other meaningful associations were found between cardiovascular fitness or gross motor skills and any of the other RSN ROIs relating to Information Processing and Control.

Last, mediation models were used to investigate the potentially mediating role of brain activity in RSN ROIs in the relations between cardiovascular fitness and gross motor skills with neurocognitive functioning (i.e., Information Processing and Control). With regard to cardiovascular fitness, we investigated the mediating role of brain activity in the Visual network (negative) ROI, the Frontoparietal network (negative) ROI, and the Somatomotor network (positive) ROI within the relation between cardiovascular fitness and Information Processing and Control. The results reveal that brain activity in the Frontoparietal network (negative) ROI and Somatomotor network (positive) ROI both mediated the relation between cardiovascular fitness and Information Processing and control (Frontoparietal network [negative]: 95% CI = .002 to .040, Figure 3b; Somatomotor network (positive): 95% CI = .002 to .042, Figure 3c). There was no evidence for a mediating role of the Visual network (negative) in the relation between cardiovascular fitness and Information Processing and Control (95% confidence interval = −.0004 to .037; Figure 3a).

With regard to gross motor skills, we investigated the mediating role of the Somatomotor network ROIs (positive and negative) within the relation between gross motor skills and Information Processing and Control. It was found that brain activity in the Somotomotor network ROIs (positive and negative) mediated the relation between gross motor skills and Information Processing and control (positive: 95% CI = .010 to .177, Figure 3d; negative: 95% CI = .006 to .179, Figure 3e). The mediation models for Visual network (negative), the Frontoparietal network (negative), and the Somatomotor network (negative) were controlled for Scanning Site and Grade and the mediation model for Somatomotor network (positive) was controlled for Scanning Site.

DISCUSSION

The current study is the first to explore the potential impact of cardiovascular fitness and gross motor skills on RSNs in healthy children. More specifically, we examined the role of RSNs in the relation of both cardiovascular fitness and gross motor skills with neurocognitive functioning. The results indicated that cardiovascular fitness and gross motor skills were related to neurocognitive functioning and brain activity in RSNs with relevance for neurocognitive functioning. Furthermore, we found evidence that brain activity in RSNs mediates the relation of both cardiovascular fitness and gross motor skills with neurocognitive functioning. Taken together, our findings support that the relation between cardiovascular fitness and gross motor skills with neurocognitive functioning in healthy children may be facilitated by changes in RSN brain activity.

Our results indicated that higher levels of cardiovascular fitness and better gross motor skills were associated

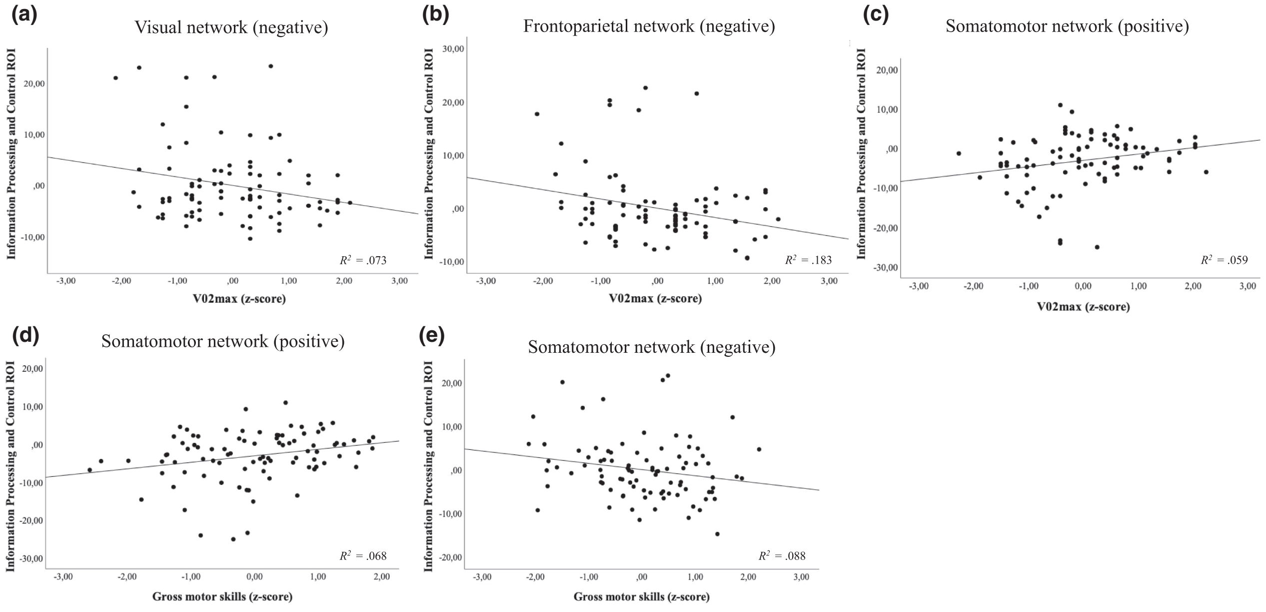

FIGURE 2 Significant associations between the Information Processing and Control ROIs and cardiovascular fitness (a–c) and gross motor kills (d, e)

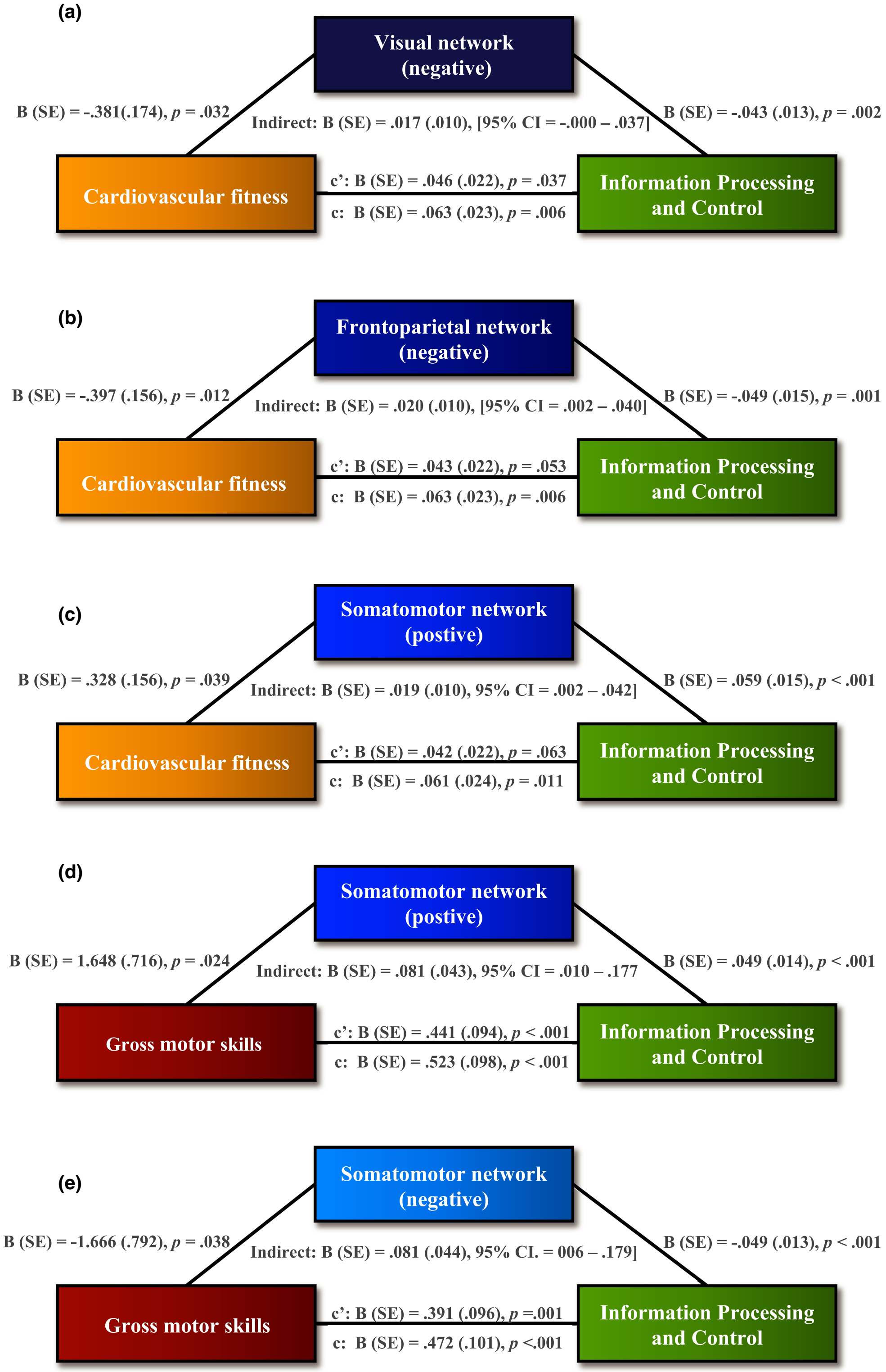

FIGURE 3 Mediation models testing the mediating role of RSNs (Visual network [a], Frontoparietal network [b], Somatomotor network [c–e]) in the relation between cardiovascular fitness or gross motor skills and Information Processing and Control. c' represents the direct effect and c the total effect of cardiovascular fitness or gross motor skills on Information Processing and Control

with better neurocognitive functioning as measured in terms of speed and variability of information processing and the efficiency of motor response inhibition (as assessed by the Information Processing and Control component). These results are largely in line with earlier studies in healthy children (de Greeff et al., 2018).

Our findings did not replicate the earlier observed relations between cardiovascular fitness, interference control and attention (de Greeff et al., 2018) and between gross motor skills and visuospatial working memory and attention (van der Fels et al., 2015). We argue that one compelling explanation for these discrepant findings between our and previous studies, may stem from the fact that the current study employed neurocognitive measures adjusted for processing speed such as contrast scores of interference control, attentional measures, and motor inhibition (more information about the variable construction could be found in Table 1). Thereby, our results may indicate that previously reported relations between physical activity and executive functioning may in fact be carried by information processing efficiency (for a more detailed description, see Meijer et al., 2020). We also explored the interrelatedness between the constructs of cardiovascular fitness and gross motor skill in their relation to neurocognitive functioning (Stodden et al., 2009). To that end, we reran our analysis now entering both cardiovascular fitness and gross motor skills as predictors of Information Processing and Control, which replicated only the reported the association between gross motor skills ($p < .001$). This result suggests, that the relation between gross motor skills and neurocognitive functioning is probably stronger than the relation between cardiovascular fitness and neurocognitive functioning. Taken together, the results support the idea that both cardiovascular fitness and gross motor skill development contribute to the relation with neurocognitive functioning with a presumably larger contribution for gross motor skills. Future research should further clarify the relative contributions of cardiovascular fitness and gross motor skill development to potential changes in neurocognitive functioning.

Five RSNs (Visual Network, Default Mode Network, Frontoparietal Network, Somatomotor Network and the Dorsal Attention Network) were associated with aspects of neurocognitive functioning relating to information processing, lapses of attention, and motor inhibition. Our results are largely in line with earlier studies carried out in adult populations (Andrews-Hanna et al., 2014; Reineberg et al., 2018; Vossel et al., 2014). These previous adult studies indicate that the Default Mode Network, Frontoparietal Network, and the Dorsal Attention Network may have an important role in neurocognitive functioning and in particular in attention, shifting, inhibition, and goal-directed behavior. Remarkably, our results suggest that in addition to these networks, the Visual Network and the Somatomotor Network also relate to information processing, lapses of attention, and motor inhibition. Taken together, our findings underline the relevance of RSNs for neurocognitive functioning in healthy children.

Our results concerning associations between both cardiovascular fitness and gross motor skills with RSNs are in line with earlier studies in adults or elderly that indicated associations between cardiovascular fitness or gross motor skills and brain activity in the Default Mode Network, Somatomotor Network, or Frontoparietal Network (Boraxbekk et al., 2016; Ma et al., 2011; Raichlen et al., 2016; Taubert et al., 2011; Vahdat et al., 2011; Voss et al., 2010; Voss et al., 2010). Moreover, our findings indicate that cardiovascular fitness and gross motor skills are both associated with the Somatomotor network, which is not surprising given its known involvement in motor function (Yeo et al., 2011). Interestingly, our results also indicate that cardiovascular fitness is related to brain activity in the Visual network and Frontoparietal network which are associated with sensory processing and executive functioning, respectively (Reineberg et al., 2015; Yeo et al., 2011). These findings may support the idea that cardiovascular fitness and gross motor skills influence functional connectivity in the developing brain by different pathways, where cardiovascular fitness may shape multiple RSNs with relevance beyond the domain of motor functioning. This idea contrasts with the hypothesis suggested by behavioral studies that gross motor skill development or cognitively demanding physical activity is a complementary pathway of aerobic exercise for physical activity-induced changes in the brain (de Greeff et al., 2018; Vazou et al., 2019). Future research should further clarify the differential effects of different forms of physical activity on the brain.

Lastly, we found that the observed relations between cardiovascular fitness and gross motor skills and neurocognitive functioning were mediated by brain activity in the Somatomotor networks (cardiovascular fitness and gross motor skill) and the Visual Network and Frontoparietal network (cardiovascular fitness). These results are in line with findings in elderly, where changes in RSNs were found to mediate the relation between cardiovascular fitness and executive functioning (Voss et al., 2010). Our findings expand these findings and indicate a mediating role of RSNs for both cardiovascular fitness and gross motor skills with neurocognitive functioning in healthy children. Interestingly, in previous work, we also found associations between both cardiovascular fitness and gross motor skills with white matter microstructure that related to the same neurocognitive functions as the current study (Information Processing and Control; Meijer et al., 2021). Together, these findings suggest that both structural and functional aspects of brain networks may respond to physical activity through effects on cardiovascular fitness or gross motor skills. The fact that RSNs have a mediating role while this was not found for white matter microstructure, may suggest that changes in functional RSNs may precede changes in structural connectivity.

Our study has some important strengths, such as the relatively large sample size of healthy children and the use of advanced neuroimaging techniques and analyses to study RSNs. This study also has some limitations. Due to practical reasons, we scanned at two locations with scanners from different vendors. Accordingly, we have matched scanning protocols and included scanning site as a covariate in all analyses. Furthermore, we included only children from eight to 10 years old, restricting the generalizability of our findings to other stages of development. The preadolescence is a particularly sensitive period for the maturation of neurocognitive functioning (Giedd et al., 1999). Furthermore, puberty-stage might play an important role in aspects of brain and cognitive development (Blakemore et al., 2010). Therefore, it is highly conceivable that the effects of physical activity depend on the child's developmental stage. Future research should further clarify the underlying mechanisms of the relation between cardiovascular fitness and gross motor skills with neurocognitive functioning. We investigated RSNs networks using fMRI with superior spatial specificity. However, a detailed assessment of brain functioning with superior temporal sensitivity (e.g., EEG) may provide a more comprehensive view on potential effects of cardiovascular fitness or gross motor skills. Future research should therefore test the effects of exercise interventions using a combination of imaging techniques such as EEG and fMRI in combination with neurocognitive assessment to measure the impact of physical activity on brain function (Meijer, Königs, Vermeulen et al., 2020; Ramnani et al., 2004). Such studies should use randomized controlled trial designs to infer on causal effects.

In conclusion, the present study shows that cardiovascular fitness and gross motor skills are associated with enhanced performance in a specific set of neurocognitive functions (i.e., relating to the speed and variability of information processing and motor response inhibition). Moreover, we found evidence that brain activity in RSNs mediates the positive relations of both cardiovascular fitness and gross motor skills with neurocognitive functioning. Thus, our findings support that reorganization in multiple RSNs in healthy children may act as an underlying mechanism in the relation between both cardiovascular fitness and gross motor skills with neurocognitive functioning, underlining the importance of physical activity for brain development during childhood.

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CONFLICTS OF INTEREST

All authors declare no conflict of interests.

ORCID

Anna Meijer https://orcid.org/0000-0002-7354-7862

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SUPPORTING INFORMATION

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