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ORIGINAL ARTICLE

Effects of aerobic versus cognitively demanding exercise interventions on brain structure and function in healthy children—Results from a cluster randomized controlled trial

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Abstract

The beneficial effects of physical activity on neurocognitive functioning in children are considered to be facilitated by physical activity-induced changes in brain structure and functioning. In this study, we examined the effects of two 14-week school-based exercise interventions in healthy children on white matter microstructure and brain activity in resting-state networks (RSNs) and whether changes in white matter microstructure and RSN activity mediate the effects of the exercise interventions on neurocognitive functioning. A total of 93 children were included in this study (51% girls, mean age 9.13 years). The exercise interventions consisted of four physical education lessons per week, focusing on either aerobic or cognitively demanding exercise and were compared with a control group that followed their regular physical education program of two lessons per week. White matter microstructure was assessed using diffusion tensor imaging in combination with tract-based spatial statistics. Independent component analysis was performed on resting-state data to identify RSNs. Furthermore, neurocognitive functioning (information processing and attention, working memory, motor response inhibition, interference control) was assessed by a set of computerized tasks. Results indicated no Group × Time effects on white matter microstructure or RSN activity, indicating no effects of the exercise interventions on these aspects of brain structure and function. Likewise, no Group × Time effects were found for neurocognitive performance. This study indicated that 14-week school-based interventions regarding neither aerobic exercise nor cognitive-demanding exercise interventions influence brain structure and brain function in healthy children. This study was registered in the Netherlands Trial Register (NTR5341).

KEYWORDS

children, independent component analysis, physical activity, resting-state fMRI, tract-based spatial statistics, white matter microstructure

1 | INTRODUCTION

It is well known that participation in moderate-to-vigorous-intensity physical activity (MVPA) for children leads to a wide range of physical benefits, such as a reduced risk of type 2 diabetes, reduced risks for cardiovascular disease and obesity and a better bone health (Janssen & LeBlanc, 2010). A growing number of studies indicates that engagement in physical activity is also related to enhanced neurocognitive functioning in children (de Greeff et al., 2018; Donnelly et al., 2016; Singh et al., 2018). This relation could be explained by several potential underlying mechanisms, including a neurobiological mechanism that assumes that enhanced neurocognitive functioning is facilitated by physical activity-induced changes in brain structure and function (Lubans et al., 2016). Although the available evidence is limited, recent systematic reviews and meta-analysis have suggested that physical activity in children indeed can impact on brain properties (Meijer, Königs, Vermeulen, et al., 2020; Valkenborghs et al., 2019). The alarming increase of the prevalence of a sedentary lifestyle among children (Gabel et al., 2016) and the rapid brain development and proliferation of neurocognitive functioning during childhood urges the need to better understand how physical activity promotes neurocognitive functioning.

Findings from fundamental neuroscience have identified several mechanisms which may explain the effects of physical activity on brain properties during childhood. Aerobic demands of physical activity, and MVPA in particular, triggers the release of neurotrophic factors (e.g., brain-derived neurotrophic factor [BDNF] and neural growth factor) and boost neural blood vessel formation and neurogenesis (Colcombe et al., 2006; Dishman et al., 2006; Swain et al., 2003). These neural mechanisms are known to elicit neuroplasticity in brain areas that support neurocognitive functioning (Vaynman & Gomez-Pinilla, 2006). The involvement of high neurocognitive demands during physical activity is thought to further boost neuroplasticity (Pesce, 2012), either through performing complex motor exercises (e.g., as in juggling) or through exercise that involves strategic elements, cooperation with others and dealing with changing task demands (Ma et al., 2011; Scholz et al., 2009; Taubert et al., 2010; Vahdat et al., 2011). Such neurocognitive demands accompanying physical activity may enhance axonal arborization and functional connectivity between brain regions involved in both motor and neurocognitive functioning (Best, 2010; Tomporowski et al., 2015). Taken together, both cardiovascular and the neurocognitive demands are considered relevant factors for the impact of physical activity on the brain.

Looking closer into the effects of exercise programs on brain properties, a distinction should be made between brain structure and brain functioning. With regard to brain structure, almost all studies concerning exercise-induced effects focused on white matter microstructure, which is a quantification of the microstructure components of white matter, including myelinization and axonal organization. Maturation of white matter tracts is an important element of development, as white matter microstructure facilitates the structural connectivity of the brain to allow functional integration of processes originating from brain areas that support neurocognitive functioning (Park & Friston, 2013; Schmithorst & Yuan, 2010). Exercise-induced changes in BDNF and growth factor expression seems to be associated with white matter microstructure. Experimental studies reported aerobic exercise-induced effects in small samples of healthy (Chaddock-Heyman et al., 2018), obese (Krafft, Schaeffer, et al., 2014; Schaeffer et al., 2014), and deaf children (Xiong et al., 2018). More specific, differences in white mater microstructure were observed in the superior longitudinal fasciculus (Krafft, Schaeffer, et al., 2014), bilateral uncinate fasciculus (Schaeffer et al., 2014), the genu of the corpus collosum, and corona radiata (Xiong et al., 2018). Thus, participation in physical activity may play an important role in changes in white matter microstructure in children

Regarding brain functioning, recent meta-analysis and systematic reviews showed that exercise has beneficial effects on brain activity (Meijer, Königs, Vermeulen, et al., 2020; Valkenborghs et al., 2019). While most evidence is based on experimental or crossover studies using electroencephalogram (EEG) and functional magnetic resonance imaging (fMRI) measures during neurocognitive tasks, it is also suggested that brain activity during rest is sensitive to the effects of physical activity (Meijer, Königs, Vermeulen, et al., 2020). Brain activity during rest in networks of co-activated brain regions, that is, resting state networks (RSNs) is characterized as a powerful model of brain function with proven sensitivity to developmental changes (Fan et al., 2021; Jolles et al., 2010; Stevens et al., 2009) and is related to neurocognitive functioning in children (Cabral et al., 2017; Gutierrez-Colina et al., 2020; Laird et al., 2011; Rubia, 2013). While there is scarce evidence for exercise-induced effects in RSNs, two experimental studies indeed reported changes in RSN activity after aerobic exercise programs in children and adults (Krafft, Schwarz, et al., 2014; Voss et al., 2010). Taken together, both white matter microstructure and RSNs may be particularly sensitive for physical activity during childhood and represent important targets of investigation to understand how physical activity promotes neurocognitive functioning. However, the majority of the studies regarding the physical activity-induced changes on brain properties in children are focusing on aerobic exercise and do not provide knowledge on the effect of different types of exercise. Hence, the optimal type of exercise for facilitating brain properties and thereby neurocognitive functioning has thus far remained unclear.

In order to understand the underlying mechanisms of the effects of physical activity during development it is highly important to include both brain measures as neurocognitive measures. One study in deaf children reported changes in white matter microstructure in combination with beneficial as well as detrimental effects on neurocognitive performance (Xiong et al., 2018). Another study reported differences in brain activity in RSNs but not in neurocognitive measures between the exercise group and the control group consisting of obese children (Krafft, Pierce, et al., 2014). However, most studies that showed physical activity-induced changes in white matter microstructure or RSNs did not report neurocognitive measures (Chaddock-Heyman et al., 2018; Krafft, Schaeffer, et al., 2014; Schaeffer et al., 2014). Therefore, it is not clear whether the exercise-induced effects are paralleled by beneficial effects in neurocognitive functioning. Hence, although findings support the idea that physical activity impacts on white matter microstructure and RSNs, the relevance of these effects for neurocognitive functioning has remained largely unexplored.

The current study is the first randomized controlled trial to assess the effects of two 14-week school-based physical exercise interventions on both brain properties and neurocognitive functioning in healthy children. More specifically, the study compares the effects of two exercise interventions consisting of four physical education lessons per week that either used aerobic or cognitively demanding exercise to a regular physical education program of two lessons per week. This distinction between exercise types is in-line with a recent meta-analysis that indicated larger beneficial effects on neurocognitive functioning for exposure to cognitively demanding exercise as compared to aerobic exercise (de Greeff et al., 2018; Sun et al., 2021). The study compares the effects of both exercise interventions to the regular physical education program on (1) white matter microstructure and RSN activity, (2) neurocognitive functioning, and (3) whether changes in white matter microstructure or RSN activity mediates the effects of the exercise intervention on neurocognitive functioning. It is hypothesized that both exercise groups would induce changes in white matter microstructure and RSN activity and in turn improve neurocognitive functioning, with the effects of the cognitively demanding exercise being larger than those of the aerobic exercise intervention. Furthermore, it is expected that physical exercise-induced changes in white matter microstructure and RSN activity mediate the effects of the exercise interventions on neurocognitive functioning.

2 | METHOD

2.1 | Participants

The current MRI study is part of the cluster randomized controlled trial "Learning by Moving" that was carried out between September 2016 and June 2017 in the Netherlands and included a total of 891 children with a mean age of 9.2 years (range: 7.4–11.14 years). A subsample of 93 children were included in the current study. At each of the participating 22 primary schools, two classes participated in this study (third and fourth grade), of which one was randomly assigned to one of the two intervention groups (aerobic exercise intervention or cognitively demanding exercise intervention) and the other class to the control group. Principals of the schools and parents or guardians gave written consent for participation of their children. Based on local guidelines regarding MRI scanning in minors, only children aged 8 years or older (at the time of the scanning procedure) without contraindications for MRI were included. Inclusion was guided by an inclusion protocol in order to balance the representation of sex, school class, and scanning site in the study sample. If the number of children willing to participate exceeded the number of available slots in a class, children were selected at random for those slots. The flow diagram, inclusion protocol and deviations from this protocol can be found in Appendix Figure A1 and Tables A1–A2. For more information about the "Learning by Moving" trial, see De Bruijn et al. (2020), Meijer, Königs, van der Fels, et al. (2020), van der Fels et al. (2020).

2.2 | Exercise interventions

The aerobic exercise intervention and the cognitively demanding exercise intervention were implemented as a physical education program that was provided four times per week for 14 weeks (De Bruijn et al., 2020; Meijer, Königs, van der Fels, et al., 2020; van der Fels et al., 2020). The interventions replaced the normal physical education lessons (two lessons per week) and in addition two physical education lessons were scheduled during the school week. Both the interventions were designed by academic experts in Human Movement Sciences and experienced physical education teachers, who were well acquainted with the regular physical education curriculum. In that way it was ensured that the aerobic exercise intervention and the cognitively demanding exercise intervention would differ from the regular physical education curriculum in terms of its aerobic and cognitively demands, respectively. The interventions were delivered by trained and certified physical education teachers that were hired for the research project.

Teachers were instructed on how to implement the interventions in a 3-hour training session, led by the intervention developers. They were familiarized with the goals and the content of the interventions and were provided with a manual including a detailed description of each intervention lesson. Observations on intervention implementation were conducted at least two times in each class, after which feedback was provided to the physical education teachers in order to promote protocol adherence. The lessons consisted of a warm-up phase of 10 min and a core phase of 20 min. The aerobic exercise intervention consisted of activities specifically designed to target moderate-to-vigorous intensity while avoiding high cognitive demands. The focus was on highly repetitive and automated exercises, such as circuit training, relay games, playing tag, and individual activities like running or doing squats. The cognitively demanding exercise intervention consisted of team games or exercises that require complex coordination of movements, strategic play, cooperation between children, anticipating on the behavior of teammates or opponents, and dealing with changing task demands (Best, 2010). Children played adapted versions of games such as dodgeball, basketball, or soccer to specifically target executive functions (Tomporowski et al., 2015). Complex rules were included in the games, in a way that children were constantly challenged to think about their actions and movements. For example, while playing soccer, the teacher suddenly blew a whistle, signaling that some rules of the game changed immediately, such as the two competing teams having to switch sides. To ensure the complexity of the games and exercises remained cognitive challenging, the rules of games changed during the lessons and intervention period. For example, hearing a whistle meant not only switching sides, but also switching teammates. Children in the control group followed their regular physical education lessons twice a week for 30–45 min. These lessons were delivered by their regular teachers and according to the national goals for physical education at primary schools (Rijksoverheid, 2016). Due to the obvious differences between the exercise interventions and control group, blinding of participants was not possible.

2.3 | Measures

2.3.1 | MRI acquisition

MRI was performed on two 3 Tesla whole-body units, a GE Discovery MR750 3T (location VU Medical Center Amsterdam), and a Phillips Intera 3T (location University Medical Center Groningen), using a 32-channel head-coil. Two-dimensional echo-planar diffusion-tensor images were acquired using six volumes without diffusion weighting and 30 (GE) or 32 (Philips) volumes with noncollinear diffusion gradients (b-value = 750 s/mm2) in 56–58 transverse oblique slices of 2.5 mm thickness (angulated parallel to the line connecting the pituitary to the fastigium of the fourth ventricle), covering the whole brain (GE TR/TE = 6000/76 ms; Phillips TR/TE = 6000/57 ms). The acquired in-plane resolution was 2.5 × 2.5 mm, reconstructed to 1 × 1 mm. Parallel imaging was applied with an acceleration factor of 2. Resting-state data were acquired using a T2*-weighted echo-planar functional scan with 202 volumes, 38 ascending slices with slice thickness of 3 mm and 0.3 mm gap, matrix size of 64 × 64, TR = 2000, TE = 35 ms, flip angle of 80 degrees and field of view = 211 mm. For both diffusion tensor imaging (DTI) and fMRI reference 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).

2.3.2 | Neurocognitive functioning tasks

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. All neurocognitive tasks and corresponding outcome measures are listed in Table 1. In addition, full scale IQ was estimated by a two-subtest short form (Information and Block Design) of the Wechsler Intelligence Scale for Children III (WISC-III; Wechsler, 1991). All neurocognitive tasks are comprehensively described in previous work (Meijer, Königs, de Bruijn, et al., 2020).

2.3.3 | Demographics

Parent questionnaires were used to assess demographic information (sex, age, socioeconomic status [SES]). SES was defined as the average level of parental education ranging from 0 (no education) to 7 (postdoctoral education; Statistics Netherlands, 2006).

2.3.4 | Intervention integrity

It is suggested that a change in physical properties due to physical activity would be a necessary condition for producing changes in the brain (de Greeff et al., 2018). Physical activity is considered as an important determinant of cardiovascular fitness levels and motor skill development during childhood and adolescence (Aires

TABLE 1 Description and operationalization of neurocognitive 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., 2021; Lacouture & Cousineau, 2008; Rueda et al., 2004). The test-retest reliability varies between studies (ICC = 0.37 to 0.60) and the validity of the test is considered as good (Fisher et al., 2011; 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 spatial cue trials and central 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). Test-retest reliability varies between studies ($r = .27–.82$) and the validity is considered as good (Alloway, Gathercole, Kirkwood, & Elliott, 2008; Alloway et al., 2006; 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). Test-retest reliability ($r = .83$) and validity of the test are considered as good (Alloway et al., 2006, 2008; Klingberg et al., 2002)	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). The test-retest reliability (ICC = .72) and validity are considered as good (Oosterlaan et al., 1998; Soreni et al., 2009)	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; ICC, intraclass correlation coefficient; GT, grid task; SST, stop signal task.

et al., 2010; Ortega et al., 2008; Sallis et al., 1997). Hence, in order to understand the effects of the exercise interventions, we also included measures of cardiovascular fitness and gross motor skills. Cardiovascular fitness was assessed with the 20 m Shuttle Run Test (20 m SRT; Adam et al., 1987). During this test, children run back and forth on a 20-m track, and need to reach the other side of the track at or before an auditory signal. The number of completed tracks were taken as an indicator of cardiovascular fitness. Gross motor skills were assessed using three subtests (jumping sideways, moving sideways, and backward balancing) of the Körper Koordinationstest für Kinder (KTK; Kiphard & Schilling, 2007) and one subtest of the Bruininks-Oseretsky Test of Motor Proficiency, second Edition (BOT-2; Ball skills; Bruininks, 2005). To reduce the number of gross motor skill measures, principal component analysis with varimax rotation was performed on all gross motor skills, resulting in one component labeled as gross motor skills. For more detailed information about these variables see (van der Fels et al., 2020).

To estimate the cardiovascular intensity of the exercise interventions, accelerometers were used to measure the amount of MVPA in the three intervention arms (ActiGraph GT3x+, Pensacola, FL, USA). Accelerometer data were collected during two designated physical education lessons. The average time in MVPA per lesson (in minutes) over the two lessons was calculated for each participant. The total exposure to MVPA (in minutes) was calculated by the product of the average time in MVPA per lesson and the total number actual received lessons for the exercise intervention groups and 28 lessons for the control group (i.e., two times per week for 14 weeks long).

2.4 | Preprocessing

2.4.1 | DTI

All processing of MRI images was performed using the Functional MRI of the Brain (FMRIB) Software Library (FSL) version 5.0.11 (Jenkinson et al., 2002). Preprocessing of DTI included estimation and correction of susceptibility-induced distortions using TOPUP, and correction of eddy currents and head motion using FSL eddy, including detection and imputation of outlier slices (~1%; average number of imputed slices: 21 per subject [range 0–71] out of the total number of ~2000 slices; Andersson et al., 2016; Andersson & Sotiropoulos, 2016). Estimation of the diffusion tensor model was performed on brain-extracted images (FSL bet; Smith, 2002) to create maps of fractional anisotropy (FA) and mean diffusivity (MD). FA is a general index of white matter microstructure and expresses the degree to which water diffuses preferentially along one axis and which is considered to be higher in tightly bundled, structurally compact fibers with high integrity (Beaulieu, 2002), MD represent the average diffusion in all directions, with higher levels indicating relatively unimpeded diffusion (i.e., negatively correlated with FA (Beaulieu, 2002). The quality of the tensor fit was visually inspected on the sum of squared error maps (Behrens et al., 2003). Voxel-wise statistical analysis of the DTI data was performed using TBSS (Smith et al., 2006). First, the FA maps of all subjects were aligned to the most typical subject, as determined by nonlinear registrations of FA maps between all children. Next, the DTI maps were transformed to MNI152 space via the most typical subject using nonlinear transformation, after which a white matter skeleton (FA > 0.30) was computed to reduce the influence of imperfect registration and inter-subject variability in white matter tract anatomy.

2.4.2 | Resting-state fMRI

The following steps were undertaken to reduce the influence of noise and motion on the fMRI data, as part of preprocessing pipeline for fMRI data based on FSL AROMA (Pruim et al., 2015). 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 distribution of the subjects' head (TOPUP tool in FSL; (Andersson et al., 2016; Smith et al., 2004). The data were then denoised by removing artifactual activation components in the data (e.g., caused by motion). 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 resting-state networks from the atlas by (Yeo et al., 2015) in subject space. After visual inspection of the results, components with lower correlation values than .3 were filtered from the data (range: .19–.51). 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 to seven well-known major resting-state networks 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. The results revealed the following five resting-state networks in the data: (1) Visual Network, (2) Default Mode Network, (3) Frontoparietal Network, (4) Somatomotor Network, and (5) Dorsal Attention (See Figure 4, left panel). No significant correlations were found for the Limbic Network and Ventral Attention Network. The resting-state networks were selected as NOIs for further analysis. The five NOIs were then used to generate group-based NOIs (See Figure 3, left panel) in the total study sample using dual regression (Beckmann et al., 2009), which were used for statistical analysis.

2.4.3 | Behavioral data

Preprocessing steps and statistical analysis of the behavioral data were performed using IBM SPSS Statistics version 25.0 (SPSS IBM, New York, U.S.A) and R for Statistical Computing (R Foundation for Statistical Computing, Vienna, Austria). To minimize bias originating from outliers, all outliers ($z \leq -3.29$ or ≥ 3.29) were winsorized, that is, replaced with a value one unit greater than the next non-outlier value (Field, 2013). To determine if data were normally distributed, histograms and values of skewness and kurtosis were inspected. Van der Waerden transformations were used to correct deviations from the normal distribution. All neurocognitive measures were recoded with higher scores indicating better performance. To reduce the number of neurocognitive measures and to enhance their reliability, principal component analysis with varimax rotation was performed on all neurocognitive baseline measures. These analyses used the group of children included in the larger "Learning by Moving" cross-sectional study ($n = 814$). The principal component analysis extracted a total of six components from the neurocognitive data, together explaining 70% of the total variance (see Appendix Table A3 for Eigenvalues and factor loading). Based on the variables with the strongest contributions to the components, the neurocognitive function components were labeled as follows: (1) Information Processing & 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). For more information of this procedure, see Meijer, Königs, de Bruijn, et al., 2020.

2.5 | Procedure

All described assessments were conducted within a period of 2 weeks before and after the 14-week period in which the intervention took place. MRI scanning took place at the Amsterdam University Medical Centers (location VU, GE; $n = 48$), or at the University Medical Center in Groningen (Philips; $n = 44$). Prior to the MRI scan, children were made familiar with the MRI procedure using a mock scanner in which the environment of the MRI scanner (including scanner sounds) was created. 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, and lasted approximately 35 min. Head movements were minimized by inserting small pillows between the head coil and the child's head. During the structural MRI scans (DTI), children watched a cartoon distracting them from the scanning environment. In between the scans, participants were reminded to keep still when necessary. Scans of poor quality due to head motion during scanning were directly repeated if time permitted. Children received a small present and a copy of their structural T1-weighted scan. The neurocognitive assessment was individually executed during the school day by trained examiners using standardized protocols, and tasks were administered in a fixed order. To limit the influence of tiredness and distraction, the neurocognitive tasks were administered in two sessions performed on separate days, with a duration of 30–35 min per session. Physical assessment (cardiovascular fitness and gross motor skills) was conducted during two physical education lessons at the primary schools and was administered by physical education teachers. 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).

2.6 | Statistical analysis

First, we examined the effects of the exercise interventions on white matter microstructure and brain activity in RSNs. To examine the effects of Time and Group on the change in FA and MD, we performed group comparisons on the FA and MD contrast maps (posttest measurement––baseline measurement), reflecting change in FA and MD over time, using permutation testing in FSL Randomise (Winkler et al., 2014). To determine the effects of Time and Group on the change in RSN activity, permutation testing was applied (FSL Randomise).

Second, we investigated the effects of the exercise interventions on neurocognitive functioning. Statistical analysis on behavioral data was performed in IBM SPSS Statistics (SPSS IBM, New York, U.S.A). To determine the effects of Time and Group on the change in each of the neurocognitive functioning components, repeated measures analyses of covariance were conducted in which Time (baseline vs. posttest) was included as within-subject variable and Group (aerobic exercise group, cognitively demanding exercise group, and control group).

Third, when an effect of the exercise interventions on the neurocognitive function components was found, we investigated whether exercise-induced changes in white matter microstructure and RSN activity mediated the effects of the exercise interventions on these specific neurocognitive function components by using bootstrap mediation analysis. The change in FA, MD, or RSN activity over time was included as mediator, the change in the neurocognitive functioning component over time was included as dependent variable and Group as independent variable. The mediation analysis was performed using the PROCESS SPSS macro developed by Hayes (2017). All indirect effects were tested using 5000 bootstrap samples and bias-corrected bootstrap confidence intervals.

All behavioral and MRI analyses used the following three group contrasts: (1) aerobic exercise intervention group versus control group; (2) cognitively demanding exercise intervention group versus control group; (3) aerobic exercise intervention group versus cognitively demanding exercise intervention group. Demographic variables (Sex, Age, Grade [three or four], BMI, and SES) were included as covariates in all models (voxel-wise permutation tests and SPSS models). Only significant covariates were retained in the final model. To investigate whether demographic characteristics moderated the effects of the interventions, the interaction between Group and the significant covariates were added to the model. To control for differences between scanning sites, scanning site was added as covariate in all MRI models. Additionally, we investigated the effects of the exercise interventions on cardiovascular fitness and gross motor skills. In all analyses, level of significance was set at .05 with FDR correction (for gross motor skill and neurocognitive measures) or family wise error correction using threshold free cluster enhancement (TFCE; Smith & Nichols, 2009).

3 | RESULTS

3.1 | Participants

Children were excluded due to drop-out from MRI scanning because of logistic problems (e.g., planning of scan time), cancelled appointments by participants due to personal circumstances at posttest or poor-quality data, leaving a total of 83 children (DTI measurement) and 79 children (resting-state fMRI measurement) for the analyses. The flow diagram can be found in Appendix Figure A1. Nonattendance of participating children during physical or neurocognitive assessments resulted in missing data. Prevalence of missing values ranged between 0 and 5% and these data were replaced by multiple imputation (Sterne et al., 2009). Table 2 shows the demographic characteristics of the total sample of participating children (*n*= 93), the two intervention groups (aerobic exercise [$n = 30$] and the cognitively demanding exercise group [$n = 32$]) and the control group ($n = 31$). Overweight and obesity as defined by Cole & Lobstein (2012) was observed in 14% and 2% of the total sample, respectively, which parallels recent figures observed in the Dutch pediatric population (Volksgezondheid en zorg, 2018). Groups did not differ in the distribution of age, sex, grade.

3.2 | Effects of exercise interventions on white matter microstructure

Figure 1 shows the white matter tracts that were compared between groups. Mean scores and standard deviations of FA and MD of the three groups are displayed in Table 3. No significant effects of Time were observed on the FA and the MD contrast maps (posttest measurement––baseline measurement). Furthermore, no significant effects of Group × Time were observed on the FA and the MD contrast maps (posttest measurement–-baseline measurement; Figure 2). Also, none of the covariates contributed significantly to the models. These results indicate that there is no evidence for effects of either the aerobic exercise intervention or the cognitively demanding exercise intervention on FA and MD.

3.3 | Effects of exercise interventions on RSN activity

Figure 3 (right panel) shows the NOIs that were that were compared between groups. Mean scores and standard deviations of the RSNs of the three groups are displayed in Table 3. For the Default Mode Network, negative effects of Time were obtained. This finding indicates that brain activity in the Default Mode Network was lower during the posttest compared to the baseline measurement for all children. No other significant effects of Time were found for any of the other five NOIs. No Group x Time effects were found on brain activity maps of the five NOIs (See Figure 4). None of the covariates contributed significantly to the models. These results indicate that there is no evidence for any effects of either the aerobic exercise intervention or the cognitively demanding exercise intervention on RSN activity.

3.4 | Effect of exercise interventions on neurocognitive components

Table 3 shows the performance of the intervention groups and control group on the neurocognitive component scores. No significant effects of Time were observed for any of the neurocognitive components. Next, we tested the Group x Time interactions using the three group contrasts (aerobic exercise vs. control group, cognitively demanding exercise vs. control group, aerobic exercise intervention group vs. cognitively demanding exercise). No Group x Time effects were observed in for any of neurocognitive components (Table 3). Concerning covariates, only Grade contributed significantly to the neurocognitive component Information Processing and Control and SES contributed significantly to Verbal Working Memory. These results indicate that there is no evidence for effects of either the aerobic exercise intervention or the cognitively demanding exercise intervention on neurocognitive functioning. Due to the absence of intervention effects on both brain properties and neurocognitive functions, mediation analyses were not performed.

3.5 | Intervention integrity

For cardiovascular fitness, a significant effect of Time was observed (F (1, 83) = 13.484, $p < .001$), indicating that cardiovascular fitness was higher during the posttest compared to the baseline measurement in all groups. No significant effects of Time were observed for gross motor skills and no Group × Time effects were observed for both cardiovascular fitness and gross motor skills (Table 3). Furthermore, we estimated the cardiovascular vascular intensity of the exercise interventions and the regular physical education lessons (control group). The aerobic exercise group was exposed to the highest total estimated time of MVPA and the control group received the lowest exposure to MVPA (Table 2).

TABLE 2 Baseline characteristics for the total sample and the two intervention groups and control group separately

	Total sample ($n = 93$)	**Aerobic exercise ($n = 30$)**	**Cognitively demanding exercise ($n = 32$)**	**Control group ($n = 31$)**	**Statistic**	***p*-value**	**Post hoc tests**
Sex, *n* (% girls)	47 (51%)	15 (50%)	16 (50%)	16 (52%)	χ^2 (2) = .22	.989	
Age in y, *M* (*SD*)	9.13 (0.62)	9.20 (0.68)	9.05 (0.55)	9.15 (0.63)	*F* (2,90) = .48	.619	
BMI in kg/m^2, *M* (*SD*)	16.80 (2.23)	16.76 (2.11)	17.00 (2.62)	16.64 (1.94)	*F* (2,90) = .21	.809	
Normal weight, *n* (%)[a]	78 (84%)	26 (87%)	25 (78%)	27 (87%)	χ^2 (4) = 2.16	.706	
Overweight, *n* (%)[a]	13 (14%)	3 (10%)	6 (19%)	4 (13%)	χ^2 (4) = 2.16	.706	
Obesity, *n* (%)[a]	2 (2%)	1 (3%)	1 (3%)	0 (0%)	χ^2 (4) = 2.16	.706	
Grade three, *n* (%)	47 (51%)	15 (50%)	17 (53%)	15 (48%)	χ^2 (2) = .15	.929	
IQ, *M* (*SD*)	101.35 (15.26)	102.23 (14.10)	103.93 (17.21)	97.81 (13.96)	*F* (2,90) = 1.35	.264	
SES, *M* (*SD*)[b]	4.60 (1.04)	4.67 (0.95)	4.56 (1.25)	4.56 (0.90)	*F* (2,89) = .098	.906	
Total MVPA exposure in min, *M* (*SD*)	441.09 (152.18)	579.25 (118.94)	444.39 (86.30)	308.76 (107.67)	*F* (2,88) = 49.51	<.001	Aerobic > Cognitive > Control

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

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

[b] The average level of parental education ranged from 0 (no education) to 7 (postdoctoral education) (Statistics Netherlands, 2006).

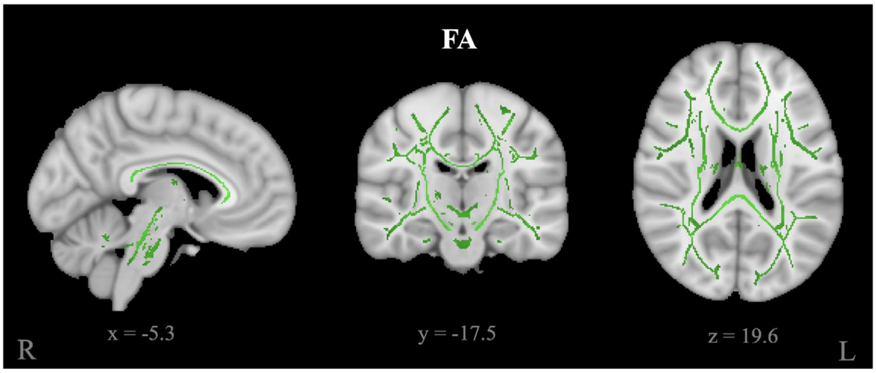


FIGURE 1 Sagittal, coronal, and axial slices of the FA skeleton of all baseline data ($n = 93$) overlaid onto the MN152 standard brain

4 | DISCUSSION

The current study is the first study to assess the effects of a 14-week school-based aerobic and cognitively engaging exercise intervention on white matter microstructure and RSN activity, compared to regular physical education lessons. We hypothesized that both exercise interventions would facilitate changes in white matter microstructure and RSN activity, in turn resulting in beneficial effects on neurocognitive functioning. Furthermore, it was expected that physical exercise-induced changes in white matter microstructure and RSN activity would mediate the effects of the exercise interventions on neurocognitive functioning. In contrast to our expectations, results did not demonstrate any effects of the exercise interventions on both white matter microstructure, RSNs and neurocognitive functioning, indicating no beneficial effects of physical activity on both brain properties and neurocognitive functioning.

Our findings contrast with the results of recent meta-analyses, reporting exercise-induced effects on both brain structure and functioning as neurocognitive functioning (de Greeff et al., 2018; Meijer, Königs, Vermeulen, et al., 2020; Sun et al., 2021; Valkenborghs et al., 2019; Vazou, Pesce, Lakes, & Smiley-Oyen, 2019). Chaddock-Heyman et al. (2018), Krafft, Schaeffer et al. (2014), Schaeffer et al. (2014) and Krafft, Pierce et al. (2014) examined the effects of aerobic exercise interventions on white matter microstructure or RSN activity in healthy or obese children. Their results did demonstrate physical activity-induced changes in both white matter structure (FA, RD) and activity in RSNs (Default Mode network, Cognitive network and Motor network). These contrasting results obtained in these studies and our study might be explained by the nature of the exercise interventions tested. The studies of Chaddock-Heyman et al. (2018), Krafft, Schaeffer et al. (2014), Schaeffer et al. (2014) and Krafft, Pierce et al. (2014) all implemented an aerobic exercise intervention of 2 hours after each school day for 9 months and compared the results of the group that received the intervention to those of a sedentary wait list group. Our intervention was implemented instead of the regular physical education program during the school day for four times a week during 14 weeks, and was compared with the control group that followed their regular physical education program twice per week. Although we did find that the MVPA dose was significantly higher in the aerobic exercise group and the cognitively demanding group compared to the control group, the exercise interventions did not cause increased levels of exercise tolerance (assessed by the number of completed Shuttle Run Test tracks) or improved gross motor skills compared to the control group. Earlier analyses on the data gathered in the larger overarching study “Learning by Moving” ($n = 891$), confirm these results and showed that our two exercise interventions were not successful in enhancing cardiovascular fitness, gross motor skills (van der Fels et al., 2020), and neurocognitive functioning (Meijer, Königs, van der Fels, et al., 2020). Earlier exercise studies achieved improvements in cardiovascular fitness or gross motor skill performance by having interventions spanning a shorter period of time and lower frequency (Costigan et al., 2015; Morgan et al., 2013). This may indicate that, in the current study, the intensity of our exercise interventions was not sufficient to evoke effects on cardiovascular fitness and motor skills and thereby on brain structure and function. This idea is confirmed in our larger behavioral study in which we observed that time spent in MVPA was associated with changes in neurocognitive functioning. More specifically, children with higher exposure to MVPA show greater improvement of verbal working memory and efficiency of alerting and orienting attention during the intervention period. These effects of MVPA were found among all children, while no differences between the study groups were found (Meijer et al., 2020).

Another possible explanation for not observing beneficial effects of physical activity on brain structure or functioning might be that the content of our exercise interventions was not adequate to influence brain properties. Our interventions were aimed on distinguishing aerobic from cognitive engaging exercise, while in recent meta-analyses and RCTs it is suggested that a combination

TABLE 3 Baseline and posttest measures of all outcome measures and results of repeated measures analysis comparing the three groups (Group × Time)

	Aerobic exercise		**Cognitively demanding exercise**		**Control group**					
	Baseline	**Posttest**	**Baseline**	**Posttest**	**Baseline**	**Posttest**	***F*-value**[b]	***p*-value**	**η_p^2**	**Covariates**[b]
White matter microstructure										
FA	.47 (.04)	.47 (.04)	.47 (.04)	.47 (.04)	.46 (.04)	.46 (.04)	.491	.614	.012	Site
MD[c]	81.00 (2.60)	80.56 (2,68)	81.83 (2.46)	81.63 (2.26)	81.44 (2.97)	81.11 (3.01)	.142	.868	.071	Site
RSNs										
Visual network	.63 (.63)	.57 (.43)	.54 (.72)	.64 (.84)	.52 (.84)	.55 (.53)	.168	.846	.004	Site
Default network	.40 (.50)	.48 (.39)	.52 (.51)	.65 (.50)	.44 (.35)	.63 (.41)	.329	.721	.009	Site, Age, Grade
Frontoparietal network	.92 (1.04)	.88 (.64)	1.01 (.84)	.90 (.61)	.99 (.72)	.83 (.41)	.096	.908	.003	Site
Somatomotor network	.24 (.57)	.33 (.60)	.31 (.92)	.31 (.39)	.29 (.72)	.38 (.39)	.046	.955	.001	Site
Dorsal attention network	.71 (.62)	.63 (.54)	.87 (.86)	.76 (.66)	.79 (.74)	.61 (40)	.188	.829	.005	Site
Neurocognitive functioning components										
Information Processing and Control	.19 (.88)	0.15 (.74)	−.10 (0.97)	−.16 (1.22)	.04 (1.16)	.30 (1.13)	.366	.547	.027	Grade
Interference Control	−.01 (.97)	-.08 (1.00)	.11 (1.11)	0.13 (0.75)	−.09 (.94)	−.18 (.95)	.171	.843	.004	–
Attention Accuracy	.07 (.68)	.14(.80)	−.16 (.96)	−.25 (.83)	−.13 (1.09)	−.07 (1.11)	.125	.882	.003	–
Visuospatial Working Memory	.09 (1.21)	.20 (1.02)	.01 (.96)	.05 (1.17)	.13 (1.15)	.0 (1.02)	.281	.756	.006	
Verbal Working Memory	.06 (.81)	.04 (.80)	.06 (1.08)	.08 (1.03)	−.18 (.98)	−.21 (.93)	.029	.972	.001	SES
Attention efficiency	.22 (1.14)	.17 (1.12)	.17 (.88)	.07 (.83)	.08 (.80)	.12 (.99)	.099	.906	.002	–
Physical measures										
Cardiovascular fitness	35.94 (16.20)[d]	41.81 (17.66)	36.40 (17.13)[d]	44.80 (15.61)	35.89 (18.02)	38.89 (23.50)	.478	.625	.035	Grade
Gross motor skills	.17 (.92)	.29 (.86)	−.25 (1.10)	−.23 (1.22)	.10 (.95)	.14 (1.11)	.164	.849	.003	

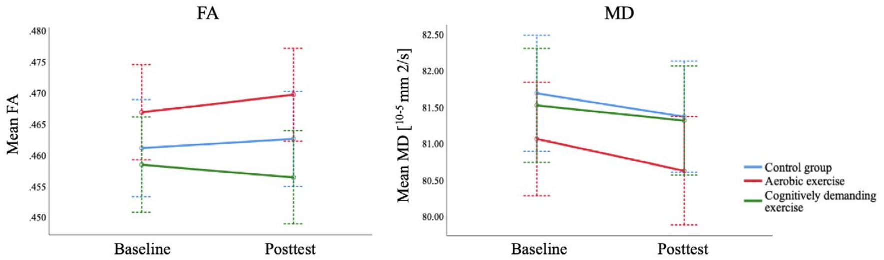
[a] Group × time.

[b] Covariates significantly related to outcome measurement.

[c] 10^{-5} mm^2/s.

[d] Significant different at baseline level.

FIGURE 2 Baseline and posttest results on white matter microstructure corrected for Scanning site. Error bars represent 95% confidence interval



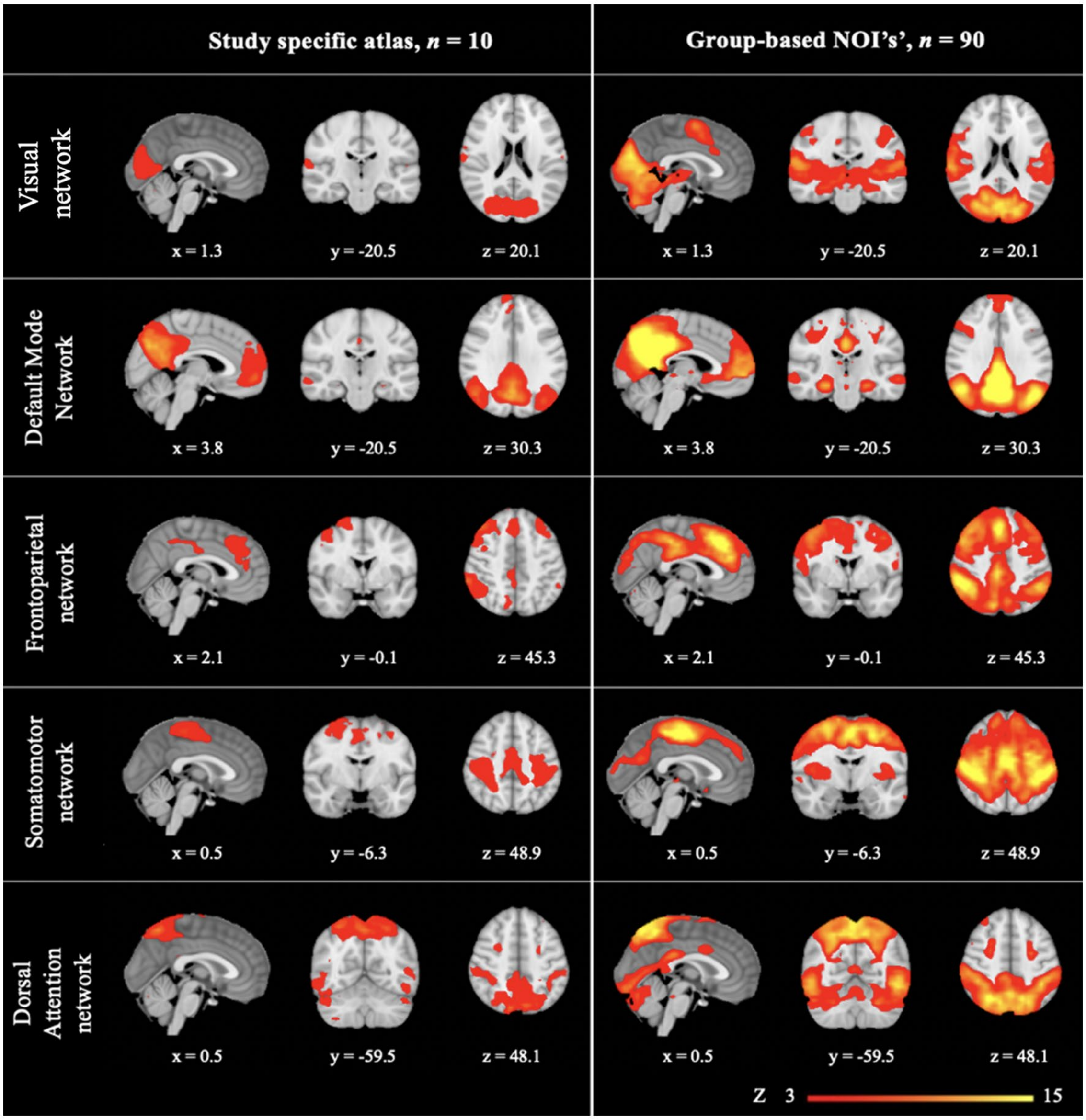


FIGURE 3 Sagittal, coronal, and axial slices of six RSNs based on ~10% of the data (*n* = 10) and all baseline data (*n* = 90) overlaid onto the MNI152 standard brain. Resting state networks are shown in FSL red-yellow color encoding using a 3 < z score < 15 threshold window

of moderate to vigorous intensity and high cognitive engagement may have the largest benefits for neurocognitive functioning (de Greeff et al., 2018; Egger et al., 2019; Schmidt et al., 2015; Sun et al., 2021; Vazou et al., 2019). It is possible that especially the combination of both moderate to vigorous intensity and cognitive engagement during exercise facilitates neurobiological mechanisms such as the upregulation of neurotrophic factors, axonal, and functional connectivity which in turn facilitates neurocognitive functioning (Dishman et al., 2006; Swain et al., 2003; Tomporowski et al., 2015). Taken together, these findings suggest that a more intensive exposure to physical activity

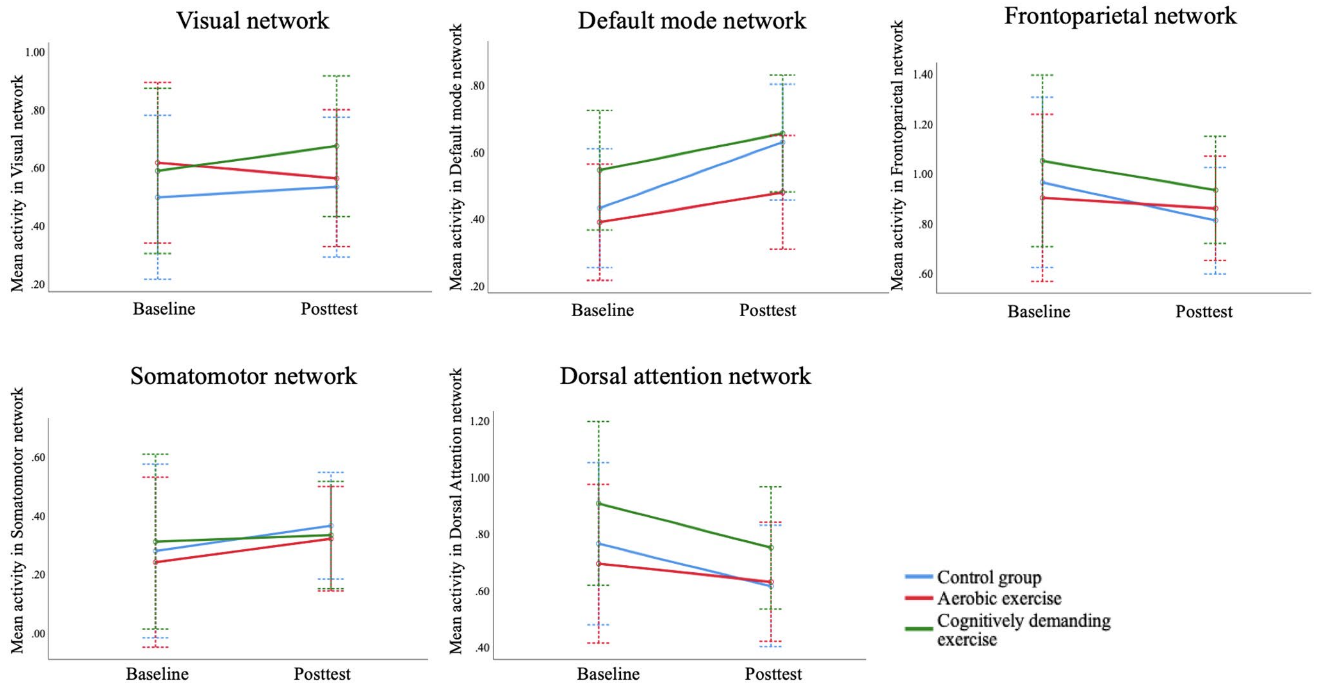


FIGURE 4 Baseline and posttest results on all RSNs corrected for Scanning site. Error bars represent 95% confidence interval

or different type of physical activity may be necessary to reach a critical threshold at which physical activity can evoke effects on brain structure and function and thereby on neurocognitive functioning. Future research should be aimed at exploring the optimal exposure parameters for physical activity interventions.

The current study is one of the few studies that included both neuro-imaging measures and behavioral measures such as neurocognitive and physical measures. Despite that most studies concerning the effects of physical activity on brain properties did not report accompanied results of physical measures, Krafft, Schaeffer, et al. (2014), Krafft, Schwarz, et al. (2014), Schaeffer et al. (2014) and Chaddock-Heyman et al. (2018) reported no effects of the exercise intervention on cardiovascular fitness, but did find effects on white matter microstructure. This makes it difficult to conclude that the reported physical activity-induced effects are entirely based on exercise participation. It is possible that other aspects of the after-school program used in these studies and including aerobic, motor, and social activities as well as a brief educational component, may have contributed to the result. Indeed, other mechanisms than the proposed neurobiological mechanisms (altered brain properties by upregulation of neurotrophic factors and neural growth factor and enhanced axonal arborization and functional connectivity) should be considered when explaining physical activity-induced effects in brain or neurocognitive functioning. Psychosocial and behavioral mechanisms may also clarify the underlying mechanisms of the proposed beneficial effects of physical activity on neurocognitive functioning in children (Lubans et al., 2016). More specifically, these mechanisms include suggested beneficial effects of increased mental health and self-esteem or associated behaviors such as improved sleep duration an efficiency (Lang et al., 2013; Lubans et al., 2016). Most studies concerning the physical-activity effects on brain properties, do not allow conclusions to be drawn on whether the delivered interventions actually led to changes in the mechanisms thought to underlie the beneficial effects of physical activity on neurocognitive functioning as these studies neither report on neurocognitive and physical performance (Meijer, Königs, Vermeulen, et al., 2020), nor do these studies report on psychosocial and behavioral aspects of the studied interventions (Lubans et al., 2016).

Another important difference between the studies by Krafft, Schaeffer, et al. (2014), Schaeffer et al. (2014) and Krafft, Pierce, et al., (2014) and our study is that that these studies specifically targeted children with obesity. This may indicate that the effects of physical activity on brain structure and brain functioning may differ between children with a healthy weight and children with obesity. Inline with this idea, exploratory analyses concerning the effects of our exercise interventions in only the children with overweight (14%) and obesity (2%) in our sample indicated a significant Group × Time effect between when we compared children in the exercise interventions (aerobic and cognitively demanding exercise taken together, $n = 9$) and the control group ($n = 4$) on brain activity in the Default Mode Network ($p = .03$). Children with overweight and obesity in the control group showed increased activity after the intervention period in the Default Mode Network and the children in the exercise interventions showed decreased activity, which may suggest that children with overweight and obesity indeed respond differently compared to children with a healthy weight. In-line with this idea, we also investigated whether BMI interacted with Time. However, exploratory results showed that BMI could not be indicated as moderator in any of the MRI Group × Time analyses. Future research may further clarify the possible differences between healthy and obese (and other clinical) populations.

Our study has some important strengths, such the randomized design, the relatively large sample size of healthy children and the use of advanced neuroimaging techniques. To date, the current study is the only neuroimaging study that allowed a direct comparison between aerobic exercise and cognitively demanding exercise. This study also has some limitations. First, although the total sample size was considerable higher than in comparable studies which did found exercise-induced effects on brain properties (Krafft, Pierce, et al., 2014; Krafft, Schaeffer, et al., 2014; Schaeffer et al., 2014), the sample size and statistical power of this study is not sufficient to determine small intervention effects. It should be mentioned that the majority of the interventions effects not exceeded the threshold for a small effect (Cohen, 1988). Second, we did not determine the level of cognitive engagement of the interventions. Measurement of cognitive engagement would possibly be limited to subjective reports, as there is no objective measure available for cognitive engagement during physical exercise. Furthermore, MVPA was only measured during two physical education lessons. It might be possible that these two measurements were not sufficient to provide a reliable estimate of the amount of MVPA and the intensity of the exercise interventions. Also, future studies should consider heart rate monitors to provide a more accurate estimate of the intensity of the exercise interventions. Last, MRI connectome analyses that utilize graph theory has become a promising technique for investigating the human brain as a network of structural and functional connections could provide novel insights into the understanding of the underlying physiological mechanisms of physical activity-induced neuroplasticity. Although we investigated resting state networks using fMRI with superior spatial specificity, detailed assessment of brain functioning with superior temporal sensitivity (e.g., EEG) may reveal other effects of physical activity on brain function.

The current increase in sedentary behavior among children and the evident benefits of physical activity for physical fitness, neurocognitive functioning, and academic achievement (de Greeff et al., 2018; Donnelly et al., 2016; Singh et al., 2018), reflect the importance of physical activity during childhood. This study demonstrates that 14-week aerobic and cognitively demanding exercise interventions (in which the exposure to physical activity was doubled) were not sufficient provoke changes in brain structure or functioning in children. These findings suggest that more intensive and/or longer exposure to physical activity might be required to evoke effects on brain structure and function. These findings underline the importance of further research concerning the optimal type, frequency, duration and intensity of exercise interventions, and the possible differential effects in specific populations such as healthy or obese children.

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AUTHOR CONTRIBUTIONS

Marsh Königs: Conceptualization; formal analysis; methodology; software; supervision; validation; writing – review and editing. **Petra J.W. Pouwels:** Formal analysis; methodology; software; supervision; writing – review and editing. **Joanne Smith:** Methodology; supervision; writing – review and editing. **Chris Visscher:** Conceptualization; methodology; supervision; writing – review and editing. **Roel J. Bosker:** Conceptualization; methodology; supervision; writing – review and editing. **Esther Hartman:** Conceptualization; funding acquisition; methodology; supervision; writing – review and editing. **Jaap Oosterlaan:** Conceptualization; methodology; supervision; writing – review and editing.

CONFLICT OF INTEREST

All authors have no conflict of interest relevant to this article to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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APPENDIX A

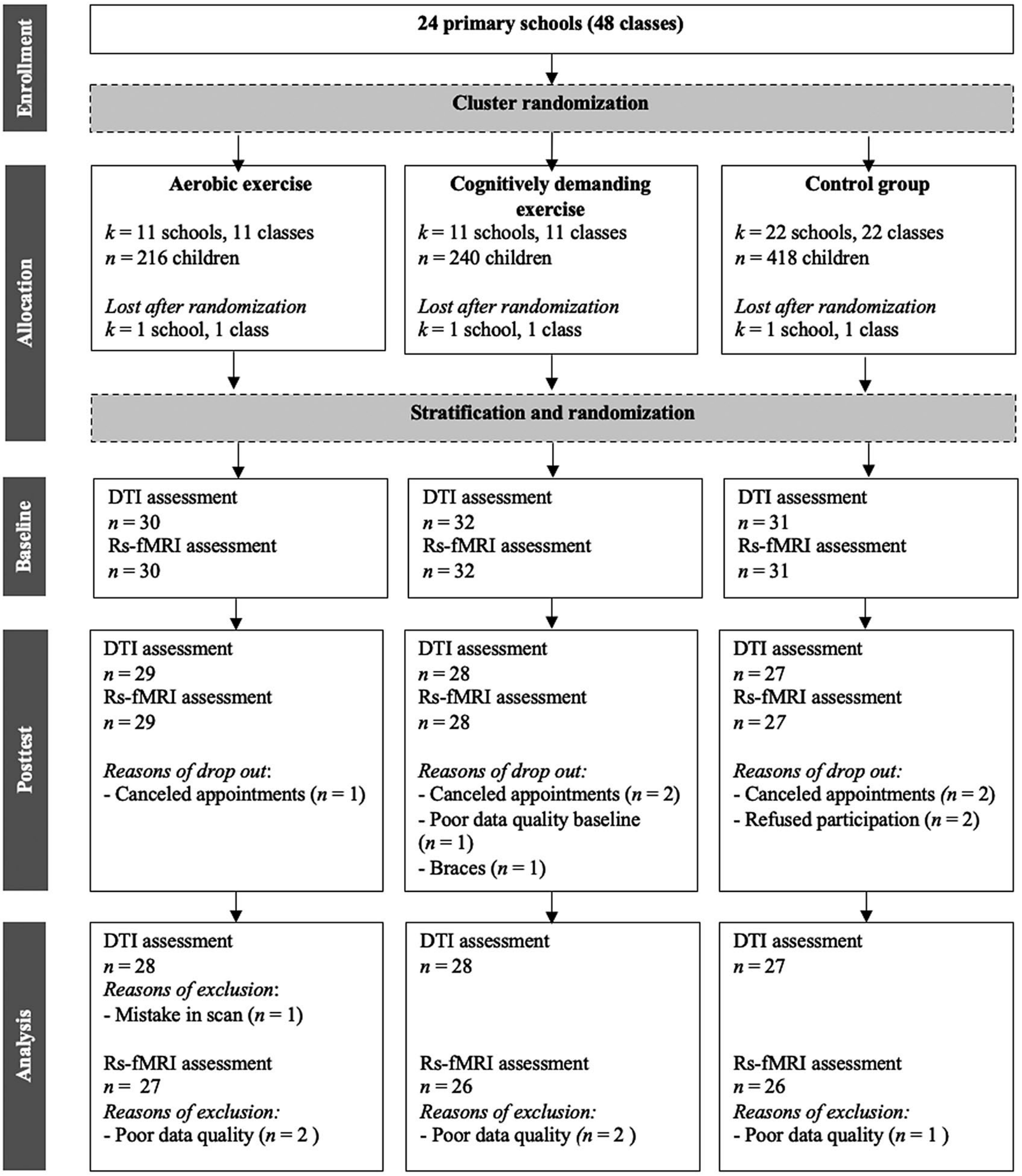

FIGURE A1 Flow diagram with the number of children in each stage of the study.

TABLE A1 Inclusion DTI measurement

DTI measurement	Aerobic exercise intervention			Cognitively demanding exercise intervention			Control group			Total		
	Grade 3	Grade 4	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4	Total
Total planned	15	15	30	17	15	32	15	16	31	47	46	93
Total scanned	14	15	29	15	13	28	11	16	27	40	44	84
Total analyzed	14	14	28	15	13	28	11	16	27	40	43	83
Total planned (Vumc)	8	7	15	12	7	19	6	8	14	26	22	48
Total scanned (Vumc)	8	7	15	10	7	17	4	8	12	22	22	44
Total analyzed (Vumc)	8	6	14	10	7	17	4	8	12	22	21	43
Total planned (UMCG)	7	8	15	5	8	13	9	8	17	21	24	45
Total scanned (UMCG)	6	8	14	5	6	11	7	8	15	18	22	40
Total analyzed (UMCG)	6	8	14	5	6	11	7	8	15	18	22	40
Total boys planned	8	7	15	8	8	16	8	7	15	24	22	46
Total boys scanned	7	7	14	8	7	15	5	7	12	20	21	41
Total boys analyzed	7	7	14	8	7	15	5	7	12	20	21	41
Boys planned (Vumc)	6	3	9	4	4	8	3	4	7	13	11	24
Boys scanned (Vumc)	6	3	9	4	4	8	2	4	6	12	11	23
Boys analyzed (Vumc)	6	3	9	4	4	8	2	4	6	12	11	23
Boys planned (UMCG)	2	4	6	4	4	8	5	3	8	11	11	22
Boys scanned (UMCG)	1	4	5	4	3	7	3	3	6	8	10	18
Boys analyzed (UMCG)	1	4	5	4	3	7	3	3	6	8	10	18
Total girls planned	7	8	15	9	7	16	7	9	16	23	24	47
Total girls scanned	7	8	15	7	6	13	6	9	15	20	23	43
Total girls analyzed	7	7	14	7	6	13	6	9	15	20	22	42
Girls planned (Vumc)	2	4	6	8	3	11	3	4	7	13	11	24
Girls scanned (Vumc)	2	4	6	6	3	9	2	4	6	10	11	21
Girls analyzed (Vumc)	2	3	5	6	3	9	2	4	6	10	10	20
Girls planned (UMCG)	5	4	9	1	4	5	4	5	9	10	13	23
Girls scanned (UMCG)	5	4	9	1	3	4	4	5	9	10	12	22
Girls analyzed (UMCG)	5	4	9	1	3	4	4	5	9	10	12	22

TABLE A2 Inclusion resting-state fMRI measurement

Resting-state fMRI measurement	Aerobic exercise intervention			Cognitively demanding exercise			Control group			Total		
	Grade 3	Grade 4	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4	Total
Total planned	15	15	30	17	15	32	15	16	31	47	46	93
Total scanned	14	15	29	15	13	28	11	16	27	40	44	84
Total analyzed	13	14	27	14	12	26	10	16	26	37	42	79
Total planned (Vumc)	8	7	15	12	7	19	6	8	14	26	22	48
Total scanned (Vumc)	8	7	15	10	7	17	4	8	12	22	22	44
Total analyzed (Vumc)	7	6	13	10	7	17	4	8	12	21	21	42
Total planned (UMCG)	7	8	15	5	8	13	9	8	17	21	24	45
Total scanned (UMCG)	6	8	14	5	6	11	7	8	15	18	22	40
Total analyzed (UMCG)	6	8	14	4	5	9	6	8	14	16	21	37
Total boys planned	8	7	15	8	8	16	8	7	15	24	22	46
Total boys scanned	7	7	14	8	7	15	5	7	12	20	21	41
Total boys analyzed	6	7	13	7	6	13	4	7	11	17	20	37
Boys planned (Vumc)	6	3	9	4	4	8	3	4	7	13	11	24
Boys scanned (Vumc)	6	3	9	4	4	8	2	4	6	12	11	23
Boys analyzed (Vumc)	5	3	8	4	4	8	2	4	6	11	11	22
Boys planned (UMCG)	2	4	6	4	4	8	5	3	8	11	11	22
Boys scanned (UMCG)	1	4	5	4	3	7	3	3	6	8	10	18
Boys analyzed (UMCG)	1	4	5	3	2	5	2	3	5	6	9	15
Total girls planned	7	8	15	9	7	16	7	9	16	23	24	47
Total girls scanned	7	8	15	7	6	13	6	9	15	20	23	43
Total girls analyzed	7	7	14	7	6	13	6	9	15	20	22	42
Girls planned (Vumc)	2	4	6	8	3	11	3	4	7	13	11	24
Girls scanned (Vumc)	2	4	6	6	3	9	2	4	6	10	11	21
Girls analyzed (Vumc)	2	3	5	6	3	9	2	4	6	10	10	20
Girls planned (UMCG)	5	4	9	1	4	5	4	5	9	10	13	23
Girls scanned (UMCG)	5	4	9	1	3	4	4	5	9	10	12	22
Girls analyzed (UMCG)	5	4	9	1	3	4	4	5	9	10	12	22

TABLE A3 Results of principal component analysis on the neurocognitive measures (baseline)

Neurocognitive measure	Information processing & control	Interference control	Attention accuracy	Visuospatial working memory	Verbal working memory	Attention efficiency
Information processing	0.864					
Lapses of attention	0.841					
Speed of alerting attention						−0.775
Accuracy of alerting attention			0.860			
Speed of spatial attention						0.824
Accuracy of spatial attention			−0.850			
Speed of interference control		0.845				
Accuracy of interference control		0.814				
Verbal short-term memory					0.836	
Verbal working memory					0.793	
Visuospatial working memory				0.803		
Visuospatial short-term memory				0.842		
Motor inhibition	0.583					
Eigenvalue	1.923	1.502	1.501	1.465	1.385	1.354
Variance explained by component	0.148	0.115	0.114	0.111	0.106	0.104

Note: Please refer to Table 2 for a description of the measures; Only factor loadings > .300 are presented.