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Childhood exercise predicts response inhibition in later life via changes in brain connectivity and structure

Toru Ishihara[a,b], Atsushi Miyazaki[b,1], Hiroki Tanaka[b,c], Takayuki Fujii[b], Muneyoshi Takahashi[b,2], Kuniyuki Nishina[b,3], Kei Kanari[b,4], Haruto Takagishi[b], Tetsuya Matsuda[b,*]

[a] Graduate School of Human Development and Environment, Kobe University, 3-11 Tsurukabuto, Nada-ku, Kobe 657-8501, Japan
[b] Tamagawa University Brain Science Institute, 6-1-1 Tamagawagakuen, Machida, Tokyo 194-8610, Japan
[c] Japan Society for the Promotion of Science, 5-3-1 Kojimachi, Chiyoda-ku, Tokyo 102-0083, Japan

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ABSTRACT

Participation in exercise during early life (i.e., childhood through adolescence) enhances response inhibition; however, it is unclear whether participation in exercise during early life positively predicts response inhibition in later life. This historical cohort study was designed to clarify whether participation in exercise (e.g., structured sports participation) during early life predicts response inhibition in adulthood and if so, to reveal the brain connectivity and cortical structures contributing to this association. We analyzed data derived from 214 participants (women = 104, men = 110; age: 26–69 years). Results indicated that participation in exercise during childhood (before entering junior high school; ≤ 12 years old) significantly predicted better response inhibition. No such association was found if exercise participation took place in early adolescence or later (junior high school or high school; ≥ 12 years old). The positive association of exercise participation during childhood with response inhibition was moderated by decreased structural and functional connectivity in the frontoparietal (FPN), cingulo-opercular (CON), and default mode networks (DMN), and increased inter-hemispheric structural networks. Greater cortical thickness and lower levels of dendritic arborization and density in the FPN, CON, and DMN also moderated this positive association. Our results suggest that participation in exercise during childhood positively predicts response inhibition later in life and that this association can be moderated by changes in neuronal circuitry, such as increased cortical thickness and efficiency, and strengthened inter-hemispheric connectivity.

1. Introduction

Inhibitory control is an aspect of top-down cognitive control (also called executive function) that refers to the ability to control one's attention, behavior, thoughts, and/or emotions to override a strong internal predisposition or external distraction and focus on more adaptive and relevant stimuli (Diamond, 2013). Inhibitory control can be subdivided into interference control (cognitive inhibition and inhibition at the level of attention) and response inhibition (inhibition at the level of behavior) (Diamond, 2013). Although both of these controls contribute to academic success (Brookman-Byrne et al., 2018; Cantin et al., 2016; Diamond, 2013; Wilkinson et al., 2020), response inhibition plays a further essential role in overruling impulsive reactions to improve health-related behaviors (Allom et al., 2016). Thus, strategies designed to enhance response inhibition have become increasingly important from public health perspectives (Allom et al., 2016; Diamond, 2013; Diamond and Lee, 2011).

Exercise, such as sports, represents a low-cost method of enhancing cognitive control, regardless of age (Ludyga et al., 2020). Notably, neuroimaging studies have demonstrated that exercise intervention affects brain structure and function in regions critically involved in cognitive control (Meijer et al., 2020; Kramer and Colcombe, 2018; Stillman et al., 2020). These reports suggest that the causal relationship between exercise and cognitive control can be explained by changes in brain structure and function. Cognitive control and related neural systems de-

* Corresponding author at: Tamagawa University Brain Science Institute, 6-1-1 Tamagawagakuen, Machida, Tokyo 194-8610, Japan.
E-mail address: tetsuya@lab.tamagawa.ac.jp (T. Matsuda).
[1] This author is now at Global Education Center, Waseda University, Tokyo, Japan.
[2] This author is now at Department of Management Science, College of Engineering, Tamagawa University, Tokyo, Japan.
[3] This author is now at Osaka University, Graduate School of Human Sciences, Osaka, Japan.
[4] This author is now at Faculty of Engineering, Utsunomiya University, Utsunomiya, Japan.

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velop gradually over many years and are fully developed at around 16 years of age (Baum et al., 2017; Luna, 2009). Response inhibition is highly sensitive to environmental changes during these maturation periods (Bezdjian et al., 2014). Accordingly, exercise during childhood and through adolescence could have a more substantial influence on response inhibition and related neural systems than during other periods. Such exercise-induced functional and neural changes related to response inhibition during maturation may have a sustained influence on inhibitory control in later life (Dik et al., 2003; Ferro et al., 2016). Although a few studies have reported a positive relationship between exercise during early life and cognitive control in later life (Dik et al., 2003; Ferro et al., 2016), no studies have yet identified the contribution of brain structure and function to this association. The present study was designed to clarify the contributions of brain structural and functional changes to the association of exercise participation during early life with response inhibition in later life.

During cognitive maturation, the modular segregation of structural and functional brain networks becomes more distinct (Baum et al., 2017; Dosenbach et al., 2010; Satterthwaite et al., 2013; Wang et al., 2020), with increased connectivity within modules and decreased connectivity between modules, which in turn, contributes to the development of cognitive control (Baum et al., 2017; Wang et al., 2020). Accordingly, if participation in exercise during early life was positively associated with response inhibition in late life, this association could be explained by modular segregation of structural and functional brain networks. Previous research has indicated that, during cognitive control tasks, particular regions of the frontoparietal network (FPN; including the dorsal and ventral prefrontal cortices, dorsal parietal cortex, and dorsal anterior cingulate cortex) and cingulo-opercular network (CON; including the anterior cingulate cortex, presupplementary motor area, and anterior insula) are activated, while the default mode network (DMN; including the medial prefrontal cortex, posterior cingulate cortex, and occipital–parietal junction) is deactivated (Anticevic et al., 2012; Dosenbach et al., 2007; Marek and Dosenbach, 2018; Smith et al., 2018). These patterns of neural activity are also seen during a response inhibition task (Elton and Gao, 2015; Swick et al., 2011; Zhang et al., 2017). Since the modular segregation of these networks supports the development of cognitive control during the age of 8 to 22 years (Baum et al., 2017), the present study focused on these three networks.

Several studies have attempted to elucidate the relationship between exercise and brain structure and function, using only a single variable in terms of cortical thickness, volume, white matter integrity, and task-evoked activation (Chaddock-Heyman et al., 2013; Davis et al., 2011; Drollette et al., 2018; Hillman et al., 2014; Hsu et al., 2018; Kamijo et al., 2011; Ludyga et al., 2018; Taubert et al., 2011; Voss, 2010). However, a comprehensive, multimodal magnetic resonance imaging (MRI) approach (i.e., analyses of structural and functional connectivity, cortical thickness, myelination, dendritic arborization, and density) is required to clarify the mechanisms underlying the positive association between exercise and response inhibition. The development of cognitive control is associated with changes in brain networks and cortical thickness (Kharitonova et al., 2013; Tamnes et al., 2010). In addition, changes in brain networks are associated with myelination (Huntenburg et al., 2017) and synaptic connections. Therefore, in the present study, we utilized a multimodal MRI approach to investigate the relationship between participation in exercise during early life and response inhibition in later life. We focused on brain connectivity, cortical thickness (which reflects the size of neurons, nerve fibers, and neuroglia), myelination (which reflects levels of cortical myelin that provides insulation for axons and is necessary for saltatory conduction), the orientation dispersion index (ODI, which reflects the bending and fanning of axons and areas of crossing fibers), and the neurite density index (NDI, which reflects the intracellular volume fraction, and estimates the density of axons within a voxel).

Previous studies have shown that brain structure and function mediate the positive association of physical fitness as a marker of physical activity (including both exercise and unstructured movement forms) with cognitive control (Hyodo et al., 2016; Ishihara et al., 2020; Kawagoe et al., 2017; Oberlin et al., 2016; Opel et al., 2019; Weinstein et al., 2012). For example, the brain network properties obtained by resting-state fMRI were shown to mediate the positive association between cardiorespiratory fitness and cognitive control (Kawagoe et al., 2017). A previous study demonstrated that the task-evoked functional activation patterns in the FPN and DMN mediated the positive association between physical fitness and cognitive control in adults (Ishihara et al., 2020). These findings suggest that exercise leads to changes in brain structure and function, which improve cognitive control.

The moderating role of brain structure and function on the positive association of physical fitness with cognitive control was also reported (Ruotsalainen et al., 2020). A previous study suggested that individual variations, such as white matter structure, influences the association between physical fitness and cognitive control (Ruotsalainen et al., 2020). These findings suggest that the cognitive benefits from exercise could be observed only when changes in brain structure and function have occurred. In addition, it may be reasonable to consider that the sustained association between exercise habits during early life and response inhibition in later life would be observed only if the changes in brain structure and function are maintained.

We examined the cross-sectional associations among retrospectively obtained early life exercise participation and response inhibition, evaluated by cognitive tests, as well as large-scale multimodal MRI data, including T1-weighted images, T2-weighted images, resting-state fMRI, and diffusion-weighted images. The first aim of the present study was to examine the possible association between early life exercise participation and response inhibition in late life. The second aim was to examine whether brain connectivity and cortical structure in the FPN, CON, and DMN influenced this association. We hypothesized that participation in exercise during early life would show a sustained positive relationship with response inhibition and that this relationship could be mediated or moderated by changes in structural and functional connectivity and cortical structure (i.e., thickness, myelination, NDI, and ODI) in the FPN, CON, and DMN.

2. Materials and methods

2.1. Participants

This study was conducted as part of a research project initiated in May 2012, and the 10th wave of the project is underway as of March 2021. Participants included the residents of suburban Tokyo and surrounding areas. From the original list of 600 registered participants, 564 were included in the first wave of the study. We included 286 potential participants who underwent MRI in accordance with the protocol recommended by the Human Connectome Project. Findings concerning some of the data collected during the 10 phases have been previously reported (Matsumoto et al., 2016; Nishina et al., 2015, 2018, 2019; Yamagishi et al., 2014, 2015, 2016, 2017).

Seventy-two participants were removed from subsequent data analysis due to head-motion artifacts ($N = 29$), missing data (physical activity: $N = 21$; exercise participation: $N = 6$; response inhibition: $N = 12$), and having a history of neurological disorders (brain tumor: $N = 1$, epilepsy: $N = 1$, cerebral infarction: $N = 1$, pituitary adenoma: $N = 1$), resulting in a total of 214 participants (women = 104, men = 110; age range: 26 to 69 years).

All experimental protocols were approved by the Ethics Committee of the Brain Science Institute at Tamagawa University, where the study was conducted. All procedures were conducted in accordance with the tenets of the Declaration of Helsinki. All participants provided written informed consent after having received a full explanation of the nature and possible consequences of the study.

2.2. Assessment of exercise participation in early life and adulthood

Data regarding exercise participation were collected using a questionnaire between July 16, 2018, and November 24, 2018 (10th wave). Exercise participation during childhood and adulthood was defined as continued participation in exercise, such as a structured physical activity program, for more than 1 year. Participants reported the starting age (years), period (years), frequency (sessions/week), and duration (hours/session) of all exercise. The frequency (sessions/week) and duration (hours/session) were reported separated for weekdays and weekends. In Japan, most schools offer extracurricular activities, such as badminton, baseball, basketball, football, table tennis, tennis, swimming, and volleyball. Approximately 65% of junior high school students and 42% of high school students participate in these activities (Ministry of Education, Culture, Sports, Science and Technology, 2018). Furthermore, approximately 80% of junior and senior high school students who engaged in these activities participated in these activities for more than 6 days per week (Ministry of Education, Culture, Sports, Science and Technology, 2018). Data regarding exercise participation were obtained and categorized based on developmental stages (childhood [before entering junior high school, ≤ 12 years], early adolescence [junior high school, 12 to 15 years], later adolescence [high school, 15 to 18 years], and adulthood [≥ 18 years, including current status]). In addition, to evaluate the dose–response relationship, the total number of hours of participation in exercise was calculated based on the period (years), frequency (sessions/week), and duration (hours/session) of the activity, following a previous study (Killgore et al., 2013). A previous study reported that the long-term recall of the amount of physical activity was reliable and that the reliability was not affected by recall interval and age (Blair et al., 1991).

2.3. Assessment of current physical activity levels

Current physical activity levels were assessed using the International Physical Activity Questionnaire (IPAQ) (Craig et al., 2003), administered between July 16, 2018, and November 24, 2018 (10th wave). The 31-item IPAQ was designed to collect detailed information regarding household and yard work activities, occupational activities, self-powered transport, leisure-time physical activity, and sedentary activity during the preceding week. We calculated overall physical activity levels (Mets × min/week) for categories that included walking, moderate-intensity activity, vigorous-intensity activity, and sedentary activity. For more details, see Craig et al. (2003).

2.4. Assessment of response inhibition

Response inhibition was assessed using a computer-based Go/No-go task, conducted between October 25, 2014, and January 25, 2015 (7th wave). The Go/No-go task is a well-known paradigm for assessing inhibitory control (Zhang et al., 2017). In this task, participants were required to respond to frequent stimuli (80% probability, letter "M") and to withhold responding to rare stimuli (20% probability, letter "W"). Prior to the task, participants read the instructions and performed practice trials (20 self-paced trials and 10 trials performed under the same conditions used for the actual trials). Participants then completed 300 trials (100 trials × 3 blocks with a 1-min rest interval between the blocks). The viewing distance was approximately 50 cm. The stimuli subtended a horizontal visual angle of 4.6° for the letter "W," 3.4° for the letter "M," and a vertical visual angle of 4.0° for the letters "W" and "M". The stimulus was presented following 1000 ms of blank and 500 ms of fixation. The stimulus duration was 500 ms and was presented until the participant responded. When participants were unable to respond to the Go stimulus (i.e., letter "M") within 500 ms, the trial was considered an omission error. Participants were informed that they would receive 5 Japanese yen per correct response as a reward. The main dependent variables were mean reaction time and response accuracy (hit rate for Go trials; false alarm rate for No-go trials).

2.5. Assessment of other confounding variables

We evaluated potential confounders, including education, number of siblings, and parental education. Education levels were determined based on responses to a single questionnaire item (obtained between May 17, 2012 and July 22, 2012 [1st wave]) ("Have you completed undergraduate studies?"), which was coded as follows: (i) *I did not complete undergraduate studies*; and (ii) *I completed undergraduate studies*. Participants reported the number of siblings using a free-response questionnaire (administered between October 6, 2012, and February 16, 2013 [2nd wave]). Parental levels of education were assessed based on responses to two questionnaire items (obtained between October 6, 2012, and February 16, 2013 [2nd wave]) ("What is the father's highest level of education?", "What is the mother's highest level of education?"), which were coded as follows: (i) *did not complete undergraduate studies*; (ii) *completed undergraduate studies*.

2.6. MRI data acquisition

MRI data were acquired between November 11, 2016 and March 3, 2018 (9th wave). All imaging data (T1- and T2-weighted images, resting-state fMRI, and diffusion-weighted images) were acquired at the Tamagawa University Brain Science Institute (Machida, Japan) using a 3-T Trio Tim scanner (Siemens, Erlangen, Germany) equipped with a 32-channel head coil. First, resting-state fMRI data were acquired using the following parameters: voxel size = 2 mm^3, 72 slices/MB8, iPAT = 0, 7/8 partial Fourier, PE =AP/PA, TR/TE = 750/33 ms, and acquisition time = 8 min. Thereafter, we acquired two sets of T1- and T2-weighted high-resolution anatomical images (voxel size = 0.8 mm^3; acquisition time = 5 to 6 min). The diffusion-weighted images were acquired using the following parameters: voxel size = 1.7 mm^3, 87 slices/MB3, iPAT = 2, 6/8 partial Fourier, PE = AP/PA, TR/TE = 4500/94 ms, b-value = 0.7, 2k HARDI, dir = 32, 64, and acquisition time = 5–6 min. The resting-state fMRI data and diffusion-weighted images were acquired twice with reversed phase-encoding direction (anterior–posterior and posterior–anterior).

2.7. Preprocessing and analysis of MRI data

2.7.1. Software

We used the following software in the preprocessing and analysis of MRI data: The FMRIB (Functional Magnetic Resonance Imaging of the Brain) Software Library (FSL) version 5.0.9, FMRIB's ICA-based Xnoiseifier (FIX) version 1.062, FreeSurfer version 5.3.0-HCP, Human Connectome Project Pipeline version 3.22.0, and ConnectomeWorkbench version 1.2.3.

2.7.2. Cortical structure

The Human Connectome Project structural preprocessing pipelines (Glasser et al., 2013) include PreFreeSurfer, FreeSurfer, and PostFreeSurfer components. The PreFreeSurfer pipeline includes the following five procedures: (i) aligning and averaging repeated T1- and T2-weighted scans of good or excellent quality, when available; (ii) removing gradient nonlinearity and readout distortion (static field [b0] distortion in three-dimensional images) to create an unbiased "native" volume space for each participant that is rigidly aligned to the Montreal Neurological Institute (MNI) template; (iii) cross-modal alignment between the T1- and T2-weighted images with FreeSurfer's boundary-based registration (BBR) method (Greve and Fischl, 2009); (iv) bias field correction using the square root (T1-weighted × T2-weighted), and (v) nonlinear volume-based registration to the MNI template using FSL's FNIRT algorithm. A customized version of FreeSurfer version 5.3′s recon-all was used to generate white and pial cortical surfaces

(using both T1- and T2-weighted volumes at 0.8-mm resolution), including subcortical segmentation, all carried out in the participants' native volume space. PostFreeSurfer was used to convert the FreeSurfer data into standard NIFTI, GIFTI, and CIFTI file formats, and to bring the data into MNI space. The Multimodal Surface Matching (MSM) surface registration algorithm (Robinson et al., 2014) was used to perform an initial, gentle, non-rigid surface registration based on folding patterns (MSMSulc). This method has replaced the FreeSurfer folding-based registration used in previous studies (Glasser et al., 2013), because it achieves slightly better initial alignment of functionally corresponding regions (e.g., task fMRI) than the FreeSurfer algorithm while inducing much lower levels of local distortion (Robinson et al., 2014). This registration, together with the FNIRT nonlinear registration, was used to bring an initial version of the data into standard grayordinates space (32-k standard mesh for each hemisphere's cortical surface at 2-mm average vertex spacing and 2-mm isotropic MNI-space voxels for the subcortical volume data). Because the gyral crowns tend to be thicker than the sulcal fundi, the FreeSurfer-generated measure of cortical thickness was corrected for folding-related bias by regressing out the FreeSurfer mean curvature measure from each participant's thickness data (Glasser and Van Essen, 2011). Myelin maps were computed using the ratio of T1-weighted/T2-weighted images and normalized for residual transmit field inhomogeneity (Glasser et al., 2014, 2013; Glasser and Van Essen, 2011; Robinson et al., 2014).

2.7.3. Resting-state fMRI

The HCP functional preprocessing pipelines include volumetric- (fMRIVolume) and surface-based (fMRISurface) components (Glasser et al., 2013; Smith et al., 2013), applied to all resting-state fMRI data. The fMRIVolume pipeline includes removing image distortions due to gradient nonlinearity and b0 inhomogeneity; motion correction; cross-modal alignment to the T1-weighted image with BBR (Greve and Fischl, 2009); concatenation of all transforms, including the nonlinear volume registration to MNI space, and resampling the original timeseries into MNI space using a single spline interpolation. Several intensity normalization steps are implemented, including a crude fMRI bias field-correction step, based on the structural data from a separate imaging session (this bias field correction is replaced by a superior strategy in the later processing steps, as described below, and has been incorporated into the latest version of the pipelines), and grand four-dimensional mean normalization to 10,000. The fMRISurface pipeline was then used to map gray matter timeseries data into the 91,282-grayordinate standard space (2-mm average cortical vertex spacing and 2-mm subcortical voxels) using a 2- mm full-width at half-maximum smoothing kernel (constrained to the cortical surface and subcortical gray matter segmentation). These steps produce a "dense timeseries" CIFTI file for each resting-state fMRI run. The crude bias field correction map was also mapped into standard CIFTI space in order to replace it with a better map (by dividing it back and multiplying it by the new correction map).

For resting-state fMRI runs, independent component analysis and FMRIB's ICA-based Xnoisiefier (ICA+FIX) pipeline (Beckmann et al., 2005; Griffanti et al., 2014; Salimi-Khorshidi et al., 2014; Smith et al., 2013) were used to remove spatially specific temporally structured artifacts. The ICA+FIX pipeline includes several steps: (i) High-pass temporal filtering with a sigma of 1000 s (run length = 864 s) to remove linear trends in the data. (ii) MELODIC ICA with auto-dimensionality selection of up to 250 components, producing component spatial maps and timeseries. (iii) Classification of these components into signal and noise categories by the FIX-trained ICA component classifier. (iv) Out-regression of the data and all ICA components of the 24 motion parameters (which were also temporal high-pass-filtered with a sigma of 1000 s). Regression coefficients were computed using all ICA component timeseries, and the noise component timeseries were then weighted by the regression coefficients and subtracted from the data (a "non-aggressive" regression approach). The ICA+FIX algorithms were run on the volumetric timeseries data, after which the high-pass filter and nuisance regression steps were applied to the grayordinates timeseries data. The ICA+FIX cleanup was reapplied to the resting state fMRI-dense timeseries data after the original, uncleaned, native mesh data had been resampled into the standard grayordinates space according to the areal feature-based MSM surface registration. Regression of the mean gray signal ("global signal") was used in early analyses, but this was discontinued because it shifted some resting-state fMRI functional connectivity gradient locations, thereby decreasing cross-modal alignment. No additional spatial smoothing or temporal low-pass filtering was performed, as these types of "lossy" preprocessing steps would reduce the accuracy of the parcellations and proved unnecessary for the purposes of the current study.

Subsequently, we created participant-specific association matrices from the timeseries signals of 360 regions of the brain using GraphVar (Kruschwitz et al., 2015). To construct the brain network, we employed the 360 areas, defined by HCP-style parcellation (Glasser et al., 2016a, b), as nodes. The affiliations of each node within the large-scale brain network and regions were defined based on previous research (Glasser et al., 2016a; Ji et al., 2019). The edges of the brain network were defined as the functional connectivity of all pairs among the 360 areas, using Pearson's correlation coefficients.

2.7.4. Diffusion MRI

Diffusion MRI data were also preprocessed using the HCP pipelines. Briefly, we performed corrections for gradient, B0, eddy current distortions, and cross-modal registration (Glasser et al., 2013; Sotiropoulos et al., 2013). The intensity was normalized by the mean of volumes with $b = 0$ s/mm^2 (b0 volumes), and the B0-inhomogeneity distortion was corrected using two opposing phase-encoded images and FSL's Topup (Andersson et al., 2003). The eddy current-induced field inhomogeneities and head motion for each image volume were corrected using FSL's Eddy, version 5.0.9, prior to HCP's recent re-computation, which included outlier detection (Andersson et al., 2012). The data were then corrected for gradient nonlinearity. The diffusion data were registered to the structural T1-weighted AC-PC space using the b0 volume and the white matter surface using the BBR cost function in FSL and FreeSurfer's BBRegister. The diffusion gradient vectors were rotated based on the rotational information of the b0 to the T1-weighted transformation matrix.

The AMICO toolbox was used to calculate the neurite orientation dispersion and density imaging (NODDI) coefficients. Because it is necessary to optimize the NODDI model when analyzing gray matter structures, as different types of brain tissue may vary considerably with regard to their intrinsic free diffusivity, we adjusted the AMICO toolbox and changed its parameter for intrinsic free diffusivity to 1.1×10^{-3} mm^2/s for our analyses of gray matter structures. Thereafter, we obtained the NDI (the amount of stick-like or cylindrically symmetric diffusion that is created when water molecules are restricted by the membranes of neurites) and ODI (a tortuosity measure, coupling the intra-neurite space and the extra-neurite space, resulting in alignment or dispersion of axons and dendrites in the gray matter). The NODDI parameters were mapped onto the cortical surface using NoddiSurfaceMapping (Fukutomi et al., 2018). For additional details, see Fukutomi et al. (2018).

The tractography matrix was obtained from the preprocessed diffusion MRI data by performing probabilistic tractography using FSL's bedpostX and probtrackX methods (Behrens et al., 2007; Jbabdi et al., 2012). BedpostX allows for the automatic determination of the number of fibers passing through each voxel within the brain and estimates their orientation distribution. ProbtrackX performs probabilistic tractography with respect to estimated fiber orientations. We seeded 1000 streamlines from each of the regions-of-interest (ROIs) and obtained a tractography matrix of the number of streamlines originating from each ROI and reaching the rest of the cerebral cortex. These matrices contained the unnormalized values, which were normalized by dividing each row by the waytotal file.

Table 1
Characteristics of the study participants.

Variable	*N* (%) or mean (*SD*)	Range
N	214	
Sex (female/male)	104 (49%)/110 (51%)	
Age (years)	48 (10)	26 to 69
Educational history (≥ 16 years, i.e., university graduate)	143 (67%)	
Current physical activity level (mets*min/week)		
Walk	1518 (1872)	0 to 11,435
Moderate intensity	1541 (2105)	0 to 14,820
Vigorous intensity	1067 (2908)	0 to 26,880
Exercise participation		
Childhood (before entering junior high school; ≤ 12 years old)	47 (22%)	
Total amount (hours)[a]	1794 (1770)	52 to 7978
Early adolescence (junior high school; 12 to 15 years old)	131 (61%)	
Total amount (hours)[b]	1900 (1019)	156 to 6805
Later adolescence (high school; 15 to 18 years old)	84 (39%)	
Total amount (hours)[c]	2014 (1073)	626 to 7196
Adulthood (≥ 18 years including current status)	124 (58%)	
Total amount (hours)[d]	3708 (7482)	52 to 64,657
Number of siblings (0/1/2 or more)[e]	20 (9%)/102 (49%)/87 (42%)	
Parents' educational history (≥ 16 years, i.e., university graduate)[e]		
Maternal	88 (42%)	
Paternal	100 (48%)	

[a] $N = 47$
[b] $N = 131$
[c] $N = 84$
[d] $N = 124$
[e] $N = 209$

2.8. Statistical analysis

All statistical analyses were conducted using R Studio software version 1.1.463 and GraphVar (version 2.0) (Kruschwitz et al., 2015). Sex, age, educational history, reaction time on the Go/No-go task, current moderate and vigorous physical activity level, adulthood exercise participation, the number of siblings, and parental educational history were used as confounders in all analyses. We assessed the normality of all continuous variables using the Kolmogorov–Smirnov test. Using a robust standard error, multiple regression analyses predicting Go/No-go task performance (hit rate for go trials; false alarm rate for no-go trials) were performed to analyze the relationship between exercise participation in early life and Go/No-go task performance, as well as the interaction effects of age or sex with exercise participation during early life on Go/No-go task performance, after controlling for confounders.

GraphVar was utilized for analyses of structural and functional connectivity (Kruschwitz et al., 2015). Since GraphVar cannot run the regression analysis using the brain network as an independent variable, Go/No-go task performance was regressed out for all confounders, and the residuals standardized before performing connectivity analyses. All confounding variables were entered as the nuisance covariates in connectivity analyses. This process produces similar statistics for the relationship between Go/No-go task performance and brain connectivity, regardless of whether Go/No-go task performance or brain connectivity is used as the independent variable.

To test the mediating role of structural and functional connectivity, regression analyses were performed separately to predict connectivity by early life exercise participation and Go/No-go task performance, followed by mediation analyses where appropriate. To test the moderating role of structural and functional connectivity, regression analyses were performed to predict connectivity by interaction effects of early life exercise participation and Go/No-go task performance. Where appropriate, post-hoc analysis was performed to analyze whether the relationship between connectivity and Go/No-go task performance was affected by participants' early life exercise participation.

To test the mediating role of cortical structure (i.e., thickness, myelination, ODI, and NDI), we performed regression analyses predicting Go/No-go task performance by cortical structure and predicting cortical structure by early life exercise participation, and then performed mediation analyses where appropriate. To test the moderating role of cortical structure, we used regression analyses predicting Go/No-go task performance by interaction effects of early life exercise participation and cortical structure.

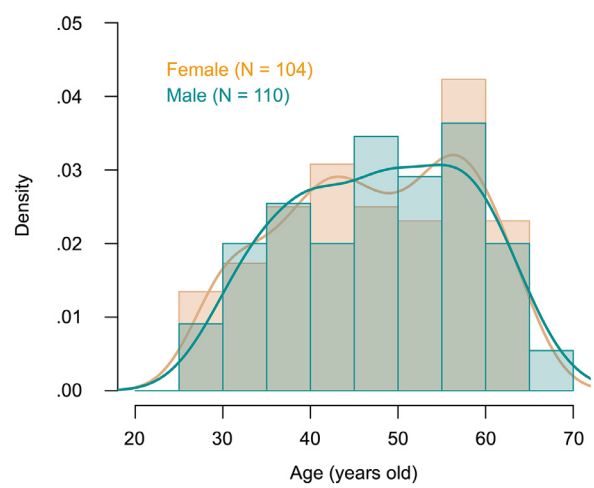

Fig. 1. Density histograms of age by sex.

Where appropriate, variables were square root-transformed to conform to the assumption of a normal distribution. Given the sample size of 214 participants and a power = 0.80, the present study theoretically had sufficient sensitivity to detect an effect size exceeding $f^2 = 0.04$ for the variance explained by each variable while accounting for confounders in the regression analysis (G*Power 3.1) (Faul et al., 2007, 2009).

3. Results

The demographic characteristics of study participants are presented in Table 1. Density histograms of age by sex is presented in Fig. 1.

Table 2
Multiple regression analyses of false alarm rate in the Go/No-go task.

Variable	Crude model					Adjusted model				
	β	*SE*	95% *CI*	*t*	*p*	*β*	*SE*	95% *CI*	*t*	*p*
Early life exercise participation (No = 0, Yes = 1)										
Childhood (before entering junior high school; ≤ 12 years old)	−.17	.07	−.30 to −.04	−2.65	.009	−.16	.07	−.30 to −.03	−2.36	.02
Early adolescence (junior high school; 12 to 15 years old)	−.07	.07	−.21 to 0.07	−1.03	.30	−.03	.07	−.17 to 0.11	−0.43	.67
Later adolescence (high school; 15 to 18 years old)	.01	.07	−.12 to 0.15	0.16	.88	−.003	.07	−.14 to 0.13	−0.05	.96
Confounders										
Sex						−.13	.06	−.25 to −.0009	−1.99	.05
Age						.003	.07	−.13 to 0.13	0.05	.96
Educational history (< 16 years = 0, ≥ 16 years = 1)						−.05	.07	−.19 to 0.09	−0.67	.50
Reaction time						−.36	.09	−.54 to −.18	−4.00	< 0.001
Current moderate physical activity level						.02	.06	−.10 to 0.14	0.39	.70
Current vigorous physical activity level						.006	.08	−.14 to 0.15	0.08	.94
Exercise participation during adulthood including current status (No = 0, Yes = 1)						.05	.06	−.07 to 0.17	0.82	.41
Number of siblings (0 siblings = 0, 1 or more siblings = 1)						.06	.07	−.07 to 0.19	0.95	.34
Maternal educational history (< 16 years = 0, ≥ 16 years = 1)						.003	.07	−.15 to 0.14	−0.05	.96
Paternal educational history (< 16 years = 0, ≥ 16 years = 1)						−.06	.08	−.21 to 0.10	−0.71	.48

Note: SE = standard error; *CI* = confidence interval. False alarm rate is square root-transformed to conform to the assumption of a normal distribution.

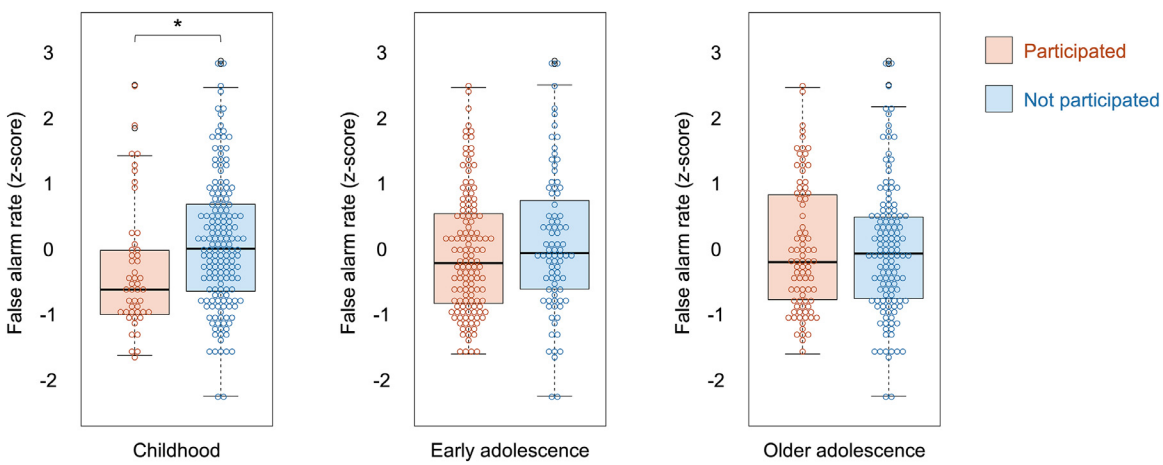

Fig. 2. The relationship between exercise participation during early life and inhibitory control. Results of the unadjusted model; * $p = .009$.

3.1. Exercise participation during early life and GO/NO-GO task performance

Since the false alarm rate was not normally distributed, the value was square root-transformed to conform to the assumption of normality. The results of multiple regression analyses are summarized in Table 2. Participation in exercise (coded as No = 0, Yes = 1) during childhood was inversely associated with the false alarm rate ($\beta = -.17$, $p = .009$), while no such association was observed in either early or late adolescence (βs = –.07 and 0.01, *p*s = 0.30 and 0.88, respectively) (Fig. 2). The same pattern was also observed after controlling for confounders (Table 2). There was no dose–response relationship between the total hours of exercise participation during childhood and the false alarm rate in any model (childhood: βs = –.11 to –.10, *p*s = 0.15 to 0.19, early adolescence: βs = –.08 to –.06, *p*s = 0.31 to 0.38, later adolescence: βs = 0.02 to 0.06, *p*s = 0.41 to 0.79; **Supplementary Table 1**). There were no age or sex × exercise participation during early life effects on the false alarm rate in any model (**Supplementary Table 2**). There was no significant relationship between exercise participation during early life and hit rate (**Supplementary Table 3**). Thus, we focused our subsequent analyses on the association between exercise participation during early life and the false alarm rate.

3.2. Structural connectivity

3.2.1. Mediation role

No patterns of structural connectivity were associated with both exercise participation during childhood and the false alarm rate (false-discovery rate [FDR] corrected $p \geq .05$). Thus, mediation effects of structural connectivity on the positive association between childhood exercise participation and false alarm rate were not verified.

3.2.2. Moderation role

In the 69 networks from 72 regions identified via diffusion tractography, the interaction between exercise participation during childhood and the false alarm rate was significant (FDR corrected $p < .05$ [uncorrected $p < .0002$]). The glass brains and circle plots are presented in Fig. 3A and B. Twenty-six connections (38%) showed positive coefficients, and 43 (62%) showed negative coefficients. Post-hoc analyses demonstrated that, in participants with childhood exercise participation, 25 connections were positively associated with the false alarm rate and 42 connections were negatively associated with the false alarm rate (FDR-corrected $p < .05$ [uncorrected $p < .0004$]; Fig. 3C), while no such associations were found in participants without childhood exercise par-

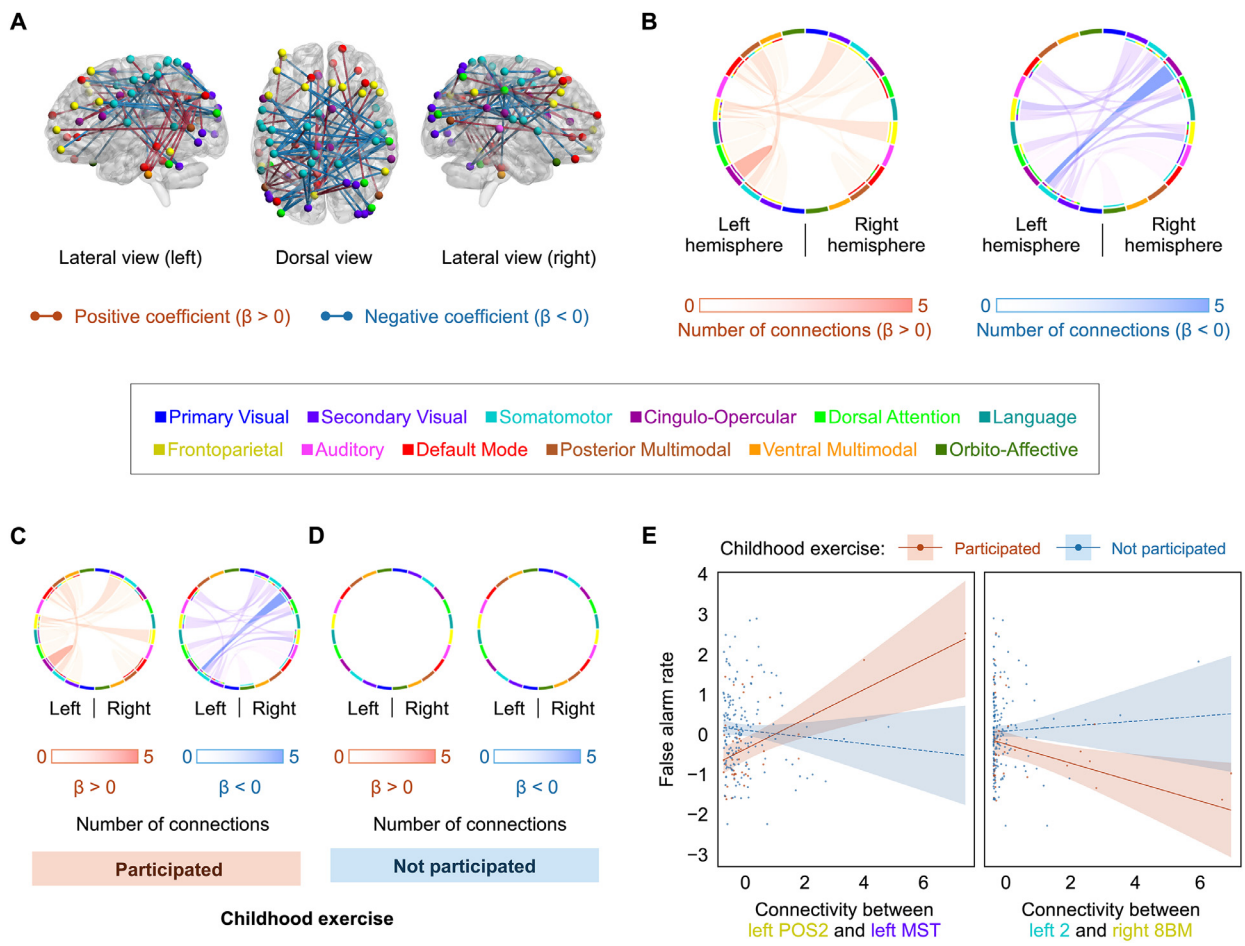

Fig. 3. Structural connectivity moderates the positive relationship between exercise participation during childhood and response inhibition. A. Glass brains showing whole-brain connectivity analyses revealed significant interactions between exercise participation during childhood (coded as No = 0, Yes = 1) and false alarm rate (FDR-corrected $p < .05$). The node color reflects the affiliation of the networks. The blue line indicates the negative value of β, whereas the orange line indicates the positive value of β. B. Circle plots showing the significant interaction between exercise participation during childhood and the false alarm rate (FDR-corrected $p < .05$). C and D. Circle plots showing the significant associations between structural connectivity and the false alarm rate in each group (C. participants with childhood exercise participation, D. Participants without childhood exercise participation; FDR-corrected $p < .05$). E. Typical examples from the results of the moderation effects of structural connectivity on the association between childhood exercise participation and the false alarm rate. Regression lines are shown with 95% confidence bands (shaded areas). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

ticipation (FDR corrected $p \geq .05$; Fig. 3D). The typical pattern of these interaction effects is presented in Fig. 3E.

The proportion of each network combination in a significant interaction is summarized in Fig. 4. Based on our hypothesis, we focused on the FPN, CON, or DMN. In the connections that showed significant positive coefficients for the interaction, 19 (73%) were inter-network connections, and seven (27%) were intra-network connections. Eighteen connections (69%) were intra-hemispheric, and eight (31%) were inter-hemispheric (Fig. 4). Fifteen connections (58%) involved inter-network connectivity of the FPN, CON, or DMN with other networks; two connections (8%) involved inter-network connectivity among the FPN, CON, and DMN, and seven connections (27%) involved intra-network connectivity among the FPN, CON, and DMN (Fig. 4).

In the connections that showed negative coefficients for interaction, 40 (93%) were inter-network connections, and seven (7%) were intra-network connections. Five connections (12%) were intra-hemispheric connections, and 38 (88%) were inter-hemispheric connections (Fig. 4). Twenty-six connections (60%) involved inter-network connectivity of the FPN, CON, or DMN with other networks; three connections (7%) involved inter-network connectivity among the FPN, CON, and DMN, and no connections involved intra-network connectivity among the FPN, CON, and DMN (Fig. 4). The detailed statistics from GraphVar (B value and p-value in all connections) are summarized in **Supplementary Files 1 to 6**.

3.3. Functional connectivity

3.3.1. Mediation role

No functional connectivity patterns were associated with both exercise participation during childhood and the false alarm rate (FDR corrected $p \geq .05$). Thus, mediation effects of functional connectivity on the positive association between childhood exercise participation and the false alarm rate were not verified.

3.3.2. Moderation role

In the 46 networks from 52 regions identified via resting-state functional connectivity, the interaction between exercise participation during childhood and the false alarm rate was significant (FDR corrected $p < .05$ [uncorrected $p < .0002$]). Glass brains and circle plots are presented in Figs. 5A and B. All connections showed positive coefficients. Post-hoc analyses demonstrated that, in participants with childhood exercise participation, 27 connections were positively associated with the false alarm rate (FDR-corrected $p < .05$ [uncorrected $p < .0003$]; Fig. 5C), while no such associations were found in participants without

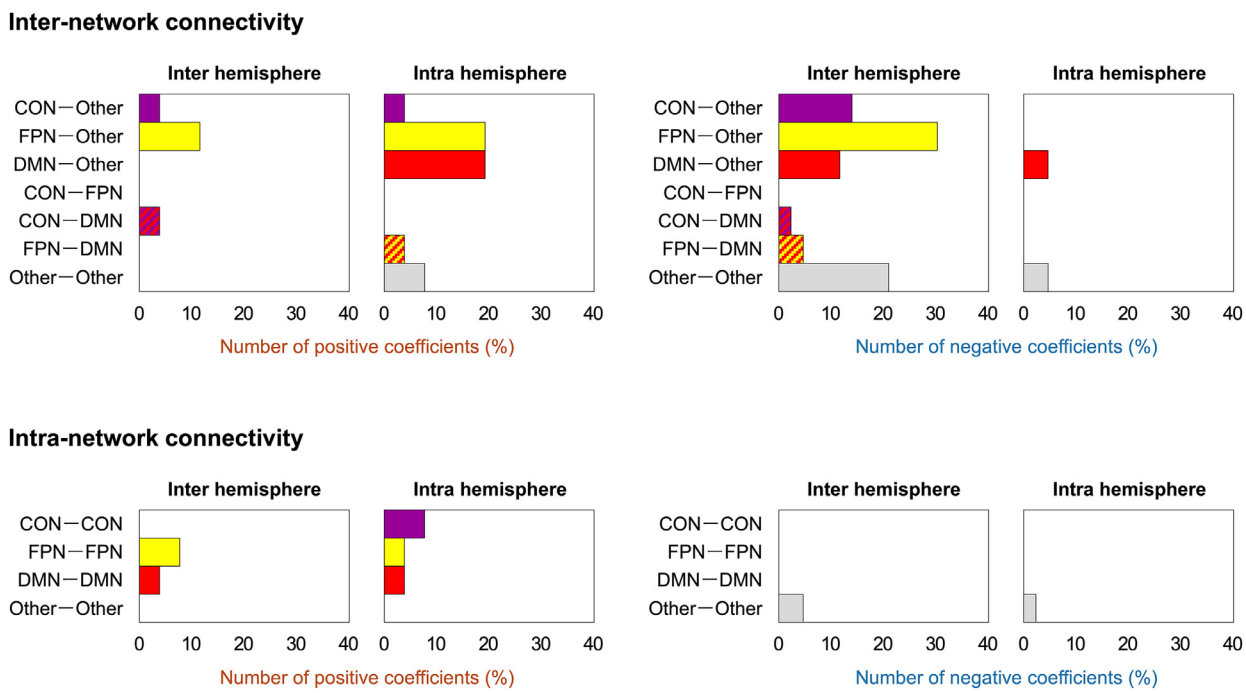

Fig. 4. The proportion of each combination of networks in a significant interaction identified via diffusion tractography. CON = cingulo-opercular network; FPN = frontoparietal network; DMN = default mode network.

childhood exercise participation (FDR corrected $p \geq .05$; Fig. 5D). The typical pattern of these interaction effects is presented in Fig. 5E.

The proportion of each network combination in a significant interaction is summarized in Fig. 6. Based on our hypothesis, we focused on the FPN, CON, or DMN. Of the connections that showed significant positive coefficients regarding the interaction, 42 (91%) were inter-network connections and four (9%) were intra-network connections. Twenty-seven connections (59%) were intra-hemispheric, and 19 (41%) were inter-hemispheric (Fig. 6). Twenty-three connections (50%) involved inter-network connectivity of the FPN, CON, or DMN with other networks; 18 connections (39%) involved inter-network connectivity among the FPN, CON, and DMN; and 4 connections (9%) involved intra-network connectivity among the FPN, CON, and DMN (Fig. 6). The detailed statistics from GraphVar (*B* value and *p*-value in all connections) are summarized in **Supplementary Files 7 to 12**.

3.4. Microstructural and macrostructural organization in the cortex

We investigated whether cortical structural indices (i.e., cortical thickness, myelination, the ODI, and the NDI), identified via either diffusion tractography or resting-state functional connectivity analyses, mediated or moderated the relationship between exercise participation during childhood and the false alarm rate via multiple regression analyses using a robust standard error. Based on our hypothesis, we focused on the 59 regions included in the FPN, CON, or DMN.

3.4.1. Mediation role

No cortical structural indices mediated the positive association between exercise participation during childhood and the false alarm rate ($p \geq .05$). Thus, mediation effects of cortical structure on the positive association between childhood exercise participation and false alarm rate were not verified.

3.4.2. Moderation role

Multiple regression analyses for predicting the false alarm rate revealed a significant interaction between exercise participation during childhood and cortical thickness in the insular cortex (left PI: $\beta = -0.25$, FDR corrected $p < .05$ [uncorrected $p = .0003$]). No other significant interaction effects were found (FDR corrected $p \geq .05$). Considering the risk of type-2 error, we further performed multiple regression analyses using the uncorrected *p*-value and confirmed whether the pattern of significant interaction was consistent.

Additional interactions between exercise participation during childhood and cortical thickness were found in eight regions involving the inferior premotor cortex (left 6r: $\beta = -0.11$, uncorrected $p = .03$), posterior opercular cortex (left PFcm and left FOP1: $\beta = -0.18$, uncorrected $p = .006$; $\beta = -0.17$, uncorrected $p = .02$, respectively), frontal opercular cortex (left FOP4: $\beta = -0.18$, uncorrected $p = .004$), inferior frontal cortex (left IFJp: $\beta = -0.15$, uncorrected $p = .008$), orbital and polar frontal cortex (left 13l and left a47r: $\beta = -0.15$, uncorrected $p = .01$; $\beta = -0.12$, uncorrected $p = .04$, respectively), and dorsolateral prefrontal cortex (right 9a: $\beta = -0.18$, uncorrected $p = .004$). The pattern of significant interactions was consistent, and individuals who participated in exercise during childhood exhibited a significantly lower false alarm rate than other participants when they had higher cortical thickness in nine regions (Fig. 7A).

Multiple regression analyses revealed no significant interaction between exercise participation during childhood and cortical myelination in any region (uncorrected $p \geq .05$).

Multiple regression analyses revealed a significant interaction between exercise participation during childhood and ODI in five regions involving the frontal opercular cortex (left FOP4: $\beta = 0.14$, uncorrected $p = .01$), posterior cingulate cortex (right 23c, left POS2, and left 31pd: $\beta = 0.12$, uncorrected $p = .047$; $\beta = 0.12$, uncorrected $p = .03$; $\beta = 0.14$, uncorrected $p = .006$, respectively), inferior frontal cortex (left IFJp: $\beta = 0.16$, uncorrected $p = .02$). The pattern of significant interactions was consistent, and individuals who participated in exercise during childhood exhibited a significantly lower false alarm rate than other participants when their ODI was lower in these five regions (Fig. 7B).

Multiple regression analyses revealed a significant interaction between exercise participation during childhood and NDI in three regions involving the insular cortex (left PI: $\beta = 0.15$, $p = .03$), posterior opercular cortex (left FOP1: $\beta = 0.16$, $p = .01$), and dorsolateral prefrontal cortex (left p9–46v: $\beta = 0.15$, uncorrected $p = .02$). The pattern of sig-

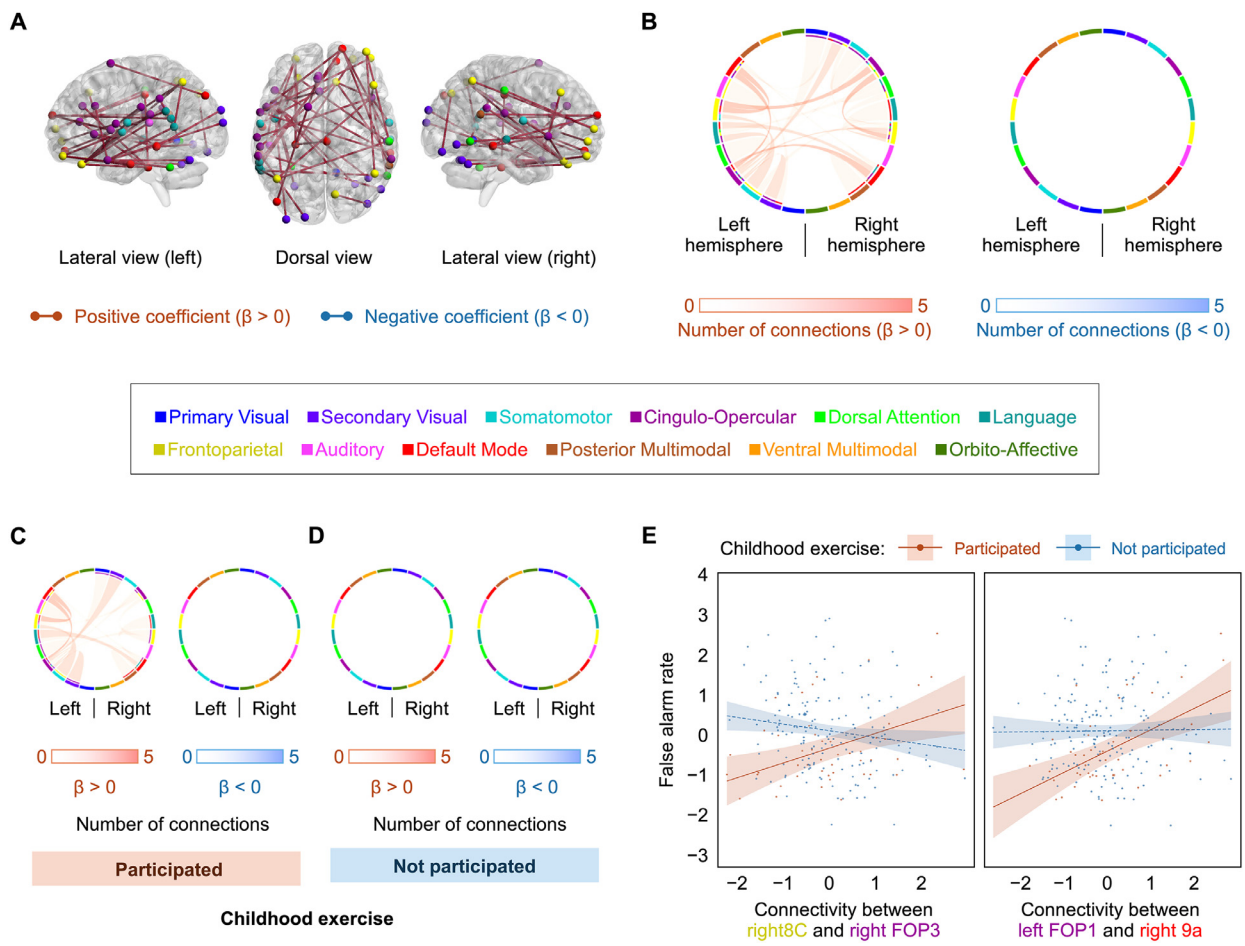

Fig. 5. Functional connectivity moderates the positive relationship between exercise participation during childhood and response inhibition. A. Glass brains showing whole-brain connectivity analyses revealed significant interactions between exercise participation during childhood (coded as No = 0, Yes = 1) and the false alarm rate (FDR-corrected $p < .05$). The node color reflects the affiliation of the networks. The blue line indicates the negative value of β, whereas the orange line indicates the positive value of β. B. Circle plots showing the significant interaction between exercise participation during childhood and the false alarm rate (FDR-corrected $p < .05$). C. Circle plots showing the significant associations between functional connectivity and the false alarm rate in each group (C. participants with childhood exercise participation, D. Participants without childhood exercise participation; FDR-corrected $p < .05$). E. Typical examples from the results of the moderation effects of functional connectivity on the association between childhood exercise participation and the false alarm rate. Regression lines are shown with 95% confidence bands (shaded areas). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

nificant interactions was consistent, and individuals who participated in exercise during childhood exhibited a significantly lower false alarm rate than other participants when their NDI was lower in these three regions (Fig. 7C).

All coefficients for interaction effects of exercise participation during childhood and cortical structure from 59 regions on the false alarm rate are presented in Fig. 8. The mean coefficients were significantly different from zero (cortical thickness: mean $\beta = -0.06$, 95% confidence interval [CI] = −0.08 to −0.05, $p < .001$; ODI: mean $\beta = 0.03$, 95% CI = 0.01 to 0.04, $p < .001$; NDI: mean $\beta = 0.03$, 95% CI = 0.01 to 0.04, $p < .001$).

4. Discussion

The current study was designed to evaluate the relationship of participation in exercise during early life to response inhibition in later life using multimodal neuroimaging data. Childhood exercise participation was positively associated with response inhibition in later life, and this association could be moderated by brain connectivity and cortical structure. More specifically, the positive association between exercise participation during childhood and response inhibition later in life was moderated by changes in neuronal circuitry, such as increased cortical thickness and efficiency, and strengthened inter-hemispheric connectivity. These findings suggest that early life exercise could contribute to life-long cognitive function and brain health. The present findings also clarified the mechanisms underlying the positive association between physical activity and response inhibition.

Consistent with our hypothesis, exercise participation during childhood was predictive of better response inhibition in later life. The positive effects of physical fitness on cognitive control in children aged 7–11 years have been reported in previous studies (Chaddock-Heyman et al., 2013; Davis et al., 2011; Drollette et al., 2018; Hillman et al., 2014; Kamijo et al., 2011). The current results expand this knowledge by demonstrating that exercise participation during childhood (before entering junior high school; ≤ 12 years old) may exert sustained effects on cognitive control in later life. However, this positive association was not observed for exercise participation during adolescence (junior high or high school; 12–18 years old) or later ages. As such, childhood may represent a sensitive period for the positive influence of physical activity on life-long cognitive health. Importantly, this positive association was observed regardless of age, indicating that this positive association may be sustained throughout the life span.

A moderating role of brain connectivity on the association between childhood exercise participation and response inhibition was observed, but the mediating role was not substantial. A possible explanation for

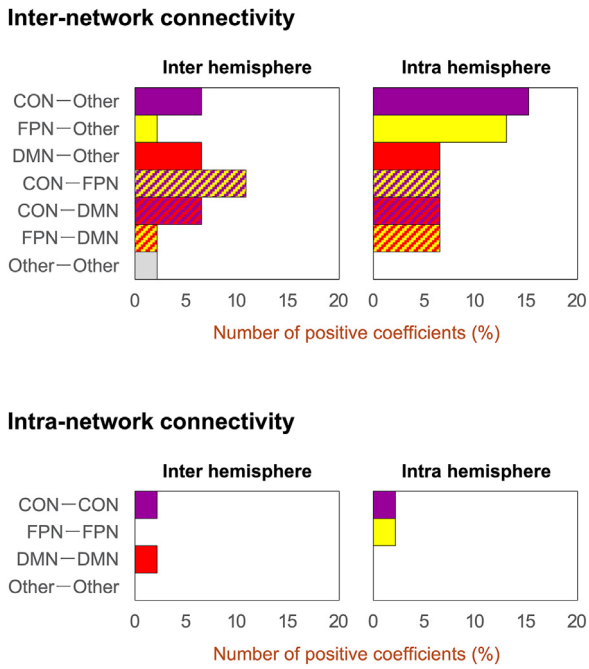

Fig. 6. The proportion of each combination of networks in a significant interaction identified via resting-state functional connectivity. CON = cingulo-opercular network; FPN = frontoparietal network; DMN = default mode network.

the moderating role is that the beneficial effects of childhood exercise on response inhibition in later life may be observed only if exercise changed participants' brain connectivity and cortical structure or if such changes caused by exercise were retained in later life. In the present study, 36 weakened structural and 46 weakened functional connections were observed (38% and 100% of significant connections, respectively) to be significantly associated with better response inhibition only in participants with childhood exercise participation. Overall, 85% of structural connections and 98% of functional connections that moderated how exercise participation during childhood positively predicted inhibitory control in later life consisted of inter-network connections of the FPN, CON, or DMN with other networks (58% structural and 59% functional), or inter-network connections among the FPN, CON, and DMN (27% structural and 39% functional). These results suggest that the positive association of exercise participation during childhood with inhibitory control in later life is fundamentally moderated by inter-network connectivity involving the FPN, CON, and DMN. These networks play a prominent role in cognitive control (Anticevic et al., 2012; Dosenbach et al., 2007; Marek and Dosenbach, 2018; Smith et al., 2018). The development of cognitive control between ages 8 and 22 years is mediated by the modular segregation of structural brain networks (i.e., weakened inter-network connectivity) (Baum et al., 2017). The association of exercise participation during childhood with sustained improvements in response inhibition across the life span may be moderated by the modular segregation of brain networks involving the FPN, CON, and DMN.

In contrast, strengthened structural connectivity (62% of significant connections) was significantly associated with better response inhibition only in participants who participated in the exercise in childhood. Of these connections, almost all (88%) were inter-hemispheric. A previous study reported that inter-hemispheric structural connectivity predicted higher cognitive task performance, including inhibitory control, while no such association was found for intra-hemispheric structural connectivity (Martínez et al., 2017). The present findings suggest that the strengthened inter-hemispheric structural connectivity could moderate the association of exercise participation during childhood with sustained improvements in response inhibition across the life span. However, the relationship of exercise to inter-and intra-hemispheric connectivity is still not well-studied. Further research is needed to clarify the effects of exercise on inter-hemispheric connectivity and its relevance to response inhibition.

Our results are inconsistent with those of some previous studies, which have reported that the positive effects of physical activity on cognitive control may be explained by the strengthening of neural networks (Taubert et al., 2011; Voss, 2010). This discrepancy may be due to differences in participant age and the lack of consideration of the differences in the role of intra- and inter-hemispheric connections. Synaptic pruning and modular segregation of brain networks (i.e., weakening of intra-network connectivity) occur during childhood, leading to the development of cognitive control (Baum et al., 2017). In contrast, intra-network connectivity that weakens as a result of the aging process is associated with decreased cognitive control (Damoiseaux, 2017). Such findings suggest that weakened neuronal networks have opposite effects during development and aging. In addition, these previous studies did not compare the role of intra- and inter-hemispheric connections. These differences may explain the apparently contradictory results between the present and previous studies.

The positive relationship between exercise participation during childhood and inhibitory control in later life was moderated by cortical thickness, ODI, and NDI. In participants with childhood exercise participation, greater cortical thickness and lower ODI and NDI were associated with better response inhibition in later life, while no such association was found in participants without childhood exercise participation. Previous meta-analyses have reported that cortical thickness is positively associated with cognitive control in healthy individuals (Waters et al., 2018; Yuan and Raz, 2014). A thicker cortex possesses a greater number of neurons (Leuba and Kraftsik, 1994) and thus might provide more power to engage in a cognitive task. A previous study demonstrated that physical fitness, a proxy of the level of physical activity, was positively associated with global gray matter volume (Cadenas-Sanchez et al., 2020). One study noted that lower levels of ODI and NDI, which result from synaptic pruning, are associated with greater intelligence, suggesting that the neuronal circuitry associated with higher intelligence is organized in a sparse and efficient manner, fostering more direct information processing and requiring less cortical activity during reasoning (Genç et al., 2018). Our results are supported by these previous findings. Childhood exercise may increase cortical thickness and the number of neurons, and lead to the organization of neuronal circuitry in a sparse and efficient manner, which may lead to better response inhibition.

The present results demonstrated that exercise participation during childhood (≤ 12 years old) may exert sustained effects on cognitive control in later life; however, this positive association was not observed for exercise participation during early adolescence or later (12 to 18 years old). Given that childhood is the most sensitive period for the development of cognitive control, cortical structure, and experience-dependent synapse formation in the prefrontal cortex (Khundrakpam et al., 2016; Lenroot and Giedd, 2006; Thompson and Nelson, 2001), exercise participation during childhood may have a stronger influence on micro- and macrostructural organization, which may, in turn, sustain this positive relationship in later life. Prefrontal gray matter volume increases throughout childhood and reaches its maximum volume at around 11–12 years old, after which it decreases from adolescence to young adulthood (Lenroot and Giedd, 2006). Prefrontal synaptic and dendritic growth and pruning during development continue from childhood until the age of approximately 15 years (Khundrakpam et al., 2016; Thompson and Nelson, 2001). Such synaptic and dendritic growth and pruning have grave consequences for cognitive performance (Riccomagno and Kolodkin, 2015). Given that the lower levels of ODI and NDI may reflect fostered synaptic and dendritic growth and pruning (Genç et al., 2018), childhood exercise may improve response inhibition via this mechanism. Since synaptic prun-

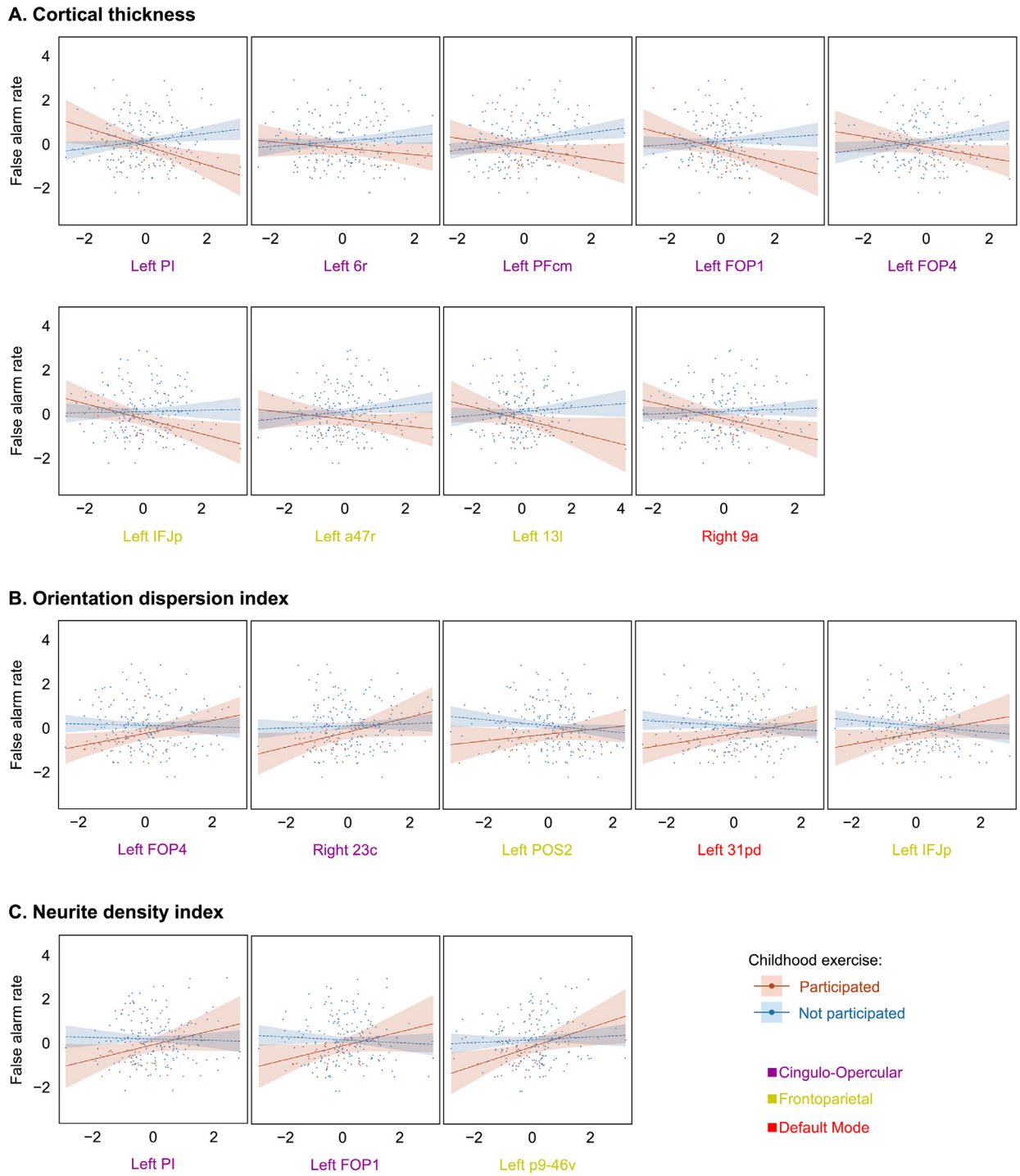

Fig. 7. Microstructural and macrostructural organizations moderate the positive relationship between exercise participation during childhood and the false alarm rate. A. Cortical thickness, B. orientation dispersion index, C. neurite density index. All variables are transformed to z-score. Regression lines are shown with 95% confidence bands (shaded areas).

ing is considered to represent a type of optimization of brain networks (Merolla et al., 2014; Navlakha et al., 2015), fostered synaptic pruning related to exercise may contribute to modular segregation of brain networks and organization of inter-hemispheric structural connections. Accordingly, exercise participation during childhood may facilitate micro- and macrostructural changes and modular segregation of brain networks, while exercise participation in early adolescence or later is likely to only exert a relatively weak influence on changes in brain structure.

These results, reflecting the moderating role of brain connectivity and cortical structure, should be interpreted with caution due to the current study's cross-sectional and retrospective nature. There are two possible explanations from individual variation perspectives for the moderating role of brain connectivity and cortical structure. First, as mentioned above, the beneficial effects of exercise on response inhibition may be observed only if the exercise changed participants' brain connectivity and cortical structure, or if the changes conferred by exercise persisted into later life. A recent systematic review and meta-

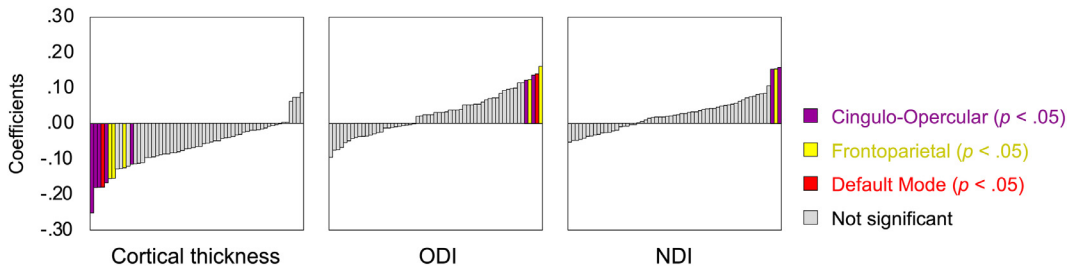

Fig. 8. Sorted coefficients for interaction effects of exercise participation during childhood and cortical structure from 59 regions on the false alarm rate. Colored bars represent significant coefficients (uncorrected $p < .05$), and gray bars represent insignificant coefficients (uncorrected $p \geq .05$). ODI = orientation dispersion index; NDI = neurite density index. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

analysis showing the effects of an exercise intervention on cognitive function demonstrated that exercise modality, such as the type of exercise and session duration, moderates the impact of exercise on cognitive function (Ludyga et al., 2020). The exercise modality that leads to changes in brain connectivity and cortical structure may be important for the sustained influence of childhood exercise on response inhibition in later life. Given that a mediating role of brain connectivity and cortical structure on the relationship between exercise participation and cognitive control has been reported (Hyodo et al., 2016; Ishihara et al., 2020; Kawagoe et al., 2017; Oberlin et al., 2016; Opel et al., 2019; Weinstein et al., 2012), the positive association of childhood exercise participation with later-life response inhibition may disappear if such changes in the brain are weakened throughout childhood to later-life.

Second, the strength of the relationship between exercise and response inhibition may be influenced by individual differences in brain networks and cortical structure. Previous studies have suggested that the strength of the association between physical fitness and cognitive control differs depending on the properties of white matter (Ruotsalainen et al., 2020) and brain network modularity (Chaddock-Heyman et al., 2020). In addition, the effects of the exercise intervention on cognitive control were moderated by genotype (Barha et al., 2020; Moreau et al., 2017). The present results could suggest that the participants who originally had higher modularly segregated brain networks, strengthened inter-hemispheric structural connectivity, greater cortical thickness, and lower ODI and NDIs benefited more from childhood exercise and showed sustained favorable influence on response inhibition in later life. Since the present study was of a cross-sectional retrospective design, we cannot elucidate which explanation might be more reasonable.

The main strengths of this study are its methodology and sample size. Although several previous studies have attempted to elucidate the relationship between physical activity and brain structure and function in terms of structural and functional connectivity, cortical thickness, volume, white matter integrity, and task-evoked activation (Chaddock-Heyman et al., 2013; Davis et al., 2011; Drollette et al., 2018; Hillman et al., 2014; Hsu et al., 2018; Kamijo et al., 2011; Ludyga et al., 2018; Taubert et al., 2011; Voss, 2010), no previous study has used a comprehensive, multimodal MRI approach for analyzing structural and functional connectivity, myelination, dendritic density, and arborization. Most of the previous neuroimaging studies had only targeted one or even a few indices and used a traditional paradigm, e.g., voxel-based volumetric analysis of data acquired at relatively coarse spatial and temporal resolutions, in small groups of subjects. It is, however, unlikely that a single or even a few indices analyzed by voxel-based volumetric analysis will have sufficient power for accurately detecting the influence of physical activity on structural and functional brain changes. In recent years, the Human Connectome Project (HCP), which aimed to map the neural pathways that underlie human brain function and to build a pipeline to collect high-quality neuroimaging data, was established (Matthew F. Glasser et al., 2016a; Matthew F Glasser et al., 2016b). This study demonstrated the relationship of exercise participation during early life on cognitive control by using large-scale multimodal MRI data acquired and analyzed using an HCP-style paradigm, which has not been reported previously.

The present study also had several notable limitations. First, because this study was performed using a historical cohort design, we merely observed the positive relationship between exercise participation during childhood and inhibitory control in later life. Accordingly, causal inferences cannot be made from this study. It might be that participants with better response inhibition engaged more regularly in exercise. Thus, longitudinal cohort studies and randomized controlled trials are required to illustrate the causal relationship between exercise participation during early life and inhibitory control in later life, and the mediation effects of structural and functional changes in the brain. Second, exercise participation data were obtained using self-reported questionnaires, and accuracy was heavily reliant on participants' recall ability. Although the reliability of long-term recall of the amount of physical activity (kilocalories per week) has been reported (Blair et al., 1991), the possible effects of recall bias on current findings should be acknowledged. Given that the accuracy of reporting on whether someone participated in sports is probably less susceptible to inaccuracy than the amount of physical activity, concern about recall bias in this study could be appeased. Conversely, the lack of a dose–response association should be interpreted with caution because recall bias could be stronger when recalling the number of hours and number of days of exercise per week. The finding that only participation in exercise during childhood predicted later-life response inhibition may reflect differences in the difficulty of recalling exercise participation in each period. Additionally, we did not collect data regarding any longer period of injury that kept participants from exercising. This issue along with mental disorders that affect one of the dependent variables may be relevant, but no related information was available. Third, throughout life, human brain connectivity faces many challenges (such as confounding), and thus validity cannot be fully established (Zuo et al., 2017). In addition, the measurement reliability within individual samples in the field of individual differences in brain and behavior study has been discussed previously (Zuo et al., 2019). Finally, we cannot disentangle the extent to which the neurocognitive benefits of exercise participation are due to the physical activity itself rather than to the features of quality structured programs (including rules, routines, cognitive challenges, and positive adult relationships). Future longitudinal studies should therefore use more objective measures of exercise participation, such as accelerometers and heart rate monitors, and address the problems of reliability and validity of neuroimaging measures.

5. Conclusions

The results of this study suggest that participation in exercise before the age of 12 years exerts sustained beneficial effects on inhibitory control in later life. This association is likely moderated by modular segregation of brain networks and strengthened inter-hemispheric structural connectivity, greater cortical thickness, lower orientation disper-

sion, and lower neurite density. The present findings suggested that the recently increasing incidence of inactivity among children may impair cognitive function and brain health in later life. Specifically, in an effort to increase academic performance, the policies that reduce or replace exercise opportunities during the school day may impair cognitive development as well as cognitive function and brain health in later life. Considering the current rapid aging of the population, our data provide evidence suggesting that children should receive more daily exercise opportunities to extend a healthy life expectancy, especially since it relates to life-long cognitive function and brain health. Given that inhibitory control plays a prominent role in life-long well-being, including academic and professional success, reduces the likelihood of having a criminal record, and promotes marital harmony and healthy behaviors (Diamond, 2013), our findings have far-reaching implications for the public health and educational sectors.

Competing interest statement

The authors declare no competing interests.

Data and Code Availability Statement: The data that supports the findings of this study is available from the corresponding authors upon reasonable request.

Credit authorship contribution statement

Toru Ishihara: Conceptualization, Data curtion, Formal analysis, Funding acquisition, Investigation, Methodology, Visualization, Writing – original draft. **Atsushi Miyazaki:** Data curtion, Formal analysis, Investigation, Methodology, Software, Visualization, Writing – original draft. **Hiroki Tanaka:** Data curtion, Investigation, Writing – review & editing. **Takayuki Fujii:** Investigation, Writing – review & editing. **Muneyoshi Takahashi:** Investigation, Writing – review & editing. **Kuniyuki Nishina:** Investigation, Writing – review & editing. **Kei Kanari:** Investigation, Writing – review & editing. **Haruto Takagishi:** Data curtion, Funding acquisition, Investigation, Methodology, Project administration, Writing – review & editing. **Tetsuya Matsuda:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing – review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2021.118196.

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