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Identification of the brain networks that contribute to the interaction between physical function and working memory: An fMRI investigation with over 1,000 healthy adults



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ABSTRACT

There is a growing consensus regarding the positive relationship between physical function and working memory; however, explanations of task-evoked functional activity regarding this relationship and its differences in physical function domains remain controversial. This study illustrates the cross-sectional relationships between cardiorespiratory fitness, gait speed, hand dexterity, and muscular strength with working memory task (*N*-back task) performance and the mediating effects of task-evoked functional activity in 1033 adults aged between 22 and 37 years. The results showed that cardiorespiratory fitness and hand dexterity were independently associated with *N*-back task performance to a greater extent and in contrast to gait speed and muscular strength. These relationships were mediated by task-evoked functional activity in a part of the frontoparietal network (FPN) and default mode network (DMN). Superior cardiorespiratory fitness could contribute to working memory performance by enhancing the compensational role of FPN-related broader region activation. Hand dexterity was associated with moderation of the interaction in terms of task-evoked activation between the FPN and DMN, which in turn, improved *N*-back task performance. Based on these findings, we conclude that cardiorespiratory fitness and hand dexterity have common and unique mechanisms enhancing working memory.

1. Introduction

Working memory is an aspect of cognitive control that is defined as “the ability to hold information in mind and mentally work with it” (Diamond, 2013). It plays an important role in everyday activities, such as mentally performing mathematical calculations, recognizing a to-do list, and translating instructions into action plans (Diamond, 2013).

Over the last two decades, there has been a growing consensus regarding the relationship between higher levels of physical function via regular physical exercise and improved working memory performance regardless of age (Kamijo et al., 2011; Kao et al., 2017; Kramer and Colcombe, 2018; Ludyga et al., 2020; Scudder et al., 2016; Voelcker-Rehage et al., 2010). Several previous studies utilizing magnetic resonance imaging (MRI) have reported that structural brain changes in the prefrontal cortex (PFC) may be related to the positive correlation between physical function and working memory (Kramer and Colcombe,

2018; Oberlin et al., 2016; Raichlen et al., 2016; Voss, 2010; Voss et al., 2013a; Wittfeld et al., 2020). For instance, a higher level of physical function has been associated with larger gray matter volume (Weinstein et al., 2012) and white matter integrity (Oberlin et al., 2016; Voss et al., 2013a) in the PFC. Additional studies examining the relationship between physical function and functional brain networks at rest (Talukdar et al., 2018; Voss et al., 2016) have shown that cardiorespiratory fitness has a positive relationship with the resting-state functional connectivity of the frontoparietal network (FPN), including the activated bilateral dorsal and ventral PFCs, dorsal parietal cortex, and dorsal anterior cingulate, as well as activation in the default mode network (DMN), including the medial PFC, posterior cingulate, and occipital–parietal junction.

Several task fMRI studies have shown that the task-evoked functional activity during cognitive tasks contributes to the positive relationship between physical function and cognitive control performance (Colcombe

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et al., 2004; Liu-Ambrose et al., 2012; Prakash et al., 2011; Rosano et al., 2010; Voelcker-Rehage et al., 2011; Wong et al., 2015); however, the findings remain inconsistent. In randomized controlled trials, Colcombe et al. (2004) have reported that the a 6-month aerobic exercise intervention significantly increased task-related activity in attentional control areas, i.e., the middle frontal and superior frontal gyrus (MFG and SFG, respectively) and the superior parietal lobule (SPL), and reduced task-related activity in the anterior cingulate cortex (ACC). Similarly, Liu-Ambrose et al. (2012) have also demonstrated that a 12-month resistance training intervention increased activation in the left middle temporal gyrus and the left anterior insula extending into the lateral orbitofrontal cortex during cognitive tasks. However, in contrast to the above studies, Voelcker-Rehage et al. (2011) have reported differential activation patterns. They have found that a 12-month exercise intervention significantly increased task-related activity in the SPL; however, it reduced task-related activity in the ACC, MFG, and SFG. This discrepancy, i.e., increased and reduced activation in the PFC, is believed to be due to strategic differences while completing cognitive tasks between high and low fit individuals (Voelcker-Rehage and Niemann, 2013). However, the relationship between physical function and strategy use during a cognitive task, i.e., increased or reduced activation patterns in the PFC, remains unclear.

Previous research on working memory has reported activation of numerous regions thought to be involved in the FPN, while the DMN activation was reduced (Barch et al., 2013). These patterns of task-evoked FPN activation and DMN reduced activity have been shown to be associated with working memory task performance (Anticevic et al., 2012; Sala-Llonch et al., 2012). Considering that previous studies have reported the relationship between physical fitness and both increased and decreased PFC activations, we hypothesized that physical fitness may modulate the interaction of task-evoked functional activity in the FPN and the DMN during the working memory task.

The positive relationship between physical function and working memory can be seen in multiple domains of physical function, such as cardiorespiratory fitness (Angevaren et al., 2008; Kao et al., 2017; Kramer et al., 1999), gait speed (McGough et al., 2011), hand dexterity (Kobayashi-Cuya et al., 2018), and muscular strength (Firth et al., 2018; Kao et al., 2017; Kobayashi-Cuya et al., 2018). Considering that previous animal studies have reported differential relationships of cardiorespiratory exercise, motor exercise, and resistance exercise to brain metabolism (Cassilhas et al., 2012; Klintsova et al., 2004), the relationship between physical function and functional brain activation may differ among the domains of physical function. A previous study has suggested that cardiorespiratory fitness, muscular strength, and speed agility are positively associated with working memory and neuroelectric activity (Mora-Gonzalez et al., 2019). An intervention study has shown that both coordination training and cardiovascular training improve cognitive task performance, while differentially affecting the task-evoked activation patterns (Voelcker-Rehage et al., 2011). Therefore, multiple domains of physical function seem to be positively associated with working memory; however, the contributing underlying mechanisms may be different in each domain.

Accordingly, clarifying how task-evoked functional activity patterns (i.e., activation of FPN and DMN) mediate the relationship between multiple domains of physical function and working memory performance may provide a better understanding of how physical function contributes to working memory performance. To this end, this study evaluated the relationship between cardiorespiratory fitness, gait speed, dexterity, and muscular strength with working memory, as evaluated by the *N*-back task, using the large-scale unique dataset of the Human Connectome Project (HCP) (Glasser et al., 2016a, 2016b; Van Essen et al., 2013). Furthermore, we investigated the way in which task-evoked functional activity patterns during the *N*-back task mediate the relationship of each domain of physical function with *N*-back task performance in adults aged between 22 and 37 years.

2. Materials and methods

2.1. Participants

We used data from the HCP database concerning 1206 healthy participants aged 22–37 years. The study was approved by Washington University in the St. Louis' Human Research Protection Office (IRB #201204036), and all participants provided informed consent. The HCP excluded participants who had a significant history of psychiatric disorders or head injury, showed evidence of neurological or cardiorespiratory diseases, were pregnant, or had unsafe levels of heavy metals in their body. Details of participant recruitment and exclusion criteria have been elucidated elsewhere (Van Essen et al., 2013). We excluded 173 participants with missing data and 2 outliers (1 participant due to muscular strength, i.e., $<\text{mean} - 5 \text{ SD}$, and 1 participant due to task-evoked functional activity, i.e., $<\text{mean} - 3$ or $>\text{mean} + 3 \text{ SD}$); therefore, we ultimately analyzed the data of 1033 participants.

2.2. Physical function measures

Four physical function domains were evaluated using four measures of the National Institutes of Health (NIH) Toolbox (Reuben et al., 2013).

2.2.1. Cardiorespiratory fitness

Cardiorespiratory fitness was measured using the NIH Toolbox 2-min walk test (Bohannon et al., 2015, 2014; Reuben et al., 2013). This test, which was performed once, measures the sub-maximal cardiorespiratory fitness by recording the distance that the participant can walk on a 50-foot (out and back) course in 2 min. This test is a shortened version of the 6-min walk test which has been previously validated for predicting the VO_2 max of healthy adults (Burr et al., 2011; Mänttari et al., 2018). We decided to use the 2-min walk test as the endurance component since previous studies have reported a strong correlation between the 2-min and 6-min walk tests ($r > 0.90$) in community-dwelling children and adults aged 3–85 years (Bohannon et al., 2014), as well as in patients with neuromuscular disease (Witherspoon et al., 2019) and multiple sclerosis (Scalzitti et al., 2018). The participants' raw scores were normalized to that of the entire NIH Toolbox Normative Sample (18 and older), regardless of age or any other variable; a score of 100 indicated the national average performance, while scores of 85 and 115 indicated performances 1 *SD* below and above the national average, respectively. The test was typically completed in approximately 4 min (with instructions and practice). It is recommended for participants aged 3–85 years.

2.2.2. Gait speed

Gait speed was measured by the NIH Toolbox 4-m walk gait speed test (Bohannon and Wang, 2018; Reuben et al., 2013). For the test, participants were asked to walk a short distance (i.e., 4 m) at their usual pace; they completed one practice and then two timed trials. Raw scores were recorded in seconds as the time required to walk 4 m on each of the two trials, with the faster trial used for scoring. The computed scores were then reported in meters per second. The test took approximately 3 min to administer (including instructions and practice). It is recommended for participants aged 7–85 years.

2.2.3. Hand dexterity

Hand dexterity was measured using the NIH Toolbox 9-hole pegboard dexterity test (Oxford Grice et al., 2003; Reuben et al., 2013) as a fine motor skill of physical function. The NIH Toolbox 9-hole pegboard dexterity test is a simple test of manual dexterity; it records the time required for the participant to accurately place and remove nine plastic pegs into a plastic pegboard. Our protocol included one practice and one timed trial with each hand. The raw scores were recorded as the time in seconds taken by the participant to complete the task with each hand (separate

scores for each hand). The participants' score was normalized to those of the entire NIH Toolbox Normative Sample (18 and older), regardless of age or any other variable; a score of 100 indicated a performance that was at the national average and scores of 85 and 115 indicated performances 1 *SD* below and above the national average, respectively. Higher scores were indicative of better dexterity (i.e., shorter time taken to complete the task) in the dominant hand. The test took approximately 4 min to administer. It is recommended for participants aged 3–85 years.

2.2.4. Muscular strength

Muscular strength was measured using the NIH Toolbox grip strength test (Reuben et al., 2013). A previous study has reported that the performance of this test is a good predictor of whole-body muscular strength level (Beenakker et al., 2010; Troscclair et al., 2011) regardless of age (Rantanen et al., 1994; Wind et al., 2010). The NIH Toolbox grip strength test is adapted from the grip strength testing protocol of the American Society of Hand Therapy. For this study, participants were seated in a chair with their feet touching the ground. With the elbow bent to 90°, the arm against the trunk, and the wrist in a neutral position, participants squeezed a Jamar Plus Digital dynamometer as hard as they could for a count of 3 s; the dynamometer provided a digital reading of the force in pounds. A practice trial at less than full force and one test trial were completed with each hand. The participants' raw score was normalized to those of the entire NIH Toolbox Normative Sample (18 and older), regardless of age or any other variable; a score of 100 indicated a performance that was at the national average and scores of 85 and 115 indicated performances 1 *SD* below and above the national average, respectively. Higher scores indicated higher dominant hand-related muscular strength. The test took approximately 3 min to administer. It is recommended for participants aged 3–85 years.

2.3. Working memory assessment

To assess working memory and task-evoked functional activity, the participants were asked to complete the HCP version of the *N*-back task in the MRI scanner (Barch et al., 2013). The *N*-back task is a well-known paradigm evaluating working memory. It comprises two conditions, the 0-back task and the 2-back task. In the 0-back task, participants compared a current stimulus with the target stimulus presented before the task, whereas in the 2-back task, participants compared a current stimulus with the one presented two displays earlier in the sequence. The stimuli comprised pictures of places, tools, faces, and body parts. Within each run, one half of the blocks used a 2-back working memory task while the other half used a 0-back working memory task. Each of the two runs contained 8 task blocks (10 trials of 2.5 s each, for 25 s) and 4 fixation blocks (15 s each). On each trial, the stimulus was presented for 2 s, followed by a 500-ms inter-trial interval. The task requires storage and active use of information within the mind (for more details, please see Barch et al. (2013)). We used the mean response accuracy as an index of working memory performance.

2.4. Task-fMRI data acquisition

We used the 3T Working Memory Task fMRI preprocessed data. All task-fMRI data were acquired on a Siemens Skyra 3T scanner (Erlanger, Germany) and processed using the HCP Pipeline, the FMRIB Software Library, and FreeSurfer. Whole-brain echo planar imaging (EPI) acquisitions were acquired with a 32-channel head coil with the following settings: repetition time = 720 ms, echo time = 33.1 ms, flip angle = 52°, bandwidth = 2290 Hz/Px, in-plane field of view = 208 × 180 mm, 72 slices, and 2.0-mm isotropic voxels, with a multi-band acceleration factor of 8. Two runs of each task were acquired, one with a right-to-left phase encoding and the other with a left-to-right phase encoding (for more details, please see Barch et al. (2013)). In brief, The HCP fMRIVolume pipeline was used to generate “minimally preprocessed” 4D time series that included gradient unwarping, motion correction, field map-based

EPI distortion correction, brain-boundary-based registration of EPI to structural T1-weighted scan, non-linear (FNIRT) registration into MNI152 space, and grand-mean intensity normalization. The HCP fMRISurface pipeline was used to project the data from the cortical gray matter ribbon onto the surface and then onto registered surface meshes with a standard number of vertices. Subcortical data were also projected to a set of subcortical gray matter parcel voxels, and when combined with the surface data formed the standard gray ordinate space (Glasser et al., 2013). In addition, inter-participant registration of the cerebral cortex was carried out using areal feature-based alignment and the Multimodal Surface Matching algorithm (“MSMall”; Glasser et al., 2016a). Data were spatially smoothed with a 4-mm full-width half-maximum Gaussian kernel. Task-related regressors were convolved with the gamma hemodynamic response function by using a general linear model (GLM). The task-related regressors were modeled to include only the correct trials. Subsequently, the contrast between each task condition (0-back and 2-back) was calculated.

2.5. Parcellations

We used group independent component analysis (group-ICA) data for resting-state fMRI provided by the HCP for brain parcellation (Smith et al., 2014) (for detailed methods regarding data acquisition, please see Smith et al. (2013)). The output from the group-averaged principal component analysis (PCA) spatial maps (weighted eigenmaps), i.e., dense connectomes of all participants' individual time series, were generated by MELODIC's Incremental Group-PCA (MIGP). Furthermore, to create spatial-ICA network maps at dimensionalities of 25, 50, 100, 200, and 300 distinct components, the dense connectome was parcellated using group-ICA (for details, please see Smith et al. (2014)).

2.6. Confounding variables

The handedness and education level were used as confounders. The Edinburgh Handedness Inventory was used to evaluate handedness. This inventory is a professionally administered, valid and reliable measure of handedness comprising 10 questionnaires of which measure hand preference. Participants were categorically coded as follows: left-handed from 100 to 71, mixed-handed from 70 to +70, and right-handed from +71 to +100 (Dragovic, 2004). Education level was defined according to SSAGA education score and participants were categorically coded as follows: ≤ 12 years (elementary, middle, and high school), 13–16 years (Higher education), and ≥ 17 years (graduate school or more).

2.7. Statistical analyses

All statistical analyses were conducted using R Studio software version 1.1.463. First, the bivariate correlation between the study variables was analyzed by using Pearson's correlation coefficient. Second, we performed multiple regression predicting *N*-back task performance with generalized linear model techniques. The dependent variables were response accuracy in the 2-back task. The independent variables were age, sex, handedness, education level, and performance on the 0-back task, and physical function measures. Third, partial correlation analyses were performed to examine the relationship between task-evoked functional activity in each component of group-ICA and 2-back task performance (adjusted for sex and age group), and cardiorespiratory fitness, gait speed, hand dexterity, and muscular strength (adjusted for age, sex, handedness, and education level). Fourth, we performed structural equation modeling to evaluate the modeling relationship of task-evoked functional activity between physical function and 2-back task performance using the lavaan package. The code used in the structural equation modeling is summarized in the supplementary information. The absolute goodness of the fit of the models was evaluated using the chi-square test, comparative fit index (CFI), and root mean square error of approximation (RMSEA). CFI values above 0.95 and RMSEA

values less than 0.06 were considered to be an adequate model fit (Hu and Bentler, 1999). To compare the relative fit of the models, we used the RMSEA (MacCallum et al., 1996) rather than the chi-square test, because the RMSEA is virtually independent of sample size. If a significant interaction was found, a simple slope analysis was performed in an individual with the lower (mean - 1SD) and higher (mean + 1SD) scores. Finally, a split-group validation analysis and a sensitivity analysis were performed. Significance level was set at $p < .05$ or FDR corrected $p < .05$. All variables were converted to z-scores before analyses.

3. Results

The participants' demographic data are provided in Table 1. To confirm that each physical function assessment reflected different domains, we confirmed the relationships among physical functions were not strong (partial $r = -0.01$ to 0.28; Supplementary Table 1).

3.1. Bivariate relationship of physical function measures to performance on the 2-back task

Scatter plots for the bivariate relation between physical function measures and 2-back task performance are presented in Fig. 1. Correlation analysis showed that performances regarding cardiorespiratory fitness, hand dexterity, and muscular strength were positively associated with the 2-back task accuracy ($r = 0.26, 0.17,$ and 0.11 , respectively; $ps < .001$), while gait speed was not ($r = -0.04, p = .19$). There was no correlation between gait speed and performance on the 2-back task, thus excluding it from further analyses.

3.2. Concomitant and independent relationship of physical function measures to performance on the 2-back task

The results of the multiple regression analyses are summarized in Table 2. The 2-back task accuracy was positively associated with cardiorespiratory fitness ($\beta = 0.10, p = .002$) and hand dexterity ($\beta = 0.13, p < .001$), while no such association was found with muscular strength ($\beta = -0.01, p = .78$) subsequent to controlling for age, sex, accuracy of the 0-back task, handedness, and education level ($\Delta F = 12.46, p < .001$, overall adjusted $R^2 = 0.24$). There was no two-to-three-way interaction among age, sex, and physical function measures (absolute value of $\beta s \leq 0.05, p \geq .07$).

3.3. Bivariate relationship of 2-back task accuracy and physical function measures with task-evoked functional activity

Partial correlation analyses were performed to evaluate the relationship between 2-back task performance and physical function with task-

Table 1
Participant demographics.

Variables	N (%) or Mean (SD)
N	1033
Female/Male (N [%])	560 (54)/473 (46)
Age (years old)	29 (4)
Handedness (N [%])	
Left-handed/Ambidextrous-handed/Right-handed	30 (3)/355 (34)/648 (63)
Education (N [%])	
≤ 12 years/13–16 years/≥ 17 years	180 (17)/690 (67)/163 (16)
Physical function	
Cardiorespiratory fitness ^a	110 (12)
Gait speed (sec)	1.3 (0.2)
Hand dexterity ^a	113 (11)
Muscular strength ^a	117 (11)
N-back task	
Accuracy in the 0-back task (%)	90 (10)
Accuracy in the 2-back task (%)	84 (11)

^a Reflects normalized score.

evoked functional activity (2-back contrast minus 0-back contrast) subsequent to controlling for age, sex, handedness, and education level. We used the contiguous parcels from the 25 resting-state networks identified using independent component analysis by the HCP (Glasser et al., 2016a, 2016b; Van Essen et al., 2013). The locus of each component is presented in Supplementary Fig. 1. Partial correlation analysis revealed a significant correlation between the 2-back task accuracy and task-evoked functional activity in 18 components, i.e., component numbers 1, 2, 4, 5, 8, 10–13, 15–17, 19, and 21–25 (Fig. 2a; absolute value of partial $r \geq .07$, FDR corrected $p < .05$). Partial correlation analysis also revealed that three components, i.e., 11, 19, and 22, were significantly associated with cardiorespiratory fitness (Fig. 2b; absolute value of partial $r \geq .09$, FDR corrected $p < .05$), while two components, i.e., 2 and 11, were significantly associated with hand dexterity (Fig. 2c; absolute value of partial $r \geq .11$, FDR corrected $p < .05$). No component was associated with muscular strength (absolute value of partial $r \leq .05, p \geq .09$). We employed the same analysis techniques used in validation analysis with the contiguous parcels from the 50, 100, 200, and 300 resting-state networks identified using independent component analysis by the HCP (Glasser et al., 2016a, 2016b; Van Essen et al., 2013). The results showed a fundamentally identical pattern as the original analysis (for details, see Supplementary Fig. 2), and thus we considered the original analysis to be reliable and independent of the number of networks.

3.4. Modeling the relationships of physical function measures to the 2-back task accuracy via task-evoked functional activity

Structural equation modeling was performed to identify the relationships of the cardiorespiratory fitness and hand dexterity to the 2-back task accuracy via task-evoked functional activity after controlling for age, sex, handedness, and education level. The details of the statistics of the structural equation modeling are summarized in Table 3.

3.4.1. Basic model without cascade associations and interaction effects

The structural equation model was the saturated model (i.e., degree of freedom = 0). In this model, the accuracy of the 2-back task was significantly associated with cardiorespiratory fitness, hand dexterity, and task-evoked functional activity in components 2, 11, and 19. No correlation was found between task-evoked functional activity in component 22 and the 2-back task accuracy. Compared with a previous study (Yeo et al., 2011), we defined components 11 and 19 as a part of the FPN, and component 2 as a part of the DMN. According to our hypothesis, we excluded component 22 (a part of cerebellum) from further analyses.

3.4.2. Cascade associations of physical function with 2-back task accuracy via task-evoked functional activation

The structural equation model showed adequate fit to the data (Fig. 3: $\chi^2 = 6.62; df = 2; CFI = 0.998; RMSEA = 0.05; 90\% CI = 0.01$ to $0.09; p$ close fit = .47). Two cascade associations were found between cardiorespiratory fitness and 2-back task accuracy via task-evoked functional activity in components 11 and 19 (Fig. 3); equally, there were two cascade associations between hand dexterity and 2-back task accuracy via task-evoked functional activity in components 11 and 2 (Fig. 3). Adding the paths from cardiorespiratory fitness to task-evoked functional activity in component 2 led to cardiorespiratory fitness being marginally associated with task-evoked functional activity in component 2 ($\beta = -0.06, SE = 0.03, z = -1.77, p = .08$). This could explain the results of partial correlation analyses using the parcels from the 100, 200, and 300 resting-state networks, i.e., the task-evoked functional activity in some components that were inversely associated with cardiorespiratory fitness (Supplementary Fig. 2).

3.4.3. Interaction effects of task-evoked functional activation on the 2-back task accuracy

Considering that a previous study reported that the relationship between task-evoked activation patterns in the FPN (components 11 and

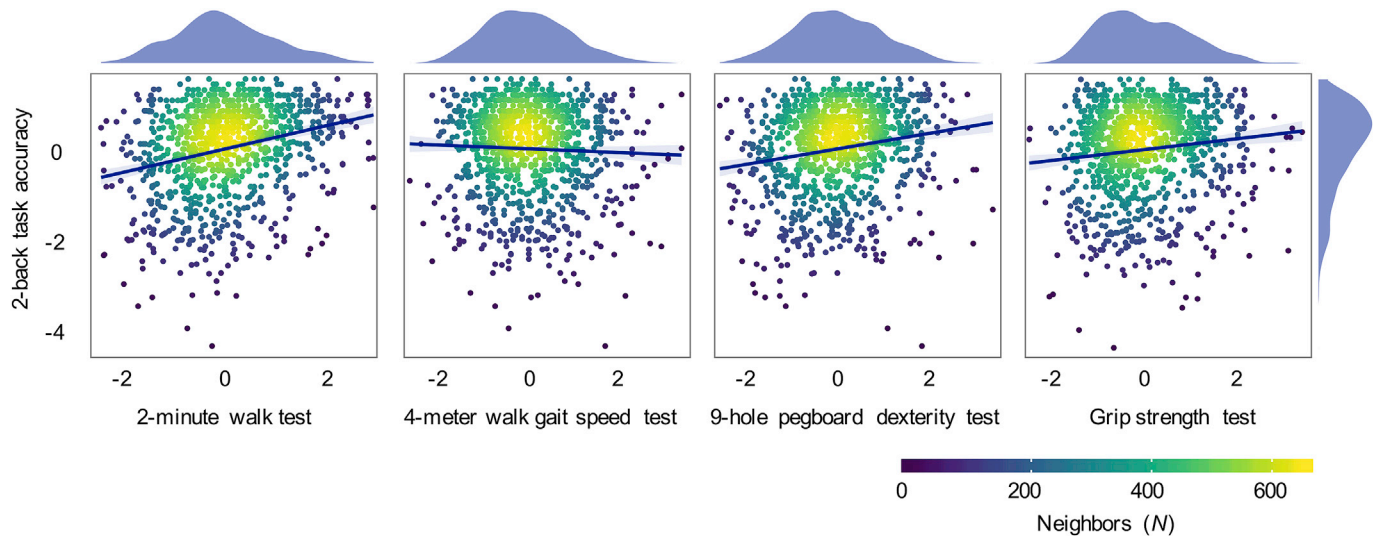


Fig. 1. Scatter plot for the bivariate relation between physical function measures and 2-back task performance. Regression lines are shown with 95% confidence bands (shaded areas).

Table 2

Results of multiple regression predicting performance on the 2-back task accuracy.

	β	SE	t	p
Age	-.09	.03	-3.09	.002
Sex (female = 0, male = 1)	.13	.04	3.16	.002
Handedness	-.05	.03	-1.95	.05
Education	.13	.03	4.44	<.001
Performance on the 0-back task	.33	.03	11.53	<.001
Cardiorespiratory fitness	.10	.03	3.13	.002
Hand dexterity	.13	.03	4.59	<.001
Muscular strength	-.01	.04	-0.28	.78
Adjusted R^2	.24			

Note: $N = 1033$; SE = standard error.

19) and DMN (component 2) was associated with N -back task performance (Anticevic et al., 2012; Sala-Llloch et al., 2012), we decided to clarify whether the combinations of task-evoked activation in the FPN and DMN contribute to working memory performance. Prior to running the main analysis, to test whether we could replicate the coupling between FPN and DMN related to N -back task performance, we confirmed that there were FPN and DMN-related interaction effects (components 11 and 19, and 2, respectively) on the 2-back task accuracy. We performed structural equation modeling predicting 2-back task accuracy from task-evoked activation in components 2, 11, and 19 after controlling for age, sex, handedness, and education level. The structural equation model was the saturated model (i.e., degree of freedom = 0). The 2-back task accuracy was significantly associated with task-evoked activation in components 2 ($\beta = -0.27$, $SE = 0.03$, $z = -9.39$, $p < .001$), 11 ($\beta = 0.23$, $SE = 0.05$, $z = 4.33$, $p < .001$), and 19 ($\beta = 0.22$, $SE = 0.06$, $z = 3.98$, $p < .001$). When adding interaction effects, all interaction effects were significant (components 2 and 11: $\beta = 0.07$, $SE = 0.03$, $z = 2.95$, $p = .003$; components 2 and 19: $\beta = 0.06$, $SE = 0.02$, $z = 2.37$, $p = .02$; and components 11 and 19: $\beta = -0.07$, $SE = 0.02$, $z = -3.42$, $p = .001$).

Subsequently, we added the interaction effects in the main analysis. The interaction became significant when the interaction effects of the task-evoked activation in components 2 and 11, 2 and 19, and 11 and 19 were added in the structural equation model (Fig. 4a–c), with adequate fit to the data (χ^2 s = 20.84, 23.23, and 14.33; χ^2_{diff} s = 14.22, 16.61, and 7.71; df_{diff} s = 5; $ps = .01$, .005, and 0.17; CFI = 0.994, 0.993, and 0.997; RMSEAs = 0.04, 0.05, and 0.03; 90% CIs = 0.02 to 0.07, 0.03 to 0.07, and 0.004 to 0.06; p close fits = .65, .54, and 0.89, respectively). The

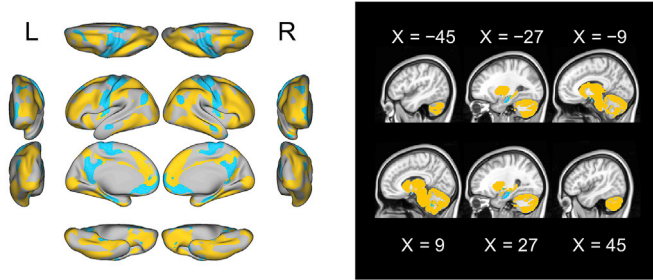
lower RMSEA and higher p close fit values showed that the model fit of these models was better than that of the model before the interaction effects were entered. In participants with higher task-evoked activation in component 2 (mean + 1SD), the relationships of components 11 and 19 with the 2-back task accuracy were stronger than those with lower task-evoked activations in component 2 (mean – 1SD) and vice versa (Fig. 4a and b). Regarding participants with lower task-evoked activation in component 11 (mean – 1SD), the relationships of component 19 with the 2-back task accuracy were stronger than those of the participants with higher task-evoked activation in component 11 (mean + 1SD) and vice versa (Fig. 4c).

3.4.4. Moderation effects of physical function on the task-evoked functional activation patterns

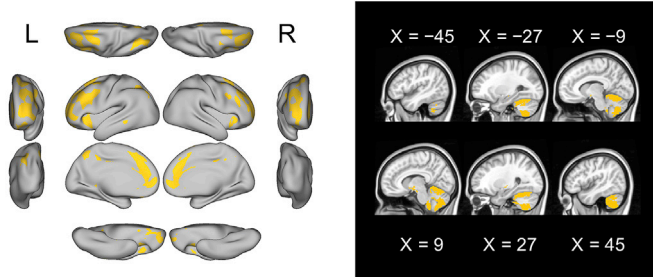
Considering that a previous study reported that the relationship between task-evoked activation patterns in the FPN and DMN was associated with N -back task performance, we decided to clarify the performance of cardiorespiratory fitness and how hand dexterity moderated the relationships among task-evoked activation in the FPN (components 11 and 19) and DMN (component 2). Therefore, we performed structural equation modeling adding the moderation effects of the cardiorespiratory fitness performance and hand dexterity in the relationship among task-evoked activation in components 2, 11, and 19.

When the interaction effects were added in the structural equation model, hand dexterity significantly moderated the relationship between task-evoked activation of components 2 and 11 and components 2 and 19 (Fig. 5a and b) with adequate fit to the data (χ^2 s = 18.33 and 16.06; χ^2_{diff} s = 11.71 and 9.44; df_{diff} s = 5; $ps = .04$ and .09; CFI = 0.995 and 0.996; RMSEAs = 0.04; 90% CIs = 0.02 to 0.06 and 0.01 to 0.06; p close fits = .75 and .84, respectively). The lower RMSEA and higher p close fit values showed that the model fit of these models was better than that of the model before the interaction effects were entered. The higher hand dexterity (mean + 1SD) exhibited a stronger relationship between task-evoked functional activity in components 2 and 11 (Fig. 5a) and components 2 and 19 (Fig. 5b), in contrast to the lower performers (mean – 1SD). Cardiorespiratory fitness marginally moderated the relationship between task-evoked activation of components 2 and 11, and components 11 and 19 (Fig. 5c and d) with adequate fit to the data (χ^2 s = 16.42 and 25.78; χ^2_{diff} s = 9.80 and 19.16; df_{diff} s = 5; $ps = .08$ and .002; CFI = 0.996 and 0.992, RMSEAs = 0.04 and 0.05, 90% CIs = 0.01 to 0.06 and 0.03 to 0.07, p close fits = .82 and .43, respectively). The lower RMSEA and higher p close fit values showed that the model fit of the former model was better than that of the model before the interaction effects

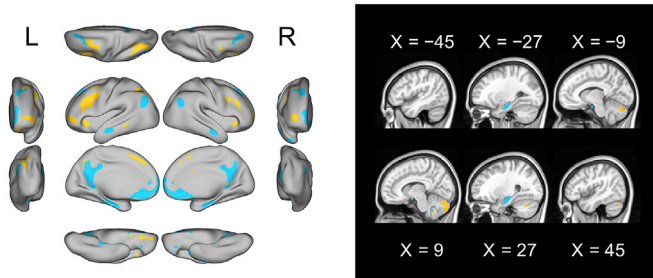
a. 2-back task accuracy



b. Cardiorespiratory fitness



c. Hand dexterity



■ Positive correlation ■ Negative correlation

Fig. 2. The relationship of 2-back task accuracy and physical function measures with task-evoked functional activity during the *N*-back task (2-back contrast minus 0-back contrast) in the parcels from the 25 resting-state networks identified using independent component analysis by the Human Connectome Project (Glasser et al., 2016a, 2016b; Van Essen et al., 2013). (a) Components significantly associated with 2-back task accuracy. (b) Components significantly associated with the cardiorespiratory fitness. (c) Components significantly associated with the hand dexterity. R, right hemisphere; L, left hemisphere.

were entered, whereas the model fit of the latter was almost the same as that of the model before interaction effects were entered.

A higher cardiorespiratory fitness performance (mean + 1SD) corresponded to a stronger relationship between task-evoked functional activity in components 2 and 11 (Fig. 5c) and a weaker relationship between task-evoked functional activity in components 11 and 19 (Fig. 5d) in contrast to lower performers (mean - 1SD). No other moderation effects of cardiorespiratory fitness performance and hand dexterity regarding the relationship among task-evoked activation in components 2, 11, and 19 reached significant levels.

3.5. Sensitivity analysis and split-group validation

As we only used the dominant hand's score of hand dexterity and muscular strength in previous analyses, the multiple regression analysis

Table 3

Results of the structural equation modeling.

	B	SE	z	p
Basic model without cascade associations and interaction effects				
Accuracy in the 2-back task ←				
Cardiorespiratory fitness	.08	.03	2.73	.006
Hand dexterity	.10	.03	3.72	<.001
Activation in component 2	-.25	.03	-8.69	<.001
Activation in component 11	.20	.05	3.64	<.001
Activation in component 19	.20	.06	3.51	<.001
Activation in component 22	.05	.04	1.52	.13
Cascade associations				
Accuracy in the 2-back task ←				
Cardiorespiratory fitness	.08	.03	2.80	.005
Hand dexterity	.10	.03	3.74	<.001
Activation in component 2	-.25	.03	-8.55	<.001
Activation in component 11	.21	.05	3.95	<.001
Activation in component 19	.22	.06	3.95	<.001
Activation in component 2 ←				
Hand dexterity	-.14	.03	-4.66	<.001
Activation in component 11 ←				
Cardiorespiratory fitness	.13	.03	4.18	<.001
Hand dexterity	.04	.02	2.43	.02
Activation in component 19 ←				
Cardiorespiratory fitness	.12	.03	3.88	<.001
Interaction effects				
Accuracy in the 2-back task ←				
Activation in component 2 × Activation in component 11	.06	.03	2.48	.01
Activation in component 2 × Activation in component 19	.05	.02	1.96	.05
Activation in component 11 × Activation in component 19	-.07	.02	-3.51	<.001
Activation in component 2 ←				
Cardiorespiratory fitness × Activation in component 11	.05	.03	1.84	.07
Cardiorespiratory fitness × Activation in component 19	.04	.03	1.33	.18
Hand dexterity × Activation in component 11	.10	.03	3.51	<.001
Hand dexterity × Activation in component 19	.08	.03	2.78	.005
Activation in component 11 ←				
Cardiorespiratory fitness × Activation in component 19	-.03	.02	-1.93	.054
Hand dexterity × Activation in component 19	.02	.02	1.00	.32

Note: *N* = 1033; after controlling for age, sex, handedness, and education level.

and structural equation modeling were performed using the average score of both hands as a sensitivity analysis. The findings, which are shown in Supplementary Tables 2 and 3, fully replicated the outcome of the original analysis.

To examine the reproducibility and validity of the current findings, the participants were divided into two groups based on their ID provided by HCP and participant demographics. The structural equation modeling and the moderation analysis were performed in each group using the same protocol as that used in the original analyses. We sorted the data using the participants' ID, sex, age, handedness, and education level and then labeled them as 1 or 2, repeatedly. The participants' demographics are provided in Supplementary Table 4. We confirmed that there were no between-group differences in the demographic data and *N*-back task performance. The findings, which are shown in Supplementary Table 5, fundamentally replicated the findings of the entire sample with all the same β -value directions.

4. Discussion

4.1. Main findings and implications

This study replicates and extends previous studies that demonstrated the positive relationship between physical function and working memory (Drollette et al., 2016; Ishihara et al., 2018; Kao et al., 2017; Scudder et al., 2016; Voss, 2010; Weinstein et al., 2012), while it adds empirical evidence that task-evoked functional activity in the FPN and DMN

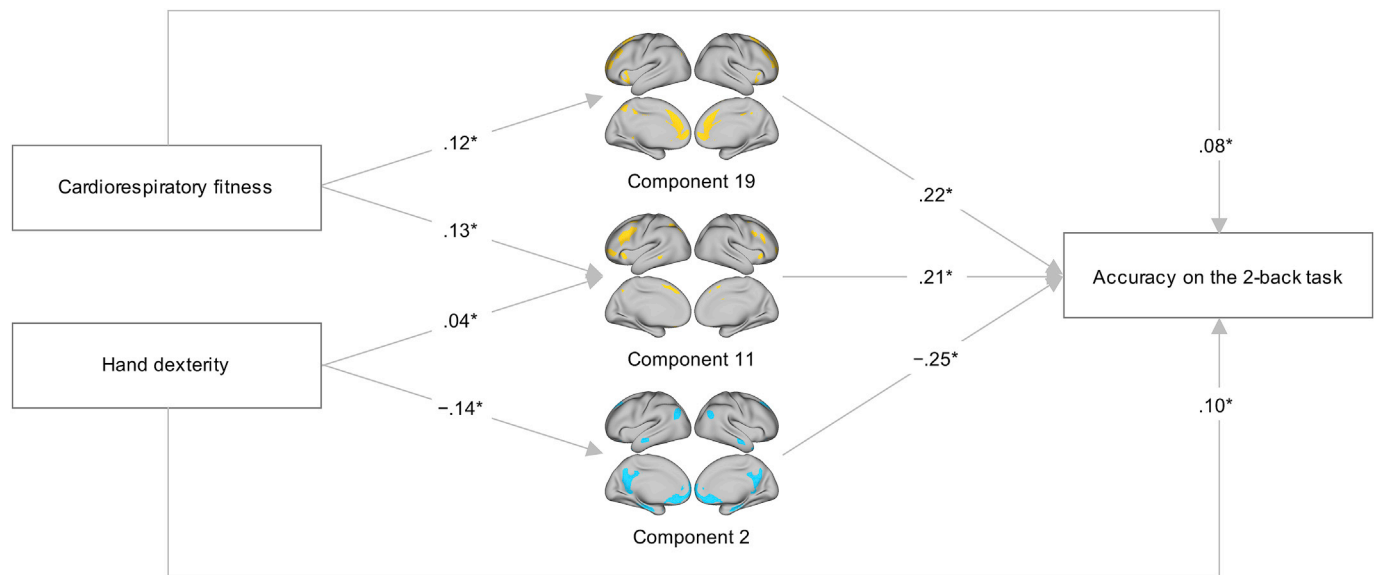


Fig. 3. The results of structural equation modeling. Values are presented as standardized β ; * $p < .05$.

mediates this relationship. Overall, two important themes are observed from the current results. First, the relationship between physical function and working memory is moderated by the physical function domains. More particularly, superior cardiorespiratory fitness and hand dexterity are more strongly and independently related to superior working memory performance than gait speed and muscular strength. Second, the relationships of both cardiorespiratory fitness and hand dexterity with working memory performance are mediated by task-evoked functional activity in parts of the FPN and DMN. In addition, both cardiorespiratory fitness and hand dexterity are associated with working memory performance via moderation of the interaction in terms of task-evoked activation between the FPN and DMN. This moderation effect is stronger in hand dexterity relative to cardiorespiratory fitness. Conversely, cardiorespiratory fitness can contribute to working memory via activation in the broader regions of the FPN. Considering that a previous randomized controlled trial illustrated the causal relationship between physical function gain and cognitive control (Angevaren et al., 2008; Colcombe et al., 2004; Drollette et al., 2018; Hillman et al., 2014; Kamijo et al., 2011; Voss, 2010), our current findings suggest that exercise enhancing cardiorespiratory fitness and hand dexterity shows beneficial effects on working memory via changes in the task-evoked brain function of the FPN and DMN.

4.2. Relationship between physical function and working memory performance

This is one of the few studies that examined the concomitant and independent relationships of multiple domains of physical function to working memory, replicating previous findings demonstrating that individuals with higher physical function have superior working memory (Drollette et al., 2016; Oberlin et al., 2016; Scudder et al., 2016; Weinstein et al., 2012), as evidenced by the bivariate positive relationships of cardiorespiratory fitness and hand dexterity to the 2-back task accuracy. Considering that cardiorespiratory fitness and hand dexterity are independently related to the 2-back task accuracy, exercises that improve cardiorespiratory fitness and hand dexterity simultaneously may be an effective way of enhancing working memory in healthy adults.

Contrary to previous studies (Firth et al., 2018; Kao et al., 2017; Kobayashi-Cuya et al., 2018; McGough et al., 2011), no significant relationship between muscular strength and gait speed, and the 2-back task accuracy was found. Although we could not elucidate the mechanisms behind this inconsistency, we speculated that the room for

improvement in each physical function domain moderated the relationship between physical function and working memory. Considering that the participants of these previous studies were children and older adults (Firth et al., 2018; Kao et al., 2017; Kobayashi-Cuya et al., 2018; McGough et al., 2011), the relationship between physical function domain and working memory may vary according to age. Previous studies have suggested that muscular strength and gait speed increase, beginning from childhood to middle-age adulthood, and then decrease with age (Dodds et al., 2016; Morita et al., 2018), whereas cardiorespiratory fitness and hand dexterity begin to decrease from an earlier age (i.e., from 20 years) (Bohannon et al., 2015; Oxford Grice et al., 2003). We speculate that the room for improvement in muscular strength and gait speed was smaller than that of cardiorespiratory fitness and hand dexterity in the participants of the present study and, thus, there were no significant relationships between muscular strength and gait speed and the 2-back task accuracy.

4.3. Contribution of task-evoked functional activation patterns to working memory performance

Previous research has reported activation of the FPN and deactivation of the DMN during a working memory-related cognitive task (Barch et al., 2013). This pattern of task-evoked activation has been shown to be associated with working memory performance (Anticevic et al., 2012; Sala-Llloch et al., 2012). Our current results support these findings; we found significant interaction effects of task-evoked functional activity in the FPN (components 11) and DMN (component 2) on the 2-back task accuracy (Fig. 4a). In addition, there were significant interaction effects of components 2 and 19, and 11 and 19 on the 2-back task accuracy (Fig. 4b and c). These results suggest that for people who are not able to downregulate DMN and upregulate FPN, an overshoot in activation in the broader regions of the FPN (component 19) keeps working memory performance high. The compensatory role of component 19 could be explained by the compensation hypothesis, which is known as higher activation in PFC in older people as compared to young adults (Reuter-Lorenz and Lustig, 2005).

4.4. Relationships of physical function to task-evoked functional activation patterns

The positive relationships between cardiorespiratory fitness and hand dexterity and working memory were mediated by task-evoked functional

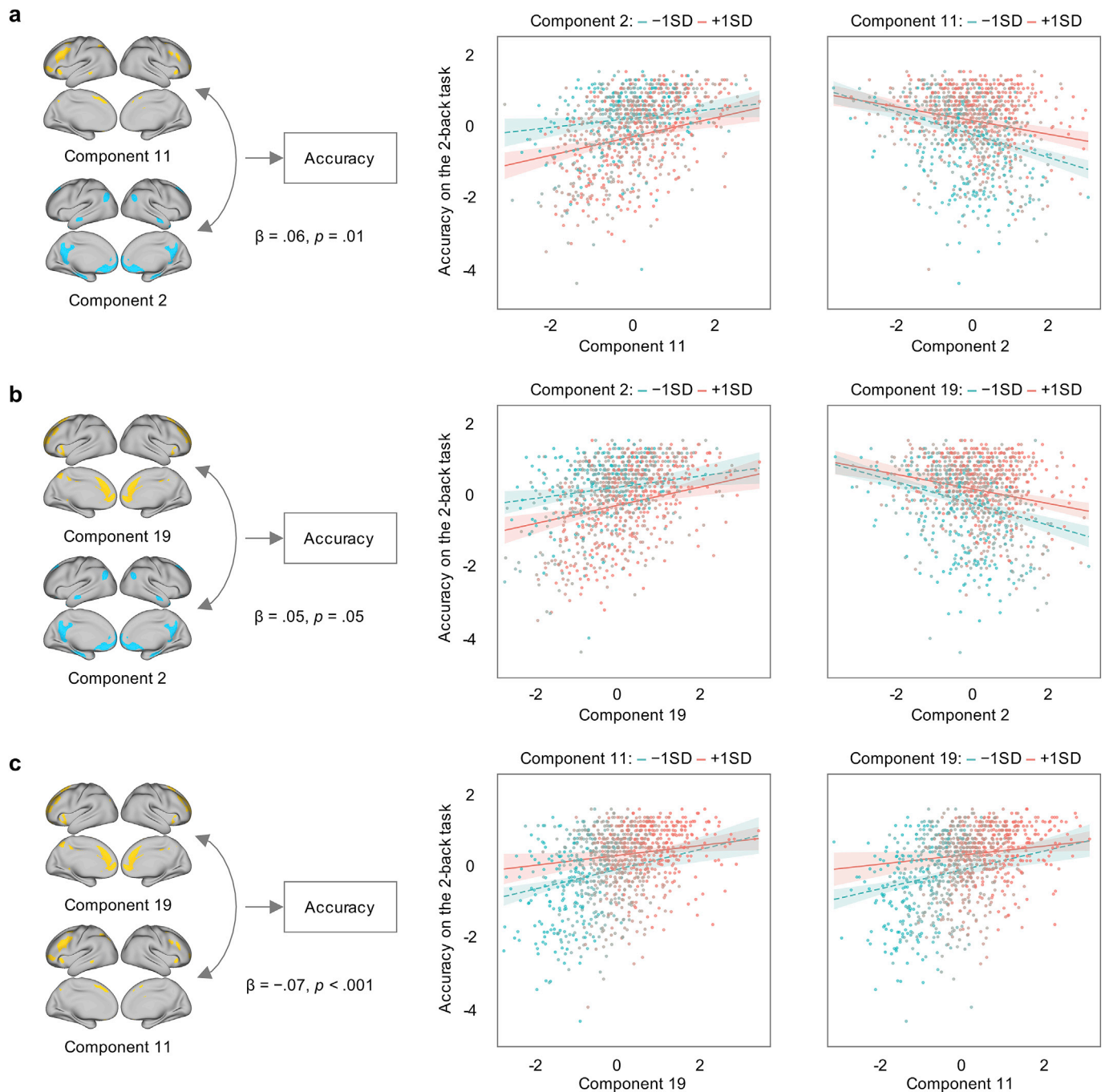


Fig. 4. Interaction effects of task-evoked functional activation in components 2, 11, and 19 on the 2-back task accuracy. Regression lines are shown with 95% confidence bands (shaded areas).

activity in the FPN (components 11 and 19) and DMN (component 2) (Fig. 3). The strength of the relationship between cardiorespiratory fitness and hand dexterity and task-evoked functional activation in the FPN and DMN appeared to be disproportionate. The mediation effects of FPN on the relationship between physical function and working memory performance were stronger in cardiorespiratory fitness relative to hand dexterity, while the mediation effects of DMN were stronger in hand dexterity relative to cardiorespiratory fitness.

Further, hand dexterity was also associated with FPN moderation (components 11 and 19) and DMN (component 2) interaction (Fig. 5a and b), while such moderating effect did not reach significance for cardiorespiratory fitness (Fig. 5c). These results suggest that the individuals with higher hand dexterity showed improved working memory performance

via higher FPN activation (components 11 and 19), when activation in the DMN (component 2) was low, and vice versa (Fig. 5a and b).

By contrast, superior cardiorespiratory fitness could contribute to working memory via activation in broader FPN regions (component 19), while no such relationship was detected regarding hand dexterity. This suggests that individuals with higher cardiorespiratory fitness exhibited activation in broader FPN regions (component 19), and this activation had a supportive role in enhancing working memory performance if the activation in the DMN (component 2) was high (Fig. 4b) and that in the FPN (component 11) was low (Fig. 4c). As such, although both cardiorespiratory fitness and hand dexterity had a positive relationship with working memory performance, the mechanisms behind this relationship may be different.

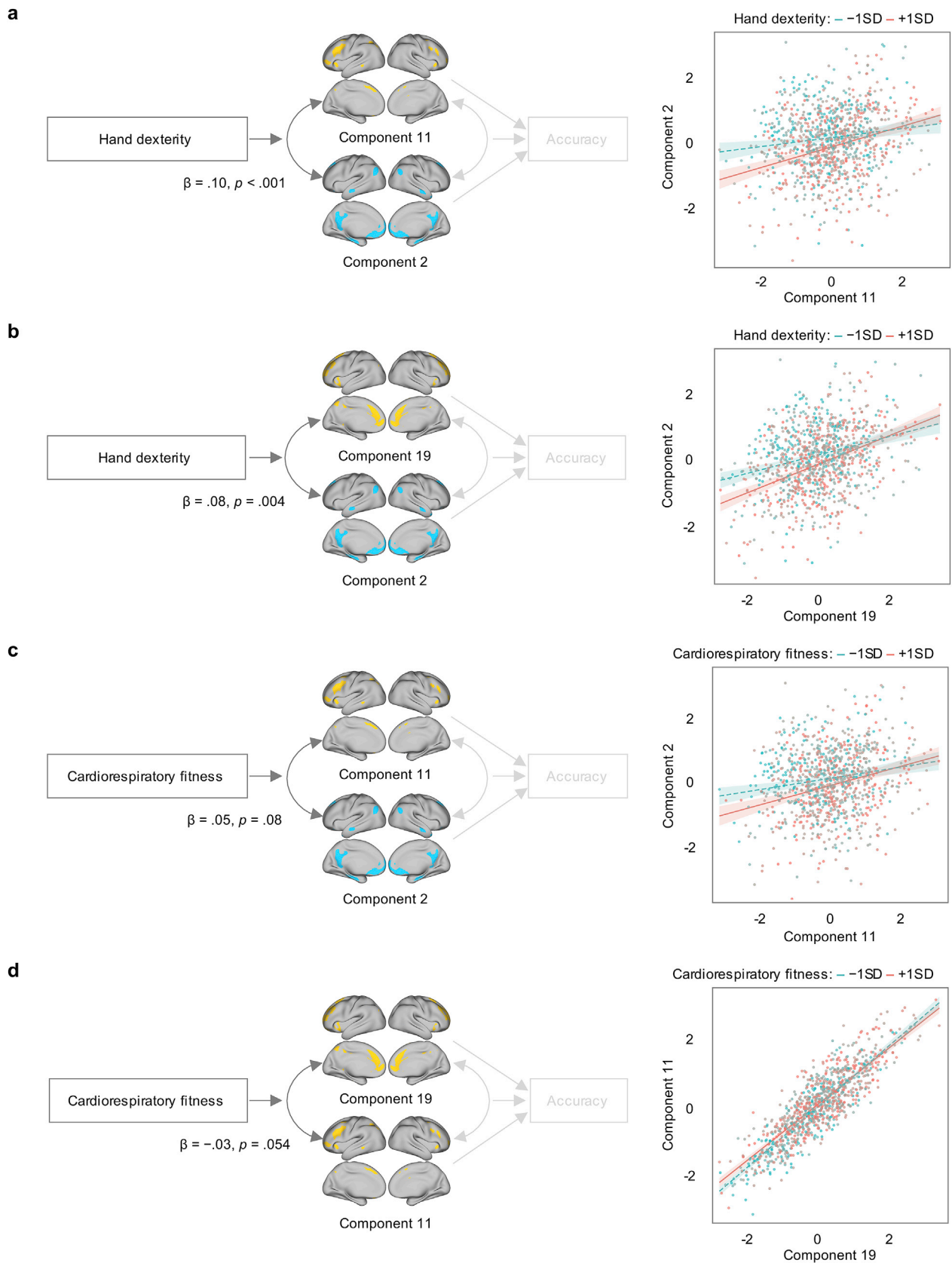


Fig. 5. Moderation effects of the physical function on the task-evoked functional activation patterns. Regression lines are shown with 95% confidence bands (shaded areas).

The FPN is a flexible hub, amongst other brain networks, contributing to cognitive control (Cole et al., 2013; Marek and Dosenbach, 2018). In addition, the functional connectivity between FPN and DMN is associated with a higher working memory performance (Sala-Llonch et al., 2012). Accordingly, it is speculated that higher cardiorespiratory fitness is associated with higher FPN performance as a flexible hub, whereas higher hand dexterity is associated with stronger connectivity between FPN and DMN. Our findings are supported by a previous randomized-control trial that showed that both a 12-month-long cardiorespiratory exercise and a motor coordination exercise intervention enhanced inhibitory control equally, while the changes in task-evoked functional activation differed with the exercise mode (Voelcker-Rehage et al., 2011).

This study demonstrated that when contribution in either component 2, 11, or 19 was high, the contribution of the other components was reduced (Fig. 4); these patterns were stronger in individuals with higher cardiorespiratory fitness and hand dexterity (Fig. 5). These results suggest that highly fit individuals use patterns of increased FPN activation with maintained DMN activation, or maintained FPN activation with decreased DMN activation, to enhance working memory performance. Thus, highly fit individuals may employ both strategies, i.e., increased and decreased activation in the PFC, to enhance working memory performance. Our findings partially explain previous contradictory results of both increased and reduced PFC activation following exercise intervention (Colcombe et al., 2004; Liu-Ambrose et al., 2012; Voelcker-Rehage et al., 2011).

We could not elucidate the mechanisms underlying the differences in related task-evoked functional activity patterns between cardiorespiratory fitness and hand dexterity. A possible explanation is the differential influence of cardiorespiratory and motor exercise on brain metabolism (Black et al., 1990; Isaacs et al., 1992; Klintsova et al., 2004). The mechanisms behind the positive effects of exercise on brain function are believed to be due to synaptic plasticity and neurogenesis, while changes in brain structure and function might depend on the presence of molecules such as vascular endothelial growth factor (VEGF), insulin-like growth factor 1 (IGF1), brain-derived neurotrophic factor (BDNF), and TrkB protein (receptor of BDNF) (Voss et al., 2013b). Previous animal studies have reported that cardiorespiratory training increases in the expression of BDNF in the motor cortex (Klintsova et al., 2004), the density of capillaries (Black et al., 1990), and shortens the diffusion distance from blood vessels in the molecular layer of the paramedian lobule (Isaacs et al., 1992) in rats, while no change was evident in the expression of the TrkB protein and the synaptic numbers. Conversely, motor-skill learning tasks have been shown to increase both the BDNF and TrkB protein expression (Klintsova et al., 2004), and increase the number of synapses per neuron, while no change in the density of capillaries was shown (Black et al., 1990). These differences in the effects of exercise mode on brain metabolism and neural processing could affect brain plasticity in different ways.

4.5. Strengths and limitations

To the best of our knowledge, this study is the first to investigate the concomitant and independent relationships among multiple domains of physical function and working memory and brain function using a task-evoked fMRI technique in a large sample of over 1000 healthy adults. We used the large-scale unique dataset of the HCP (Glasser et al., 2016a; Glasser et al., 2016b) acquired with high spatial and temporal resolution and preprocessed with minimal distortions, blurring, and temporal artifacts. However, there are also several limitations that should be acknowledged. As this study employed a cross-sectional observational design, causal inferences cannot be made. Future studies employing a longitudinal design or a randomized-controlled trial to investigate whether physical function gain affects working memory and task-evoked functional activity over time are, therefore, desirable.

5. Conclusions

Cardiorespiratory fitness and hand dexterity play important roles in working memory and related brain function. Importantly, these relationships are mediated by task-evoked functional activity, including increased activation in the FPN and reduced activation in the DMN. Hand dexterity is also positively associated with working memory performance by moderating the relationship of task-evoked FPN and DMN activation, whereas cardiorespiratory fitness is positively associated with working memory performance via activation in broader regions of the FPN. An exercise training program enhancing cardiorespiratory fitness and hand dexterity could seemingly present beneficial effects on working memory through changes in brain functioning, as there may be both common and unique mechanisms underlying these relationships.

CRedit authorship contribution statement

Toru Ishihara: Conceptualization, Data curation, Formal analysis, Methodology, Validation, Visualization, Writing - original draft, Writing - review & editing. **Atsushi Miyazaki:** Data curation, Formal analysis, Methodology, Software, Visualization, Writing - original draft, Writing - review & editing. **Hiroki Tanaka:** Writing - review & editing. **Tetsuya Matsuda:** Conceptualization, Funding acquisition, Supervision, Writing - review & editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.neuroimage.2020.117152>.

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