OPEN

Association of Cardiovascular Risk Markers and Fitness with Task-Related Neural Activity during Animacy Perception

TORU ISHIHARA[1], ATSUSHI MIYAZAKI[2], HIROKI TANAKA[3,4], and TETSUYA MATSUDA[3]

[1]*Graduate School of Human Development and Environment, Kobe University, Kobe, JAPAN;* [2]*Global Education Center, Waseda University, Tokyo, JAPAN;* [3]*Tamagawa University Brain Science Institute, Tokyo, JAPAN; and* [4]*Japan Society for the Promotion of Science, Tokyo, JAPAN*

ABSTRACT

ISHIHARA, T., A. MIYAZAKI, H. TANAKA, and T. MATSUDA. Association of Cardiovascular Risk Markers and Fitness with Task-Related Neural Activity during Animacy Perception. *Med. Sci. Sports Exerc.*, Vol. 54, No. 10, pp. 1738–1750, 2022. **Purpose:** Numerous studies have demonstrated the association between cardiovascular risk markers and fitness, and broad aspects of cognition; however, the possible association of cardiovascular risk markers and fitness with social cognition, which plays a significant role in the development and maintenance of social relationships, has largely been ignored. Herein, we investigated the relationship of cardiovascular risk markers and fitness with task-related neural activity during animacy perception. **Methods:** We analyzed data from the Human Connectome Project derived from 1027 adults age 22–37 yr. Canonical correlation analysis (CCA) was conducted to evaluate the association between participants' body mass index, systolic and diastolic blood pressure, submaximal endurance, gait speed, hand dexterity, and muscular strength with task-related neural activity during animacy perception. **Results:** We observed a single significant CCA mode. Body mass index and blood pressure demonstrated negative cross-loadings with task-related neural activity in the temporoparietal, superior and anterior temporal, posterior cingulate, and inferior frontal regions, whereas submaximal endurance, hand dexterity, and muscular strength demonstrated positive cross-loadings. The observed CCA variates did not seem highly heritable, as the absolute differences in CCA variates in monozygotic twins, dizygotic twins, and nontwin siblings were not statistically different. Furthermore, the cardiovascular risk markers and fitness CCA variates were positively associated with animacy perception and emotion recognition accuracy, which was mediated by the task-related neural activity. **Conclusions:** The present findings can provide new insights into the role of markers for cardiovascular health and fitness, specifically their association with social cognition and the underlying neural basis. The intervention for cardiovascular risk and fitness could be a potentially cost-effective method of targeting social cognition. **Key Words:** OBESITY, BLOOD PRESSURE, PHYSICAL FITNESS, MOTOR FITNESS, SOCIAL COGNITION, THEORY OF MIND

Cardiovascular disease accounts for one-third of deaths worldwide (1) and represents a significant threat to global health. Cardiovascular risk factors, such as obesity and high blood pressure (BP), combined with low fitness are associated with cardiovascular disease as well as poor cognitive and overall brain health (2–6). Previous studies have focused narrowly on varying domains of cognition, such as global cognitive function, attention, processing speed, language, executive function, memory, and visuospatial abilities (2–6). The potential association of cardiovascular risk markers and fitness with social cognition remains unclear.

Social cognition is an umbrella term that refers to the sum of those processes that allow individuals of the same species to interact with one another (7), and generally refers to the mental operations that underlie social interactions, including perceiving, interpreting, and generating responses to the intentions, dispositions, and behaviors of others (8). The most heavily researched and central components of social cognition are emotion recognition and theory of mind, because of their crucial role in interpersonal interactions and mental health (8,9). Emotion recognition is defined as the ability to identify emotionally salient information in the environment, that is, verbal and nonverbal cues to the emotions of other people (8). The

Address for correspondence: Toru Ishihara, Ph.D., Graduate School of Human Development and Environment, Kobe University, 3-11 Tsurukabuto, Nada-ku, Kobe 657-8501, Japan; E-mail: tishihara@people.kobe-u.ac.jp.

Submitted for publication August 2021.
Accepted for publication May 2022.
Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.acsm-msse.org).

0195-9131/22/5410-1738/0
MEDICINE & SCIENCE IN SPORTS & EXERCISE®
Copyright © 2022 by the American College of Sports Medicine. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.
DOI: 10.1249/MSS.0000000000002963

theory of mind is defined as the ability to infer and predict other people's intentions, thoughts, desires, intuitions, behavioral reactions, plans, and beliefs (8). Emotion recognition and theory of mind have been defined as components of social cognition that are closely related to each other, and they have conceptual and neuroanatomical overlap (8). Emotion recognition and theory of mind deficit seem to be a core cognitive phenotype of many clinical conditions, such as psychiatric, neurological, and developmental disorders (9). Social cognition plays a pivotal role in our social lives and mental health; however, the potential association of markers for cardiovascular risk and fitness with social cognition has not been thoroughly investigated (10).

A recent novel finding demonstrated the positive association between cardiorespiratory fitness and emotion recognition in police officers (10). However, no studies have assessed the possible association of markers for cardiovascular risk and fitness with social cognition and its underlying neural mechanisms. An existing social brain network is consistently involved in social cognitive processes (11,12): the medial prefrontal cortex (MPFC) and temporoparietal junction (TPJ), which are involved in thinking about mental states; the superior temporal sulcus (STS), which is involved in observing faces and biological motion; the anterior temporal cortex (ATC), which is involved in applying social knowledge; the posterior cingulate cortex/precuneus (PCC), which is involved in generating knowledge regarding both our own mind and the minds of others; and the inferior frontal gyrus (IFG), which is involved in emotional judgment and might have a role in top-down aspects of emotion recognition. Previous task-related functional magnetic resonance imaging (fMRI) studies consistently demonstrated that the different experimental social cognitive tasks requiring emotion recognition and theory of mind elicit neural activation in the social brain network (13,14). Cardiovascular risk markers and fitness are associated with altered brain structure and function in some regions overlapping with regions associated with social cognition, such as the MPFC, STS, and IFG (15–18), and may affect social cognition by altering the functional activity of the respective networks.

Social cognition involves processes at several levels, from perceptual to conceptual. Classically, emotion recognition and the theory of mind have been evaluated by high-level verbal stimuli or visual depictions of humans (8). For example, emotion recognition ability has been tested by the paradigm of reading emotion from photographs of the face or a part of the face (8), whereas theory of mind ability has been tested by the paradigm of reading and answering questions about stories involving complex mental states (8). A previous seminal meta-analysis revealed that the beneficial effects of physical fitness are disproportionately greater for executive functions governed by the dorsolateral prefrontal cortex (DLPFC)–associated networks (5). Emotion recognition and theory of mind using higher-order stimuli also induce task-dependent neural activity outside the social brain network, including the DLPFC (8,14,19). Accordingly, whether the previously reported positive association of fitness with emotion recognition from facial expression (10) is dependent on dedicated neurocognitive mechanisms for social cognition (i.e., social brain network) or on other mechanisms, such as the DLPFC, remains unclear. To better understand how cardiovascular risk and lower fitness could impair social cognition, it is worth focusing on social cognitive processing of low-level stimuli that purely elicit activity in the social brain network. If cardiovascular risk and fitness are related to the social brain network rather than to the DLPFC, it would suggest that they may be related to broader aspects of social cognition.

Animacy perception from the movement of simple geometrical shapes (20,21) is useful for investigating whether markers for cardiovascular risk and fitness are associated with the function of the social brain network. Animacy perception is conceptualized as the tendency for observers to perceive simple animated geometric shapes as characters with emotions, intentions, and other social attributes (20,21). This paradigm was developed to investigate whether the social brain network as demonstrated in earlier studies using high-level visual and verbal materials could also be triggered by a very minimalistic and low-level input. Previous studies revealed that neural activation during animacy perception was demonstrated in broad regions associated with the social brain network, including the MPFC, TPJ, STS, ATC, and IFG, but no such neural activation was observed in the DLPFC (13,20,21).

The present study was designed to evaluate the association of cardiovascular risk markers (i.e., body mass index [BMI] and systolic and diastolic BP) and physical and motor fitness (i.e., submaximal endurance, gait speed, hand dexterity, and muscular strength) with neural activity during animacy perception using the large-scale data set of the Human Connectome Project (HCP) (22–24). In addition, we examined whether altered task-related neural activity due to higher cardiovascular risk and poor fitness are associated with lower animacy perception. To test whether such association can be expanded to social cognition using higher-level stimuli, the relationships between cardiovascular risk markers and physical and motor fitness, and emotion recognition from facial expression (via neural activity during animacy perception) were tested. We hypothesized that higher cardiovascular risk and poor fitness are associated with altered neural activities in the regions associated with the social brain network, resulting in poor animacy perception, for which the association could be expanded to emotion recognition.

METHODS

Participants. We used cross-sectional data from the HCP database derived from 1206 healthy participants age 22–37 yr. The HCP began in 2010, and the behavioral and 3T MRI data used in this study were collected from 2012 to 2015. By gathering data from 1200 healthy adults, the HCP consortium aims to characterize human brain connectivity and function in detail and enable comparisons between circuits, behavior, and genetics in an individual subject-based manner (24). The study was approved by the Washington University in St. Louis' institutional review board (Human Research

Protection Office, No. 201204036) and was conducted in accordance with the Declaration of Helsinki. All participants provided informed consent. Participants were excluded if they had a significant history of psychiatric disorders or head injury, showed evidence of a neurological or cardiorespiratory disease, were pregnant, or had unsafe levels of heavy metals in their bodies. Details of participant recruitment and exclusion criteria have been reported previously (24).

Cardiovascular risk markers. BMI and systolic and diastolic BP were used as markers for cardiovascular risk. To calculate the BMI in metric units (in kilograms per meter squared), we used the following formula: BMI = 703 × weight (lb)/height (inches)^2. Each participant's BP was taken and recorded at their visit.

Physical and motor fitness. Four fitness measures (i.e., submaximal endurance, hand dexterity, muscular strength, and gait speed) were evaluated by the National Institutes of Health (NIH) Toolbox (25). Submaximal endurance was measured using the 2-min walk test (26). Hand dexterity was measured using the nine-hole pegboard dexterity test (27). Muscular strength was measured using the grip strength test (25). Gait speed was measured by the 4-m walk gait speed test (28). The participant's score was normalized to those in the entire NIH Toolbox Normative Sample (18 yr and older) except for the gait speed. 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 higher fitness. Gait speed score was reported in meters per second. The HCP provides unadjusted and age-adjusted scores on submaximal endurance, hand dexterity, and muscular strength, and we used the unadjusted scores in the analyses. Because normalizing grip strength measures by body mass has been proposed to be superior to simple grip strength in predicting health status and is strongly associated with health outcomes relative to raw grip strength (29), the score on the grip strength was regressed out for bodyweight before the analyses. In the current data set, the score on grip strength had a positive correlation with body weight (Pearson's $r = 0.49$). The extensive reliability and validity of these measures have been reported (25).

Animacy perception. To assess animacy perception and task-related functional activity, participants were asked to complete the HCP version of a task used to probe animacy perception while inside the MRI scanner. The task consisted of two conditions: random and social. Participants were presented with short video clips (20 s). In the random condition, the videos showed objects (i.e., squares, circles, triangles) moving randomly, whereas in the social condition, the videos showed objects interacting in some way. For example, in the social condition, the two triangles moved as if they were doing something together, such as the big triangle coaxing the reluctant little triangle to come out of an enclosure. After watching the video clips, participants chose among the following three options: 1) the objects had a social interaction, 2) unsure about the objects' interaction, and 3) the objects had no interaction (30). Each task condition comprised five trials (two social and three random in the first session, three social and two random in the second session). We used the accuracy of the social condition (i.e., percentage of selection of the option "the objects had a social interaction") as an index of accurate animacy perception. This is a well-validated and reliable task used to probe animacy perception. The stimuli used generated robust task-related neural activity in the brain regions associated with social cognition (13,20,21). Video clips were shortened from the 40 s of the original clips to 20 s (21); however, a pilot study in phase I of HCP confirmed that shorter videos elicited similar responses to those associated with the longer videos (30). To verify that participants had completed the task, we checked the data for the number of nonresponses and confirmed that all participants responded to all trials.

Task-fMRI data acquisition. All the task-fMRI data were acquired on a Siemens Skyra 3T scanner. Whole-brain echo-planar imaging acquisitions were acquired using a 32-channel head coil with the following parameters: 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 multiband 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 (30). The fMRI data were preprocessed using the HCP pipeline (22,23). The data were spatially smoothened using a 4-mm full-width half-maximum Gaussian kernel. A blocked-design approach was used for a preprocessed data analysis. Task-related regressors were convolved with the gamma hemodynamic response function using a general linear model. The duration of task blocks was 23 s (20-s movie, 3-s response). The difference between the social and random conditions was subsequently calculated.

Emotion recognition. To assess the ability of emotion recognition, Penn Emotion Recognition Test was used (30,31). In this test, participants were shown a series of faces one at a time and were asked to choose what emotion the face is showing from five choices, that is, happy, sad, angry, scared, and no feeling. Four female faces for each emotion (20 female faces) and 4 male faces for each emotion (20 male faces) were used as stimuli, for a total of 40 faces. A total number of correct responses and median reaction time were used to measure participants' ability of emotion recognition.

Parcellations (group-independent component analysis). We used the group-independent component analysis (group-ICA) data for resting-state fMRI provided by HCP for brain parcellation. The output from the group-averaged principal component analysis (PCA) spatial maps (weighted eigenmaps; i.e., dense connectomes of all participants' individual time series) was generated by MELODIC's incremental group-PCA. To create spatial-ICA network maps at dimensionalities of 15, 25, 50, and 100 distinct components, the dense connectome was subsequently parcellated using the group-ICA (32). We used 100 parcels in the main analyses and 15, 25, and 50 parcels in the validation analyses.

Confounding variables. Age, sex, handedness, and education level were included as confounds that could be associated with both independent (i.e., cardiovascular risk markers and physical and motor fitness) and dependent variables (i.e., task-related neural activity). Age, sex, and education level are associated with cardiovascular risk markers and fitness (26–28,33–35), and resting-state functional connectivity (36,37), which accurately predicts task-related neural activity in the various tasks including animacy perception (38). Differences in brain structure and resting-state functional connectivity in the right- and left-handed participants have been reported (39,40). Handedness was evaluated using the Edinburgh Handedness Inventory (41). Participant education level was defined according to the Semi-Structured Assessment for the Genetics of Alcoholism (42) education score. To avoid sample size reduction due to missing data and overadjustment, we used the minimal number of confounding variables in the main analysis. In addition, we then used race and ethnicity, other Semi-Structured Assessment for the Genetics of Alcoholism demographic measures (i.e., employment status, household income, in school for a degree course, and married or in a live-in relationship), sleeping habits evaluated by the total score of the Pittsburgh Sleep Questionnaire (43), drinking habits (total drinks in the past 7 d), and smoking habits (total times used/smoked any tobacco in the past 7 d) in the sensitivity analysis.

Statistical analysis. Task-fMRI data were collected from 1049 participants; 22 participants were excluded because of missing data (education level, 2; BMI, 1; submaximal endurance, 2; muscular strength, 1; systolic and diastolic BP, 12; animacy perception accuracy, 1; and emotion recognition task, 3), resulting in 1027 participants included in the analyses. All statistical analyses were conducted using R Studio (version 1.1.463). The brief analysis procedure used in this study is presented in Figure 1. To test the association of cardiovascular risk markers and fitness with task-related functional activity in each component derived by the group-ICA, canonical correlation analysis (CCA) (44) was performed using the *cc* function in the *CCA* package. The CCA is a powerful multivariate tool that jointly investigates the relationships among multiple data sets that have been successfully applied in recent neuroimaging studies (45). The objective of CCA was to find linear functions of cardiovascular risk markers and fitness that maximally correlate with linear functions of the neural activity during animacy perception. The main strength of CCA is that it can simultaneously evaluate the correlations between two different sets of variables (here cardiovascular risk markers and fitness and task-related functional activity), without assuming any particular form of precedence or directionality. Because CCA allows us to identify patterns that describe many-to-many relationships, it has the advantage of allowing interpretations that go beyond techniques of mapping one-to-one relations or many-to-one relationships, such as Pearson's correlation and multiple regression. CCA is a method to model the relationship between two sets of variables X (cardiovascular risk markers and fitness) and Y (task-related functional activity) of dimensions $n \times p$ (here n = 1027 [sample size] and p = 7 [BMI, systolic and diastolic BP, submaximal endurance, gait speed, hand dexterity, and muscular strength]) and $n \times q$ (here q = 100 [100 parcels of group-ICA]) based on their correlation. The goal of CCA is to successively build orthogonal linear combinations of X and Y, such that at each step, the correlation between the pair of latent variables is maximal. Mathematically, the CCA seeks vectors A and B such that the relation of the two indices $A^{\mathrm{T}}X$ and $B^{\mathrm{T}}Y$ is quantified in some interpretable way. More precisely, it is looking for the projections of A and B in the sense that they maximize the correlation. The first CCA mode ($U1$ and $V1$) is reflected in a linear combination of the variables in X and another linear combination of the variables in Y that maximize the first mode's correlation ρ.

$$U1 = a1x1 + a2x2 + \ldots + apxp = A^{\mathrm{T}}X, a \in R^{\mathrm{p}}$$

$$V1 = b1y1 + b2y2 + \ldots + bqyq = B^{\mathrm{T}}Y, b \in R^{\mathrm{q}}$$

$$\rho = \mathrm{corr}(U1, V1) = \mathrm{corr}\left(A^{\mathrm{T}}X, B^{\mathrm{T}}Y\right)$$

U and V are canonical variates, and A and B are weight vectors. In addition to optimizing the correspondence between $U1$ and $V1$ as the first canonical mode, it is possible to continue to seek additional pairs of linear combinations of A and B that are uncorrelated with the first canonical mode(s) until the maximum number of sets, min (p, q), is reached. The permutation test to assign the statistical significance of canonical correlation coefficients was performed using the *p.perm* function in the *CCP* package. The number of permutation resamples calculated was 1000, and Wilks' lambda was used as a test statistic. Before performing the CCA, all variables were regressed from confounds (i.e., age, sex, handedness, and educational level), and the residuals were standardized.

The HCP data set included a combination of monozygotic and dizygotic twins and nontwin siblings. This allowed us to determine whether related participants had a more similar CCA variate profile than nonrelated individuals. A one-way ANOVA was performed to test whether the absolute differences in CCA variates differed among monozygotic and dizygotic twin pairs, nontwin sibling pairs, and nonrelated participants. The significant main effects of the group were further analyzed via unpaired t-tests with Bonferroni correction. This approach has been applied when analyzing the HCP data set (46).

The mediation effects of the neural activities during animacy perception on the relationship between CCA cardiovascular risk markers and fitness, and animacy perception accuracy and emotion recognition task performance were evaluated using the *sem* function in the *lavaan* package with 5000 bootstrap samples.

We performed the following three sensitivity analyses separately: 1) to consider possible confounding effects of race and ethnicity, all variables were additionally regressed from race and ethnicity before the CCA; 2) to consider possible confounding effects of other demographic measures (i.e., employment status, household income, studying for a degree, and being married or in a live-in relationship), all variables were

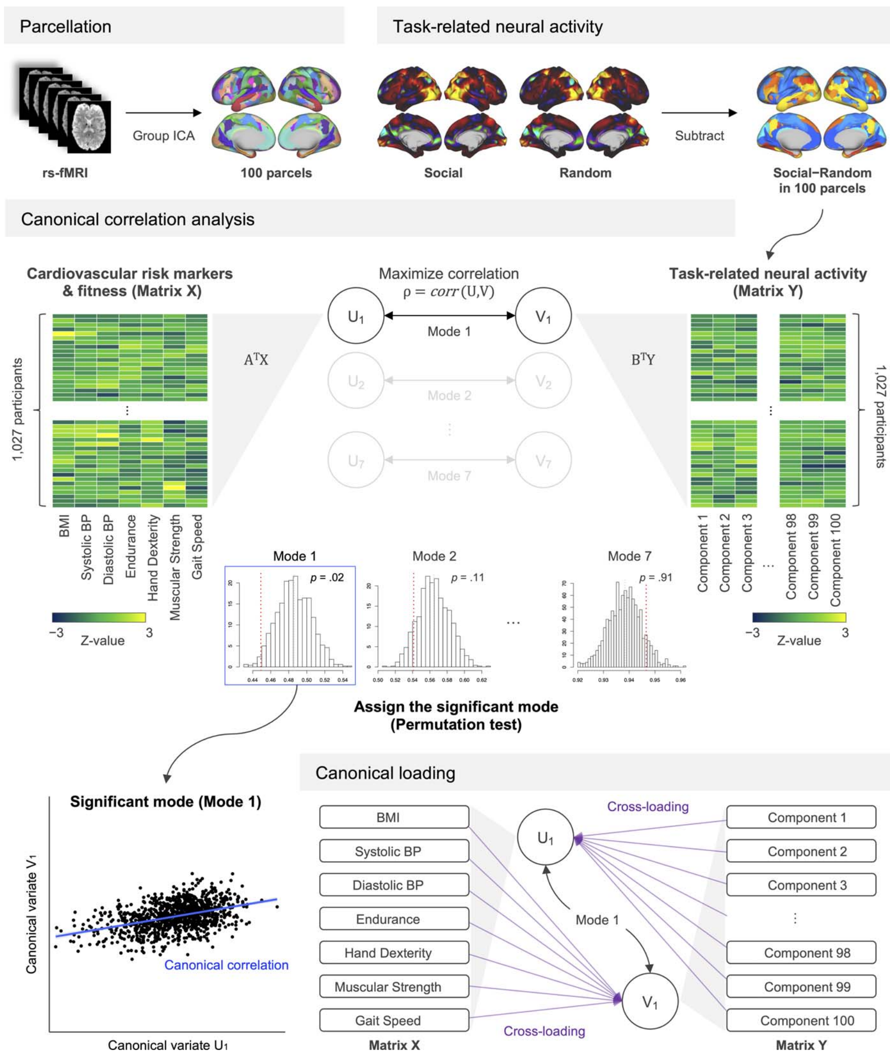

FIGURE 1—Brief analysis procedure used in the current study.

additionally regressed from these measures before the CCA; 3) to consider possible confounding effects of health behaviors and reverse causation, that is, poor social cognition detrimental to cardiovascular health and fitness, via less engagement in healthy behaviors, all variables were additionally regressed from sleeping, drinking, and smoking habits, before the CCA.

The significance level was set at $P < 0.05$. All variables were converted to *z*-scores before analysis. Because the present study was a secondary analysis of the HCP database, we did not perform *a priori* sample size calculation. However, the sample size of 1027 was larger enough to detect a small effect size with adequate power in the CCA, mediation analysis, and structural equation modeling.

RESULTS

The participants' demographic data are outlined in Table 1. Briefly, of the 1027 participants, 54% were women, and the mean age was 28.8 yr (age range, 22–37 yr). The numbers of participants with overweight, obese, and elevated BP variables were 351, 207, and 591, respectively. Seven hundred and sixty-four participants (74%) had excessive weight or elevated/high BP. Participants' scores on submaximal endurance, hand dexterity, and muscular strength were relatively higher than the national average (unadjusted: 110.6, 112.7, and 116.8, respectively; age-adjusted: 108.3, 100.4, and 103.8, respectively).

Main analyses. A single significant CCA mode was observed to be related to cardiovascular risk markers and fitness measures to task-related neural activity (r = 0.41, Wilks' lambda = 0.45, P = 0.02). Permutation test revealed no other statistically significant mode (r < 0.37, Wilks' lambda = 0.54–0.94, P = 0.06–0.84). The relationship of the cardiovascular risk markers and fitness with CCA neural activity is shown in Figure 2A. Cardiovascular risk markers demonstrated negative canonical cross-loadings with task-related neural activity (BMI: ρ = −0.34; systolic BP: ρ = −0.16; diastolic BP: ρ = −0.13), whereas physical and motor fitness measures revealed positive canonical cross-loadings (submaximal endurance: ρ = 0.24; hand dexterity: ρ = 0.22; muscular

TABLE 1. Participants' demographics.

Variables	n (%) or Mean (SD)	Range
N	1027	
Women	550 (54%)	
Men	477 (46%)	
Age (yr)	28.8 (3.7)	22 to 37
Race		
White	784 (76%)	
Black or African American	141 (14%)	
Asian, Native Hawaiian, and Other Pacific Islander	60 (6%)	
Other	42 (4%)	
Ethnicity		
Hispanic	89 (9%)	
Not Hispanic	926 (90%)	
Unknown or not reported	12 (1%)	
Handedness	66.0 (45.0)	−100 to 100
Education (yr)	14.9 (1.8)	11 to 17
Household income		
<$10,000	69 (7%)	
$10,000–19,999	77 (7%)	
$20,000–29,999	130 (13%)	
$30,000–39,999	119 (12%)	
$40,000–49,999	101 (10%)	
$50,000–59,999	218 (21%)	
$60,000–69,999	145 (14%)	
$60,000–79,999	163 (16%)	
Missing	5 (<1%)	
In school for degree course		
Yes	204 (20%)	
No	823 (80%)	
Employment status		
Not working	150 (15%)	
Part-time employment	178 (17%)	
Full-time employment	699 (68%)	
Married or in live-in relationship		
Yes	465 (45%)	
No	562 (55%)	
Pittsburgh Sleep Questionnaire (total score)	4.7 (2.7)	0 to 19
Total drinks in the past 7 d	4.9 (7.0)	0 to 55
Total times used/smoked any tobacco in the past 7 d	7.8 (24.6)	0 to 195
Height (in)	67.5 (3.9)	58 to 80
Weight (lb)	171.3 (38.4)	93 to 305
BMI (kg·m^{-2})	26.3 (4.9)	16.5 to 47.8
Healthy weight (BMI <25)	469 (46%)	
Overweight (BMI 25–30)	351 (34%)	
Obesity (BMI ≥30)	207 (20%)	
Systolic BP (mm Hg)	123.5 (13.9)	87 to 185
Diastolic BP (mm Hg)	76.4 (10.6)	38 to 115
Normal BP (systolic BP <120 and diastolic BP <80)	436 (42%)	
Elevated/high BP (systolic BP ≥120 or diastolic BP ≥80)	591 (58%)	
Submaximal endurance (normalized score)	110.6 (12.0)	80 to 145
Gait speed (m·s^{-1})	1.3 (0.2)	0.8 to 2.0
Hand dexterity (normalized score)	112.7 (10.7)	85 to 149
Muscular strength (normalized score)	116.8 (11.2)	55 to 155

BMI was calculated using the equation: 703 × weight (lb)/height (inches)^2.

strength: ρ = 0.13; gait speed: ρ = 0.09). The scatter plots showing the relationship of CCA cardiovascular risk markers and fitness with CCA neural activity colored by cardiovascular risk markers and fitness are presented in Figure 2B.

The relationships of the task-related neural activity with CCA cardiovascular risk markers and fitness variate are shown in Figures 2C and D. The task-related neural activity in the TPJ, STS, ATC, IFG, and PCC revealed positive canonical cross-loadings with the cardiovascular risk markers and fitness. On the other hand, the task-related neural activity in the region involving visual, dorsal attention, cingulo-opercular, and frontoparietal networks (visual and premotor cortices, parietal lobe, insula, and DLPFC) revealed negative canonical cross-loadings with cardiovascular risk markers and fitness. Consistent results were observed in the validation analysis using the same analysis techniques with contiguous parcels from the 15, 25, and 50 resting-state networks identified using independent component analysis by the HCP (22–24) (Supplemental Fig. S1, Supplemental Digital Content 1, Results of the CCA, http://links.lww.com/MSS/C617). Detailed statistics for canonical vector and cross-loading are summarized in Supplemental Table S1 (Supplemental Digital Content 2, Summary of the results of canonical vector and cross-loading, http://links.lww.com/MSS/C618).

The heritability analysis demonstrated that the groups had a significant effect on CCA cardiovascular risk markers and fitness variates (F = 5.33, P = 0.001). *Post hoc* testing demonstrated that the absolute differences in CCA cardiovascular risk markers and fitness variates among monozygotic twins were significantly lower than those among unrelated pairs (Cohen's d = 0.54, Bonferroni adjusted P = 0.0008), whereas no other statistically significant difference was observed (Cohen's $d \leq 0.41$, Bonferroni adjusted $P \geq 0.08$; Fig. 2E). The absolute CCA neural activity variate's differences were not statistically different among the groups (F = 0.73, P = 0.53; Fig. 2E).

The CCA cardiovascular risk markers and fitness were positively associated with animacy perception accuracy (β = 0.08, P = 0.01) and emotion recognition accuracy (β = 0.20, P = 0.001), which was partially mediated by task-related neural activity CCA weight (animacy perception: β = 0.04, P = 0.01; emotion recognition: b = 0.08, P = 0.006; Fig. 3). The detailed results of the direct and indirect association analyses are summarized in Supplemental Table 2 (Supplemental Digital Content 3, Results of direct and indirect association analyses of CCA cardiovascular risk markers and fitness, http://links.lww.com/MSS/C619).

Sensitivity analyses. The results of sensitivity analyses are summarized in Supplemental Figure 2 (Supplemental Digital Content 4, http://links.lww.com/MSS/C620) and Supplemental Table 3 (Supplemental Digital Content 5, http://links.lww.com/MSS/C621). All sensitivity analyses supported the main analyses except for the results of gait speed. After controlling for race and ethnicity, positive canonical cross-loadings of gait speed disappeared. The mediation effects were consistent with the main analysis in all sensitivity analyses.

Subgroup analyses. Main analyses revealed that BMI, BP, submaximal endurance, hand dexterity, muscular strength, and gait speed were associated with altered neural activity during animacy perception. The present participants were young adults, and the fitness scores were relatively high (~1 SD above the national average; Table 1). Performing subgroup analyses based on participants' health status can help understand whether one factor is protective against the detriments of the other, or *vice versa*, and the generalizability of the present findings. Thus, we performed *post hoc* subgroup analyses based on participants' health status. The participants were assigned to either unhealthy or

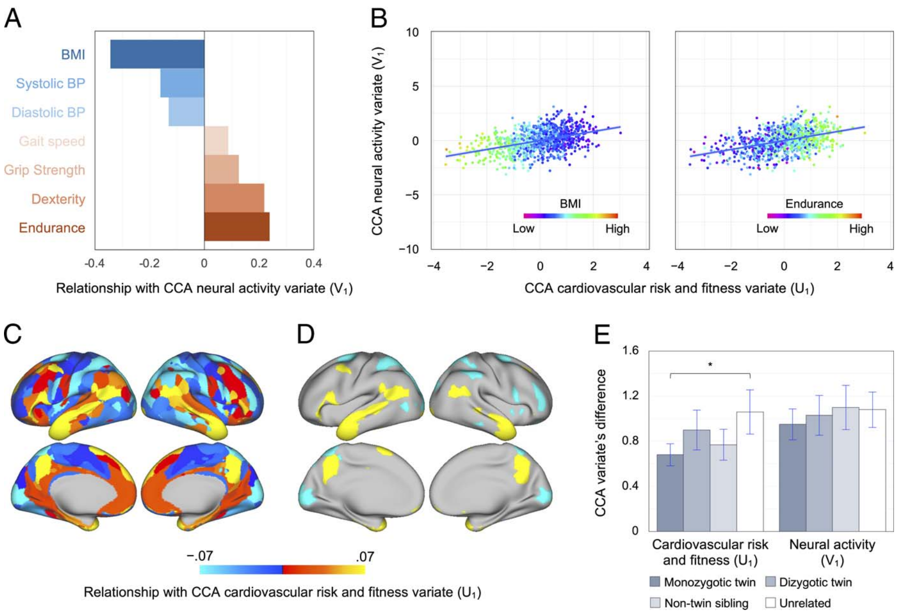

FIGURE 2—Results of the CCA. A, Relationship of cardiovascular risk markers and fitness with the CCA neural activity variate. B, Scatter plots showing the relationship of the CCA cardiovascular risk markers and fitness variate with the CCA neural activity variate colored by the BMI and submaximal endurance. The regression lines are shown with 95% confidence intervals (*shaded areas*). C, Relationship of the task-related neural activity with the CCA cardiovascular risk markers and fitness variate. D, To aid interpretation, the neural activities in 20 components that are most strongly associated with the CCA cardiovascular risk markers and fitness variate are shown. E, The absolute CCA variate's differences in monozygotic (127 pairs) and dizygotic (68 pairs) twins, nontwin siblings (65 pairs), and unrelated pairs (84 pairs). Values are presented as mean ± 95% confidence interval. *Bonferroni adjusted *P* < 0.05.

healthy groups based on BMI (overweight/obese: BMI ≥25 kg·m^{-2} (n = 558); healthy weight: BMI <25 kg·m^{-2} (n = 469)), BP (elevated or high BP: systolic BP ≥120 mm Hg or diastolic BP ≥80 mm Hg (n = 591); normal BP: systolic BP <120 mm Hg and diastolic BP <80 mm Hg (n = 436)), submaximal endurance (low: residual score <0 (n = 546); high: residual score >0 (n = 481)), hand dexterity (low: residual score <0 (n = 536); high: residual score >0 (n = 491)), muscular strength (low: residual score <0 (n = 520); high: residual score >0 (n = 507)), and gait speed (low: residual score <0 (n = 539); high: residual score >0 (n = 488)). Thereafter, CCA was performed in each group.

The negative canonical cross-loadings of cardiovascular risk markers and positive canonical cross-loadings of physical and motor fitness with task-related neural activity observed in the main analysis were consistently observed in the unhealthy groups, whereas those were inconsistent in the healthy group (Fig. 4A). The negative canonical cross-loadings of BMI were seen in all subgroups; however, the association was relatively weak in healthy participants. The negative canonical cross-loadings of BP were not observed for participants with normal BP, high endurance, and high muscular strength. The positive canonical cross-loadings of submaximal endurance were not observed in the healthy weight group. The positive canonical cross-loadings of hand dexterity were not observed in the high hand dexterity and muscular strength groups. The positive canonical cross-loadings of muscular strength were not observed in the healthy weight and BP, and high hand dexterity groups.

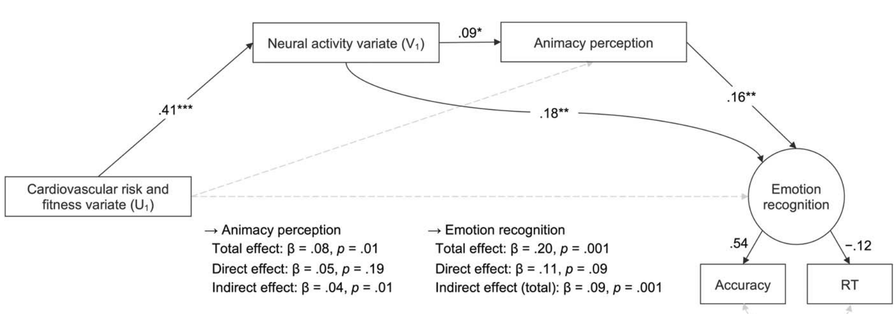

FIGURE 3—Results of the mediation analysis of the direct and indirect relationship between the CCA cardiovascular risk markers and fitness variate and animacy perception and emotion recognition. The model showed an adequate fit (χ^2 = 0.39, *P* = 0.53, comparative fit index = 1.00, goodness of fit index = 1.00, adjusted goodness of fit index = 0.99, root mean square error of approximation = 0.00, 90% CI = 0.00–0.07, *P* close fit = 0.85, standardized root mean square residual = 0.005). *Solid* and *dashed lines* represent the significant and nonsignificant paths, respectively. **P* < 0.05, ***P* < 0.01, ****P* < 0.001. CI, confidence interval; RT, response time.

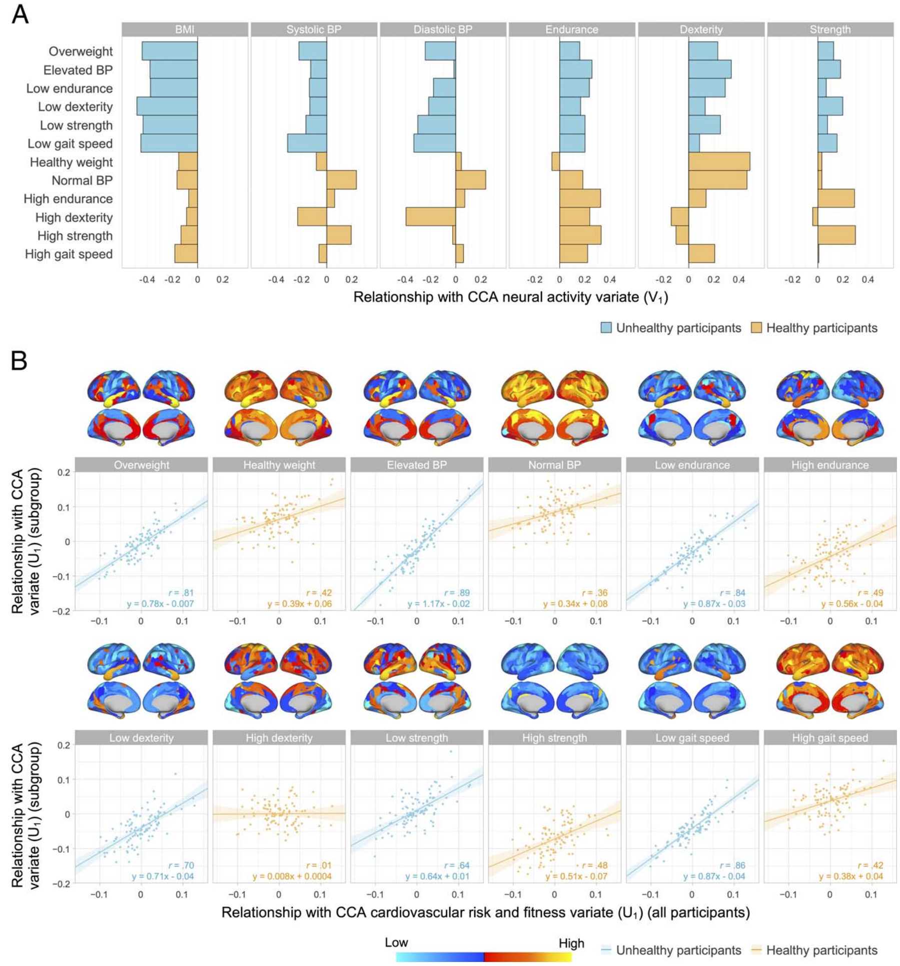

FIGURE 4—Results of subgroup analyses. A, Relationships of the cardiovascular risk markers and fitness with the CCA neural activity in each subgroup. B, Relationship of the task-related neural activity with the CCA cardiovascular risk markers and fitness variate in each subgroup (cortical maps) and their correlation with main results from all participants (scatter plots).

Similarly, the canonical cross-loadings of task-related neural activity with cardiovascular risk markers and fitness observed in the main analysis were consistently observed in the unhealthy groups, while being inconsistent in the healthy groups (Fig. 4B). The loadings in unhealthy groups were strongly correlated with those of the main analyses (Pearson's r = 0.64–0.89), whereas the loadings in healthy groups had relatively weak correlations with those of the main analyses (Pearson's r = 0.01–0.49). However, it is important to note that the permutation tests did not reach significance for mode 1 in any subgroup ($P \geq 0.06$).

DISCUSSION

The present study examined the association of cardiovascular risk markers and fitness with neural activity during animacy perception using the large-scale data set of the HCP. As hypothesized, the present results demonstrated that higher cardiovascular risk and poor fitness were associated with altered neural activities in specific regions associated with social brain network. Specifically, higher BMI and BP were negatively associated with neural activities in the TPJ, STS, ATC, IFG, and PCC, whereas submaximal endurance, hand dexterity, muscular strength, and gait speed were positively associated with neural activities in these regions. Clear effects of heritability on the observed CCA variates for cardiovascular risk markers and fitness and neural activity were not observed. In addition, these neural activity patterns mediated the association of higher cardiovascular risk and poor fitness with lower accuracy in animacy perception. These could be expanded to broad social cognition using higher-level stimuli, as evidenced by the relations of cardiovascular risk markers and physical and motor fitness with facial emotion recognition via neural activity and performance during animacy perception. These findings expand previous research by identifying a negative association of higher cardiovascular risk and poor fitness with the social aspects of cognition and clarifying their underlying neural mechanisms. Because cardiovascular risk and fitness are factors modifiable by low-cost healthy behaviors, such as regular exercise, adequate sleep, prevention of excessive alcohol consumption, and smoking cessation, management of cardiovascular risk and fitness could be a potentially cost-effective method of targeting social cognition.

Previous studies in the obesity–cognition field have demonstrated that BMI is negatively associated with certain aspects of cognitive function, such as attention, executive function, language, and memory (4,6). These findings were supported by previous task-based fMRI studies showing altered task-related neural activities in the frontoparietal, salience, and default mode networks in individuals with obesity (47). A recent systematic review also demonstrated that increased BP is associated with impairment of global cognitive functions, attention, processing speed, executive functions, memory, and visuospatial abilities (3). The association between BP and task-related neural activity has not been well established; however, the findings were supported by altered functional brain connectivity in patients with hypertension, including within the dorsal attention, sensorimotor, visual, and frontoparietal networks (48). The association of cardiovascular risk markers with social cognition and related neural activity has not been previously examined; therefore, we revealed that higher BMI and BP were negatively associated with the social aspect of cognition via lower neural activity in the regions associated with social cognition.

After a seminal meta-analysis that revealed that the beneficial effects of physical fitness are disproportionately greater for the DLPFC-dependent executive functions (5), most studies examining the interaction between fitness and cognition have focused on executive function. These findings were consistent with earlier fMRI studies demonstrating the association between fitness and frontoparietal, default mode, and hippocampal networks (49,50); however, there was limited understanding of the potential association between fitness and social cognition via task-related neural activity. A previous study examined the association between cardiorespiratory fitness and social cognition in police officers and demonstrated a positive association between cardiorespiratory fitness and facial emotion recognition task performance (10). Our results support these findings by demonstrating a positive association between fitness and accuracy of animacy perception and emotion recognition. The present study expands previous knowledge by identifying the contribution of task-related neural activities on the association between fitness and social cognition.

The present findings revealed that the association of cardiovascular risk markers and fitness with social cognition could be seen even in a very minimalistic and low-level input compared with previous work using higher-level visual stimuli (10). The findings suggest that cardiovascular risk and fitness could have an important role in broad aspects of social cognition. Indeed, we observed the significant association of cardiovascular risk markers and fitness with emotion recognition from facial expression via neural activity in the TPJ, STS, ATC, IFG, and PCC and performance during animacy perception. Theory of mind and emotion recognition induce neural activity in areas other than the social brain network (including the DLPFC) (8,14,19); however, the neural mechanism of the association of cardiovascular risk markers and fitness with social cognition seems to be seen in the dedicated neurocognitive mechanism for social cognition. The association of cardiovascular risk markers and fitness with emotion recognition was stronger than with animacy perception ($\beta = 0.20$ vs 0.08), and only 44% of this association was mediated by neural activity. This disproportionate association might be due to the contributions of cardiovascular risk markers and fitness on the brain function outside of the social brain network, elicited during emotion recognition, such as the DLPFC. A part of the remaining mediation effects might be caused by this task-dependent neural activity.

The independence of neural mechanisms in the association of cardiovascular risk markers and fitness with social cognition from the mechanisms of executive function is also supported by the greater activation in dorsal attention and frontoparietal networks during animacy perception in participants with higher cardiovascular risk and lower fitness. Our previous study using the HCP data set revealed that higher submaximal endurance and hand dexterity are associated with greater neural activity in the frontoparietal network during executive function tasks (49), whereas the present results demonstrated the opposite association during animacy perception. Thus, the mechanisms of the contribution of fitness to executive function and social cognition seem to be different. Because animacy perception is an automatic and irresistible process (51), the greater activations in dorsal attention and frontoparietal networks in participants with higher cardiovascular risk and poor fitness can be interpreted as having overrecruited attentional and cognitive control during animacy perception. A previous study suggested that individuals with autism-spectrum disorder, characterized by social skill deficits, overrecruit attentional and cognitive control regions to compensate for decreased processing capabilities for social cues (52). Considering the compensation hypothesis (53,54), the present results suggest that individuals with more health detriments demonstrate some form of accelerated or accentuated aging, which contributes to compensatory activation in the dorsal attention and frontoparietal networks. The present findings speculate that individuals with higher cardiovascular risk and poor fitness have poor processes of animacy perception skills and overrecruit attentional and cognitive control regions to compensate.

The association of higher cardiovascular risk and poor fitness with animacy perception via decreased neural activity in the corresponding network is consistent with previous structural MRI studies. A meta-analysis of 21 studies on obesity and voxel-based morphometry reported that obesity-related variables, such as BMI and waist circumference, were consistently associated with lower gray matter volume in the MPFC, cerebellum, and ATC (16). Another meta-analysis of 10 studies reported gray matter reduction in the IFG, medial temporal gyrus, left precentral gyrus, and cerebellum of individuals with obesity (17). Moreover, higher BP was associated with smaller gray matter volume in broad regions, including the STS, IFG, PCC, and MPFC (18). Another study observed that higher cardiorespiratory fitness and speed–agility were associated with greater gray matter volume in the STS and IFG in overweight and obese children (15). Furthermore, a randomized controlled trial revealed that aerobic exercise training increased gray matter volume in the STS and IFG (55). Considering these findings, the altered brain structure of regions associated with social brain network (i.e., MPFC, TPJ, STS, ATC, IFG, and PCC) may account for the harmful association of higher cardiovascular risk and poor fitness with animacy perception. However, because of the complex nature of the association between gray matter volume and neural activity, this hypothesis should be accepted with caution. Gray matter volume is positively associated with cognitive function (56); however, greater gray matter volume might not necessarily be associated with increased neural activity. For instance, it has been shown that gray matter volume decreases with age (57), but neural activity in the same area may increase (58). Further studies are needed to clarify the association of cardiovascular risk markers and fitness with social cognition via coupling of brain structure and function by the integrated use of multimodal neuroimaging data.

In the subgroup analyses, the permutation tests did not reach significance for mode 1 in any subgroup. The analyses were performed in *post hoc*; therefore, the results of subgroup analyses should be regarded with caution. However, the findings from the subgroup analyses have information worth discussing. Subgroup analyses showed that the main findings were robustly detected in unhealthy participants; however, some inconsistencies were detected in healthy participants. These results suggest that maintaining a healthy weight, normal BP, and high physical and motor fitness may be protective against the detriments of the other group. For example, the detrimental relationship between low hand dexterity and neural activity seems absent in individuals with high muscular strength and *vice versa*. Similarly, the detrimental relationship with elevated/high BP was not noted in individuals with high submaximal endurance and muscular strength. Furthermore, negative cross-loading of BMI was stronger in participants with overweight/obesity, elevated/high BP, and low fitness than in participants with healthy weight, normal BP, and high fitness. These results suggest that maintaining healthy conditions may protect against the negative effects of other unhealthy factors for individuals with some specific good health conditions. In contrast, lower cardiovascular risk and greater physical and motor fitness may have a significantly greater positive association with social cognition in individuals in unhealthy conditions compared with healthy individuals.

The findings from the subgroup analyses have clinical implications because metabolically healthy but obese individuals—characterized by having lower amounts of visceral adipose tissue and adipose cell size as well as higher cardiorespiratory fitness and physical activity levels than in metabolically unhealthy overweight/obese individuals—account for 10%–30% of obese adults (59). The results of the subgroup analysis suggest that in metabolically healthy (having high submaximal endurance) obese individuals, the detrimental association of obesity with social cognition is mitigated. The difference in health outcomes, such as the risk of cardiovascular mortality between metabolically healthy but obese individuals and metabolically unhealthy and obese individuals, is well studied; however, whether these differences may also extend to the brain and cognitive functions has been understudied. A previous study demonstrated that metabolically healthy overweight/obese children had greater gray matter volume, hippocampal connectivity, and academic achievement compared with metabolically unhealthy overweight/obese children (50,60), suggesting that maintaining appropriate metabolic factors could protect against the harmful influences of obesity on the brain and cognitive health. The present findings support this conclusion.

Because the present study population comprised young adults and predominantly fit individuals (~1 SD above the national average; Table 1) with high cardiovascular risk factors (58% and 54% having elevated BP and excessive weight, respectively; Table 1), the applicability of our findings to the general population needs to be carefully verified. The main findings were robustly observed in individuals with lower fitness in the subgroup analysis; thus, they could likely be applied to lower fitness populations. In contrast, as mentioned previously, the present main results may not be directly applicable to healthy individuals. Accordingly, the observed association of cardiovascular risk markers and fitness with social cognition in the main analysis may be ascribed to the general population with a high cardiovascular risk. However, the main results do not seem necessarily inapplicable to healthy people. The contribution of submaximal endurance and hand dexterity on neural activity during animacy perception was consistently detected in the high-fitness and low-cardiovascular-risk groups, respectively. Because the association of cardiovascular risks and fitness with social cognition has been tested only in young adults (10), whether the current findings can be applied in older populations remains unclear. Considering the reported association in middle-age and elderly populations between cardiovascular risk and fitness and brain structures related to the social brain network (16,17,55), the present results may be applicable to middle-age and elderly people as well. Consequently, the results of this study may also apply, to some extent, to the general population; however, further studies are necessary.

The novelty of the present study lies in the finding of an association of multiple indices of cardiovascular risk markers and fitness with large-scale task-related neural activity data of social cognition using CCA. Previous research mainly focused on a single or few indices of cardiovascular risk markers and fitness. We demonstrated the strength of the contribution of each index on social cognition and related neural activities, and observed that BMI, BP, hand dexterity, and submaximal endurance may have a stronger association with social cognition. We speculate that these results could be interpreted by Porges' polyvagal theory (61), which proposes that the mammalian autonomic nervous system has evolved to support the survival, reproduction, and social engagement of the species. According to the theory, the vagal brake promotes social interaction and allows individuals to detect social cues when the environment is safe. A higher heart rate variability at rest, a measure of vagal predominance, is a biological marker of emotion recognition capacity in humans (62) and is relevant to neural function in the regions associated with the social brain network (63). Because regular exercise increases heart rate variability at rest (64), improved physical and motor fitness may increase social cognition via adaptation of heart rate variability. The effects of the type of exercise are inconsistent in the literature; however, some evidence suggests the stronger effects of endurance and motor exercise relative to resistance exercise on heart rate variability at rest (65). Furthermore, overweight/obesity and hypertension are powerful markers for low heart rate variability (66,67). Therefore, we speculated that the present results revealed the stronger association of BMI, BP, submaximal endurance, and hand dexterity with social cognition and neural activity in the social brain network. To elucidate the mechanisms of the disproportionate association, more studies are necessary.

Based on the present findings, cardiovascular risk and fitness interventions could be a potentially cost-effective method of targeting social cognition. CCA cardiovascular risk markers and fitness and neural activity variates do not seem to be strongly heritable, as evidenced by the fact that absolute differences in CCA variates in monozygotic twins, dizygotic twins, and nontwin siblings were not statistically different. Thus, the contributions of cardiovascular risk markers and fitness to social cognition have room for improvement by behavior and environment. For example, cardiovascular risk and fitness are factors modifiable by regular exercise, adequate sleep, prevention of excessive alcohol consumption, and smoking cessation, and these could be cost-effective behaviors for enhancing social cognition. Considering the strength of the observed association, we hypothesize that health behaviors that lead to weight loss and improvement of endurance and fine motor skills are useful behaviors, especially in unhealthy populations.

The main strength of our current study is the use of the HCP data set comprising large-scale data derived from healthy adults (22,23), acquired with high spatial and temporal resolution and preprocessed with minimal distortions, blurring, and temporal artifacts; however, it is important to note that there are limitations to this study due to the cross-sectional design. Thus, causal inferences cannot be formulated, and the current model could work reverse. That is, individuals with poor social cognition may be less likely to engage in health behaviors that promote fitness and cardiovascular health. However, because the main findings were consistently observed after controlling for existing health behavior data in the HCP data set (i.e., sleeping, drinking, and smoking habits), the reverse causation was ruled out to some extent. In addition, physical activity data were not available in the HCP data set, and we could not determine if any relations of cardiovascular risk markers and fitness to social cognition are due to physical activity behavior. Regardless, the present findings provided important clinical implications that individuals with higher cardiovascular concerns combined with lower fitness simultaneously demonstrated the risk of poor social cognition. To confirm the proposed hypothesis in the present study that increasing physical and motor fitness and reducing cardiovascular risks improve social cognition via changes in neural activity, future intervention studies that examine the effects of behavioral health intervention on social cognition are needed.

CONCLUSIONS

In summary, the present study provides new insight into the negative association of higher cardiovascular risk and poor fitness with social cognition, using task-based fMRI data. Higher BMI and BP, poor hand dexterity, submaximal endurance, muscular strength, and gait speed were associated with poor performance in animacy perception and emotion recognition. This observation was coupled with altered task-related neural activity in brain regions associated with the social brain network. Considering that the social brain network has an essential role in broad social cognition, which is an important factor in human social lives and mental health, the present findings have important clinical implications that will be of interest to the public health sector.

Data were provided by the Human Connectome Project, WU-Minn Consortium (Principal Investigators: David Van Essen and Kamil Ugurbil; 1U54MH091657) funded by the 16 NIH institutes and centers that support the NIH Blueprint for Neuroscience Research, and by the McDonnell Center for Systems Neuroscience at Washington University. This work was supported by MEXT/JSPS KAKENHI (grant numbers JP18K17832 (to T. I.), JP21K17546 (to T. I.), JP21H05332 (to T. I.), JP20K22273 (to A. M.), JP21K12617 (to A. M.), JP16K00216 (to T. M.), JP17H05928 (to T. M.)).

The authors declare no conflicts of interest with respect to the authorship or the publication of this article. The results of the present study do not constitute an endorsement by the American College of Sports Medicine. The results of this study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

REFERENCES

1. Roth GA, Johnson C, Abajobir A, et al. Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. *J Am Coll Cardiol*. 2017;70(1):1–25.
2. Yang Y, Shields GS, Guo C, Liu Y. Executive function performance in obesity and overweight individuals: a meta-analysis and review. *Neurosci Biobehav Rev*. 2018;84:225–44.
3. Forte G, De Pascalis V, Favieri F, Casagrande M. Effects of blood pressure on cognitive performance: a systematic review. *J Clin Med*. 2019;9(1):34.
4. Veronese N, Facchini S, Stubbs B, et al. Weight loss is associated with improvements in cognitive function among overweight and obese people: a systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2017;72:87–94.
5. Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults: a meta-analytic study. *Psychol Sci*. 2003;14(2):125–30.
6. Smith E, Hay P, Campbell L, Trollor JN. A review of the association between obesity and cognitive function across the lifespan: implications for novel approaches to prevention and treatment. *Obes Rev*. 2011;12(9):740–55.
7. Frith CD, Frith U. Social cognition in humans. *Curr Biol*. 2007;17(16):R724–32.
8. Mitchell RLC, Phillips LH. The overlapping relationship between emotion perception and theory of mind. *Neuropsychologia*. 2015;70:1–10.
9. Cotter J, Granger K, Backx R, Hobbs M, Looi CY, Barnett JH. Social cognitive dysfunction as a clinical marker: a systematic review of meta-analyses across 30 clinical conditions. *Neurosci Biobehav Rev*. 2018;84:92–9.
10. Ludyga S, Schilling R, Colledge F, Brand S, Pühse U, Gerber M. Association between cardiorespiratory fitness and social cognition in healthy adults. *Scand J Med Sci Sports*. 2020;30(9):1722–8.
11. Adolphs R. The social brain: neural basis of social knowledge. *Annu Rev Psychol*. 2009;60(1):693–716.

12. Blakemore S-J. The social brain in adolescence. *Nat Rev Neurosci*. 2008;9(4):267–77.
13. Schurz M, Radua J, Aichhorn M, Richlan F, Perner J. Fractionating theory of mind: a meta-analysis of functional brain imaging studies. *Neurosci Biobehav Rev*. 2014;42:9–34.
14. Fusar-Poli P, Placentino A, Carletti F, et al. Functional atlas of emotional faces processing: a voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. *J Psychiatry Neurosci*. 2009;34(6):418–32.
15. Esteban-Cornejo I, Cadenas-Sanchez C, Contreras-Rodriguez O, et al. A whole brain volumetric approach in overweight/obese children: examining the association with different physical fitness components and academic performance. The ActiveBrains project. *Neuroimage*. 2017;159:346–54.
16. García-García I, Michaud A, Dadar M, et al. Neuroanatomical differences in obesity: meta-analytic findings and their validation in an independent dataset. *Int J Obes (Lond)*. 2019;43(5):943–51.
17. Herrmann MJ, Tesar A-K, Beier J, Berg M, Warrings B. Grey matter alterations in obesity: a meta-analysis of whole-brain studies. *Obes Rev*. 2019;20(3):464–71.
18. Schaare HL, Kharabian Masouleh S, Beyer F, et al. Association of peripheral blood pressure with gray matter volume in 19- to 40-year-old adults. *Neurology*. 2019;92(8):e758–73.
19. Jamieson AJ, Davey CG, Harrison BJ. Differential modulation of effective connectivity in the brain's extended face processing system by fearful and sad facial expressions. *eNeuro*. 2021;8(2):ENEURO.0380–20.2021.
20. Blakemore S-J, Boyer P, Pachot-Clouard M, Meltzoff A, Segebarth C, Decety J. The detection of contingency and animacy from simple animations in the human brain. *Cereb Cortex*. 2003;13(8):837–44.
21. Castelli F, Happé F, Frith U, Frith C. Movement and mind: a functional imaging study of perception and interpretation of complex intentional movement patterns. *Neuroimage*. 2000;12(3):314–25.
22. Glasser MF, Coalson TS, Robinson EC, et al. A multi-modal parcellation of human cerebral cortex. *Nature*. 2016;536(7615):171–8.
23. Glasser MF, Smith SM, Marcus DS, et al. The Human Connectome Project's neuroimaging approach. *Nat Neurosci*. 2016;19(9):1175–87.
24. Van Essen DC, Smith SM, Barch DM, Behrens TE, Yacoub E, Ugurbil K, WU-Minn HCP Consortium. The WU-Minn Human Connectome Project: an overview. *Neuroimage*. 2013;80:62–79.
25. Reuben DB, Magasi S, McCreath HE, et al. Motor assessment using the NIH Toolbox. *Neurology*. 2013;80(11 Suppl 3):S65–75.
26. Bohannon RW, Wang Y-C, Gershon RC. Two-minute walk test performance by adults 18 to 85 years: normative values, reliability, and responsiveness. *Arch Phys Med Rehabil*. 2015;96(3):472–7.
27. Oxford Grice K, Vogel KA, Le V, Mitchell A, Muniz S, Vollmer MA. Adult norms for a commercially available nine hole peg test for finger dexterity. *Am J Occup Ther*. 2003;57(5):570–3.
28. Bohannon RW, Wang Y-C. Four-meter gait speed: normative values and reliability determined for adults participating in the NIH toolbox study. *Arch Phys Med Rehabil*. 2019;100(3):509–13.
29. Chun S-W, Kim W, Choi KH. Comparison between grip strength and grip strength divided by body weight in their relationship with metabolic syndrome and quality of life in the elderly. *PLoS One*. 2019;14(9):e0222040.
30. Barch DM, Burgess GC, Harms MP, et al. Function in the human connectome: task-fMRI and individual differences in behavior. *Neuroimage*. 2013;80:169–89.
31. Gur RC, Richard J, Hughett P, et al. A cognitive neuroscience-based computerized battery for efficient measurement of individual differences: standardization and initial construct validation. *J Neurosci Methods*. 2010;187(2):254–62.
32. Smith SM, Hyvärinen A, Varoquaux G, Miller KL, Beckmann CF. Group-PCA for very large fMRI datasets. *Neuroimage*. 2014;101:738–49.
33. Jousilahti P, Vartiainen E, Tuomilehto J, Puska P. Sex, age, cardiovascular risk factors, and coronary heart disease. *Circulation*. 1999;99(9):1165–72.
34. Lindle RS, Metter EJ, Lynch NA, et al. Age and gender comparisons of muscle strength in 654 women and men age 20-93 yr. *J Appl Physiol (1985)*. 1997;83(5):1581–7.
35. Kubota Y, Heiss G, MacLehose RF, Roetker NS, Folsom AR. Association of educational attainment with lifetime risk of cardiovascular disease: the Atherosclerosis Risk in Communities Study. *JAMA Intern Med*. 2017;177(8):1165–72.
36. Biswal BB, Mennes M, Zuo X-N, et al. Toward discovery science of human brain function. *Proc Natl Acad Sci U S A*. 2010;107(10):4734–9.
37. Shen X, Cox SR, Adams MJ, et al. Resting-state connectivity and its association with cognitive performance, educational attainment, and household income in the UK biobank. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2018;3(10):878–86.
38. Tavor I, Jones OP, Mars RB, Smith SM, Behrens TE, Jbabdi S. Task-free MRI predicts individual differences in brain activity during task performance. *Science*. 2016;352(6282):216–20.
39. Pool E-M, Rehme AK, Eickhoff SB, Fink GR, Grefkes C. Functional resting-state connectivity of the human motor network: differences between right- and left-handers. *Neuroimage*. 2015;109:298–306.
40. Jang H, Lee JY, Lee KI, Park KM. Are there differences in brain morphology according to handedness? *Brain Behav*. 2017;7(7):e00730.
41. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*. 1971;9(1):97–113.
42. Bucholz KK, Cadoret R, Cloninger CR, et al. A new, semi-structured psychiatric interview for use in genetic linkage studies: a report on the reliability of the SSAGA. *J Stud Alcohol*. 1994;55(2):149–58.
43. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989;28(2):193–213.
44. Hotelling H. Relations between two sets of variates. *Biometrika*. 1936;28(3–4):321–77.
45. Smith SM, Nichols TE, Vidaurre D, et al. A positive-negative mode of population covariation links brain connectivity, demographics and behavior. *Nat Neurosci*. 2015;18(11):1565–7.
46. Vidaurre D, Smith SM, Woolrich MW. Brain network dynamics are hierarchically organized in time. *Proc Natl Acad Sci U S A*. 2017;114(48):12827–32.
47. Donofry SD, Stillman CM, Erickson KI. A review of the relationship between eating behavior, obesity, and functional brain network organization. *Soc Cogn Affect Neurosci*. 2020;15(10):1157–81.
48. Carnevale L, Maffei A, Landolfi A, Grillea G, Carnevale D, Lembo G. Brain functional magnetic resonance imaging highlights altered connections and functional networks in patients with hypertension. *Hypertension*. 2020;76(5):1480–90.
49. Ishihara T, Miyazaki A, Tanaka H, Matsuda T. 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. *Neuroimage*. 2020;221:117152.
50. Esteban-Cornejo I, Stillman CM, Rodriguez-Ayllon M, et al. Physical fitness, hippocampal functional connectivity and academic performance in children with overweight/obesity: the ActiveBrains project. *Brain Behav Immun*. 2021;91:284–95.
51. Heider F, Simmel M. An experimental study of apparent behavior. *Am J Psychol*. 1944;57(2):243–59.
52. Herrington JD, Riley ME, Grupe DW, Schultz RT. Successful face recognition is associated with increased prefrontal cortex activation in autism spectrum disorder. *J Autism Dev Disord*. 2015;45(4):902–10.
53. Martins R, Joanette Y, Monchi O. The implications of age-related neurofunctional compensatory mechanisms in executive function and language processing including the new temporal hypothesis for compensation. *Front Hum Neurosci*. 2015;9:221.
54. Reuter-Lorenz PA, Cappell KA. Neurocognitive aging and the compensation hypothesis. *Curr Dir Psychol Sci*. 2008;17(3):177–82.

55. Colcombe SJ, Erickson KI, Scalf PE, et al. Aerobic exercise training increases brain volume in aging humans. *J Gerontol A Biol Sci Med Sci*. 2006;61(11):1166–70.
56. Nave G, Jung WH, Karlsson Linnér R, Kable JW, Koellinger PD. Are bigger brains smarter? Evidence from a large-scale preregistered study. *Psychol Sci*. 2019;30(1):43–54.
57. de Mooij SMM, Henson RNA, Waldorp LJ, Kievit RA. Age differentiation within gray matter, white matter, and between memory and white matter in an adult life span cohort. *J Neurosci*. 2018; 38(25):5826–36.
58. Li H-J, Hou X-H, Liu H-H, Yue C-L, Lu G-M, Zuo X-N. Putting age-related task activation into large-scale brain networks: a meta-analysis of 114 fMRI studies on healthy aging. *Neurosci Biobehav Rev*. 2015;57:156–74.
59. Ortega FB, Cadenas-Sánchez C, Sui X, Blair SN, Lavie CJ. Role of fitness in the metabolically healthy but obese phenotype: a review and update. *Prog Cardiovasc Dis*. 2015;58(1):76–86.
60. Cadenas-Sanchez C, Esteban-Cornejo I, Migueles JH, et al. Differences in brain volume between metabolically healthy and unhealthy overweight and obese children: the role of fitness. *J Clin Med*. 2020;9(4):1059.
61. Porges SW. The polyvagal perspective. *Biol Psychol*. 2007;74(2):116–43.
62. Quintana DS, Guastella AJ, Outhred T, Hickie IB, Kemp AH. Heart rate variability is associated with emotion recognition: direct evidence for a relationship between the autonomic nervous system and social cognition. *Int J Psychophysiol*. 2012;86(2):168–72.
63. Thayer JF, Åhs F, Fredrikson M, Sollers JJ 3rd, Wager TD. A meta-analysis of heart rate variability and neuroimaging studies: implications for heart rate variability as a marker of stress and health. *Neurosci Biobehav Rev*. 2012;36(2):747–56.
64. Sandercock GRH, Bromley PD, Brodie DA. Effects of exercise on heart rate variability: inferences from meta-analysis. *Med Sci Sports Exerc*. 2005;37(3):433–9.
65. Grässler B, Thielmann B, Böckelmann I, Hökelmann A. Effects of different exercise interventions on heart rate variability and cardiovascular health factors in older adults: a systematic review. *Eur Rev Aging Phys Act*. 2021;18(1):24.
66. Köchli S, Schutte AE, Kruger R. Adiposity and physical activity are related to heart rate variability: the African-PREDICT study. *Eur J Clin Invest*. 2020;50(12):e13330.
67. Schroeder EB, Liao D, Chambless LE, Prineas RJ, Evans GW, Heiss G. Hypertension, blood pressure, and heart rate variability. *Hypertension*. 2003;42(6):1106–11.