ORIGINAL ARTICLE

Aerobic Fitness Explains Individual Differences in the Functional Brain Connectome of Healthy Young Adults

Tanveer Talukdar[1,2], Aki Nikolaidis[3], Chris E. Zwilling[1,2], Erick J. Paul[1,2], Charles H. Hillman[4,5], Neal J. Cohen[2,6,7], Arthur F. Kramer[2,4,8,9] and Aron K. Barbey[1,2,6,7,10,11,12]

[1]Decision Neuroscience Laboratory, University of Illinois, Urbana, IL 61801, USA, [2]Beckman Institute for Advanced Science and Technology, University of Illinois, Urbana, IL, USA, [3]Center for the Developing Brain, The Child Mind Institute, New York, NY 1022, USA, [4]Department of Psychology, Northeastern University, Boston, MA 02115, USA, [5]Department of Health Sciences, Northeastern University, Boston, MA 02115, USA, [6]Department of Psychology, University of Illinois, Urbana, IL 61801, USA, [7]Neuroscience Program, University of Illinois, Champaign, IL 61801, USA, [8]Office of the Provost, Northeastern University, Boston, MA 02115, USA, [9]Department of Mechanical and Industrial Engineering, Northeastern University, Boston, MA 02115, USA, [10]Department of Internal Medicine, University of Illinois, Champaign, IL 61801, USA, [11]Department of Bioengineering, University of Illinois, Champaign, IL 61801, USA and [12]Carle R. Woese Institute for Genomic Biology, University of Illinois, Champaign, IL 61801, USA

Address correspondence to Decision Neuroscience Laboratory, Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana Champaign, 405 North Mathews Avenue, Urbana, IL 61801, USA. Email: ttanveer@illinois.edu (T.T.); barbey@illinois.edu (A.K.B.) https://www.DecisionNeuroscienceLab.org

Abstract

A wealth of neuroscience evidence demonstrates that aerobic fitness enhances structural brain plasticity, promoting the development of gray matter volume and maintenance of white matter integrity within networks for executive function, attention, learning, and memory. However, the role of aerobic fitness in shaping the functional brain connectome remains to be established. The present work therefore investigated the effects of aerobic fitness (as measured by VO_2max) on individual differences in whole-brain functional connectivity assessed from resting state fMRI data. Using a connectome-wide association study, we identified significant brain-fitness relationships within a large sample of healthy young adults ($N = 242$). The results revealed several regions within frontal, temporal, parietal, and cerebellar cortex, having significant association with aerobic fitness. We further characterized the influence of these regions on 7 intrinsic connectivity networks, demonstrating the greatest association with networks that are known to mediate the beneficial effects of aerobic fitness on executive function (frontoparietal network), attention and learning (dorsal and ventral attention network), and memory (default mode network). In addition, we provide evidence that connectivity strength between these regions and the frontoparietal network is predictive of individuals' fluid intelligence.

Key words: aerobic fitness, brain plasticity, connectome-wide association, functional connectivity, individual difference

Introduction

Physical activity and aerobic fitness are among the most well-established lifestyle factors to promote brain plasticity across the lifespan (Erickson and Kramer 2009; Voss et al. 2011, 2013b). An extensive animal literature demonstrates that the observed benefits reflect system-wide changes in structural brain plasticity, including (1) increased production of neurotrophic proteins (Knaepen et al. 2010); (2) the development of new vasculature structure (Bullitt et al. 2009); (3) increased connections among neurons throughout the brain (Kempermann 2002); and (4) increased volume of brain structures underlying executive function (prefrontal cortex), attention and learning (basal ganglia), and memory (hippocampus) (Erickson et al. 2015). These benefits have been observed across the lifespan and in a multitude of species, including rodents, dogs, and nonhuman primates (Voss et al. 2013b).

The neuroscience literature on exercise effects in animals provides the foundation for contemporary neuroscience research in humans, which has increasingly investigated the effects of aerobic fitness on functional brain plasticity. This burgeoning research program is motivated by the hypothesis that aerobic fitness may promote the integration of new neurons into existing brain networks through system-wide mechanisms that enhance neuronal growth and survivability. The observed effects of exercise on the upregulation of neurotrophic factors, for example, may enhance functional connectivity within a distributed network of regions in the cerebral cortex and hippocampus (Knaepen et al. 2010). The hippocampus, a primary site for fitness-induced neuroplasticity, has widespread connections with association cortices, including strong connections with the frontal and temporal cortex, and projections to the parietal and lateral occipital cortex through cingulate pathways (Miller 1991). Thus, physical activity and aerobic fitness may promote functional brain plasticity, delivering global effects that shape the functional connectivity of multiple brain networks.

Consistent with this emergent view, a growing body of evidence indicates that aerobic fitness promotes efficient functional connectivity within brain networks for executive function (frontoparietal network), attention and learning (dorsal and ventral attention networks), and memory (default mode network) (Colcombe et al. 2004; Voss et al. 2010b, 2011). For example, Voss et al. (2010a) demonstrated that a 1-year walking intervention was associated with increased functional connectivity within networks for executive function and memory in healthy older adults. These findings complement the system-wide changes in structural plasticity observed in the animal literature and motivate fundamental questions about the influence of aerobic fitness on individual differences in whole-brain functional connectivity. Although prior research has focused on the beneficial effects of aerobic fitness on brain plasticity assessed at the group level, scientists have long recognized that aerobic fitness (Hautala et al. 2006) and functional brain connectivity demonstrate high individual variability (Finn et al. 2015). Indeed, the association between aerobic fitness and functional connectivity may reflect individual differences in physical activity and engagement of corresponding brain networks for sensory, motor, and/or cognitive processes across the lifespan.

A central question is whether individual differences are sufficiently observable through aerobic fitness testing (VO_2max) and resting-state functional MRI to enable a transition from group level studies to investigations of the effects of aerobic fitness on functional brain connectivity within single participants. The emerging field of human connectomics has established a data-driven technique for connectome-wide association studies that provides a comprehensive voxel-wise survey of brain-fitness relationships to characterize individual differences in the functional brain connectome, entitled Multivariate Distance-Based Matrix Regression (MDMR) (Shehzad et al. 2014). This approach represents a significant methodological advance—breaking away from the standard assumption that brain-fitness associations are univariate, whereby aerobic fitness is associated with only one functional connection at a time (i.e., between regions of interest or between voxels in a whole-brain analysis). In this multivariate framework, the simultaneous contribution of entire sets of functional connections to aerobic fitness are evaluated, enabling the simultaneous assessment of multiple connections that may characterize the global effects of aerobic fitness on individual differences in functional connectivity more accurately.

The present study therefore applied a multivariate modeling approach to identify individual differences within the functional connectome of healthy young adults that are associated with aerobic fitness ($N = 242$) (Shehzad et al. 2014) and examined their influence on multiple intrinsic connectivity networks (ICNs). We investigated the functional connectivity of brain regions that explain variability in aerobic fitness with respect to 7 ICNs; namely, the frontoparietal network, dorsal attention network, ventral attention network, default mode network, visual network, limbic network, and somatomotor network. Furthermore, we explored whether the functional interactions between these brain regions and specific ICNs were also linked with individuals' cognitive ability. Prior research has demonstrated that higher fit and physically active individuals benefit from improved brain function in relation to executive function, learning, and memory (Erickson et al. 2011; Voss et al. 2011; Raine et al. 2013). We therefore investigated the influence of aerobic-fitness sensitive regions on ICNs and examined their role in predicting adaptive reasoning and problem solving skills as measured by a test of fluid intelligence.

By conducting a comprehensive investigation based on a connectome-wide association study, the present work examined the respects in which the functional brain connectome—spanning all regions, functional connections, and ICNs—is associated with aerobic fitness, moving beyond standard univariate methods to elucidate the global effects of aerobic fitness on individual differences in functional brain plasticity and fluid intelligence.

Material and Methods

Participants

A total of 249 participants were enrolled in the study (female: 126, male: 123, ages 18–30, mean 22.1 ± 2.6 years). Seven participants were removed from subsequent data analysis due to high head motion artifacts in their fMRI data, resulting in a total of 242 participants (female: 125, male: 117). All participants were clinically healthy, native English speakers with normal or corrected-to-normal vision. Each participant provided written informed consent in accordance with guidelines established by the University of Illinois Institutional Review Board for resting-state fMRI scans and VO_2max testing.

MRI Data Acquisition

All data were collected on a Siemens Magnetom 3 T Trio scanner using a 32-channel head coil in the MRI Laboratory of the Beckman Institute Biomedical Imaging Center at the University of Illinois.

A high-resolution multiecho T1-weighted magnetization prepared gradient-echo structural image was acquired for each participant (0.9 mm isotropic, TR = 1900 ms, TI = 900 ms, TE = 2.32 ms, with GRAPPA and an acceleration factor of 2). The fMRI data were acquired using an accelerated gradient-echo echo-planar imaging (EPI) sequence (Auerbach et al. 2013) sensitive to blood oxygenation level dependent (BOLD) contrast (1.9 × 1.9 × 2.0 mm^3 voxel size, 56 slices with 10% slice gap, TR = 2000 ms, TE = 30 ms, FOV = 240 mm, 90° flip angle, 10 min acquisition, or 300 volumes). During the resting-state fMRI scan, participants were shown a white crosshair on a black background viewed on an LCD monitor through a head coil-mounted mirror. Participants were instructed to lie still, focus on the visually presented cross hair, and to keep their eyes open (Van Dijk et al. 2010).

MRI Preprocessing Analysis

All MRI data processing was performed using FSL tools available in FMRIB Software Library version 5.0 (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). The high-resolution T1 MPRAGE was brain extracted using the BET analysis tool (Smith 2002). FAST segmentation (Zhang et al. 2001) was performed to delineate gray matter, white matter, and CSF voxels. The resting-state fMRI data were preprocessed using the FSL FEAT analysis tool (Jenkinson et al. 2012; Satterthwaite et al. 2013). Preprocessing entailed: slice timing correction, motion correction, spatial smoothing (3 mm FWHM kernel), nuisance signal regression (described below), temporal bandpass filtering (0.009–0.1 Hz), linear registration of functional images to structural images, and nonlinear registration of structural images to the MNI152 brain template (2 mm isotropic voxel resolution). Based on the FSL FEAT head motion parameter estimates, we excluded fMRI data of participants, which displayed greater than 0.5 mm absolute displacement (mean head movement) in at-least one-third of the total number of volumes. Of the 249 participants that were scanned, data from 7 participants were excluded due to large absolute displacements in head motion.

Nuisance variables were modeled via GLM analyses to remove spurious correlations, noise introduced by head motion, in addition to variables of no interest. These included head motion correction parameters (using the extended 12 motion parameters estimated in the FEAT preprocessing), modeling of individual volume motion outliers estimated using DVARS (Power et al. 2012) (outliers flagged using the boxplot cutoff 1.5 × IQR), and mean white matter and cerebrospinal fluid signals averaged across all voxels identified from the segmentation of the high-resolution MPRAGE. The fully preprocessed resting-state fMRI data was taken as the residuals from this GLM model. The residual image was then transformed into normalized MNI152 space and re-sampled to 4 mm isotropic voxels. Although these preprocessing steps help in eliminating non-neuronal artifacts from the BOLD signal, they can by no means remove all sources of physiological noise, which could potentially confound the residual image.

Aerobic Fitness Analysis

Aerobic fitness was assessed using a gold-standard test of maximal oxygen consumption (VO$_2$max), which describes the physiological limit to the rate at which an individual can consume oxygen. A modified Balke protocol was followed to assess VO$_2$max (Thompson et al. 2013). Specifically, a computerized indirect calorimetry system (with averages for oxygen uptake and respiratory exchange ratio; ParvoMedics True Max 2400) was assessed every 20 s as the participant performed exercise on a motor-driven treadmill at a constant speed and a 2.0% increase in grade every 2 min until volitional exhaustion. A Polar heart rate (HR) monitor (Model A1, Polar Electro, Finland) measured HR throughout the test, and ratings of perceived exertion were assessed every 2 min using the Borg Perceived Exertion Scale (Borg 1970). Relative peak oxygen consumption is expressed in ml/kg/min and is evidenced by the participant achieving 2 of the following 4 criteria: (1) a plateau in oxygen consumption corresponding to an increase of less than 2 ml/kg/min despite an increase in workload; (2) HR within 10 beats per min (bpm) of age-predicted maximum (i.e., 220—age); (3) respiratory exchange ratio greater than 1.10; or (4) perceived exertion greater than 17.

Body composition was assessed by dual-energy radiograph absorptiometry (DXA) using a Hologic QDR 4500 A bone densitometer (software version 13.4.2; Hologic, Bedford, MA). Participants wore light-weight clothing and no shoes; any metal material was removed. Participants were positioned in the center of the DXA machine and the total scan was approximately 3 min. DXA utilizes low-dose X-rays to determine bone mineral tissues as well as soft tissues. These tissues are then divided into lean and fat mass through calibration techniques.

Fat-free VO$_2$max (ml/kg lean/min) was next calculated based on individuals' absolute VO$_2$max and lean mass measures. Fat-free VO$_2$max is increasingly considered a more accurate measure of aerobic fitness than traditional VO$_2$max (Kamijo et al. 2012; Khan et al. 2015). Aerobic fitness tests need to be adjusted for body composition to enable comparison between individuals. Traditional weight based measures of aerobic fitness are confounded by adiposity which lessens their interpretation. Individuals with different weights typically have different amounts of fat and lean tissue. An individual's muscle is what is utilizing oxygen during a VO$_2$max test for aerobic metabolism. Thus, when comparing aerobic fitness of a group of people, dividing by lean mass provides the best measure of oxygen utilizing capabilities (Tompuri et al. 2015). The fat-free VO$_2$max scores were also controlled for age and gender effects by partialing out the respective confounding variables. The mean and standard deviation for the raw fat-free VO$_2$max scores were 57.05 ± 6.96 for the sample size of 242 participants, with males (N = 117) having a slightly higher mean fat-free VO$_2$max of 60.09 compared with 54.20 (N = 125) for females.

Investigating Individual Differences in the Functional Connectome That are Associated With Aerobic Fitness Using MDMR

To assess individual differences in functional connectivity that were associated with variation in aerobic fitness, we conducted MDMR (Shehzad et al. 2014). The MDMR analysis was implemented within MATLAB R2014a and entailed: (1) extracting the BOLD time series signal from participants' fMRI preprocessed data; (2) computing a dissimilarity metric between every pair of participants' functional connectivity profiles for each brain region; and (3) generating a statistical map displaying significant associations between brain regions and aerobic fitness (as measured by fat-free VO$_2$max). We applied Craddock's parcellated brain atlas in MNI space (Craddock et al. 2012) as a mask to extract the mean BOLD time course from grey matter voxels within each parcel. For maintaining regional specificity, 800 grey matter parcellation units were selected based on the findings from Shehzad et al. (2014), who observed substantial

overlap at this resolution with whole-brain, voxel-wise MDMR analyses. We restricted all participants to have the same number of overlapping grey matter parcels. A total of 662 parcellated regions (out of the 800 parcels) were found to be common across all participants.

The dissimilarity metric in MDMR was derived from individual differences in functional connectivity profiles between each brain parcel. For each participant, functional connectivity profiles with respect to each brain region were computed as pairwise correlations between the mean BOLD time courses extracted from grey matter voxels within that brain parcel unit and all other remaining parcellation units. The correlations were then Z-transformed by applying Fisher's Z-transformation to improve normality. Next, dissimilarities between participants' functional connectivity profiles were calculated using the distance metric $d = \sqrt{2(1 - r)}$, where, r represents the Pearson correlation between the connectivity profiles for a participant pair and brain region. MDMR was applied to test the degree to which aerobic fitness (as measured by fat-free VO_2max) explained the variability in distances between participants' functional connectivity profiles at each region separately.

The statistical parametric map computed from the MDMR analysis is a pseudo-F statistic at each region. This measure represents the proportion of variance in distances predicted by aerobic fitness (Zapala and Schork 2006). Because the pseudo-F statistic does not have a known null distribution, significance was determined by permutation testing. We simulated the null distribution by performing 10 000 random permutations of the participant indices and computing the pseudo-F statistic for each iteration. A P-value was then calculated for each region by comparing the pseudo-F statistic from the original data to the simulated null distribution. The P-values were converted to one-sided Z-scores and adjusted for multiple comparisons using Gaussian Random Field (GRF) correction (Li et al. 2009). The Z-scores were then projected onto the MNI152 brain template and center of mass (COM) coordinates of clustered regions were identified using FSL autoaq tool after applying a one-tailed voxel level threshold of $Z > 1.65$ ($P < 0.05$). A one-tailed threshold was employed due to the unidirectional nature of the F-test.

Investigating the Influence of Aerobic Fitness-Sensitive Brain Regions on Core ICNs

We applied graph theory to compute the connectivity strength for the aerobic fitness-sensitive regions identified by MDMR with respect to 7 well-established resting-state ICNs (Yeo et al. 2011). Specifically, we assessed the frontoparietal network, dorsal attention network, ventral attention network, default mode network, visual network, limbic network, and somatomotor network. To derive a measure of connectivity strength, the connection weights between brain regions were determined within each ICN consisting of: (1) 8 nodes representing the COM coordinates of clustered regions identified in the MDMR step, and (2) nodes belonging to specific ICNs, whose number of distinct elements were 44 (frontoparietal network), 51 (dorsal attention network), 34 (ventral attention network), 89 (default mode network), 69 (visual network), 38 (limbic network), and 47 (somatomotor network). ICN nodes were assigned the COM coordinates of the Craddock's brain parcels overlapping with voxels masked by ICN brain maps (available at: https://surfer.nmr.mgh.harvard.edu/fsl-wiki/CorticalParcellationYeo2011). For each ICN, pairwise correlations between the mean BOLD time

courses extracted from each node's parcellation unit were entered into correlation matrices ($N \times N$), with N representing the number of nodes in an ICN. These correlations (reflecting functional connectivity between the nodes) were Fisher's Z-transformed and then converted into standard normal Z-scores. To transform Fisher's Z into standard normal Z-scores, the Fisher's Z were multiplied by their standard deviation approximated as $\sigma = 1/\sqrt{(N - 3)}$, where, N is the number of samples comprising the BOLD signal. Next, a Bonferroni-corrected statistical Z-threshold was applied to identify significant positive correlations ($P < 0.05$) (Fox et al. 2009; Murphy et al. 2009). The thresholded Z-scores were rescaled to represent connection weights ranging from 0 to 1.

Connectivity strength was obtained using the MATLAB based brain connectivity toolbox (https://sites.google.com/site/bctnet/) (Rubinov and Sporns 2010), which requires connection weights as inputs. Connectivity strength was computed as the sum of the connection weights of each node linked to every other node within an ICN and normalized by the number of the nodes within each ICN. The resulting connectivity strength measure provided an index of the MDMR nodes' influence on each ICN.

Predicting Fluid Intelligence

In light of recent physical fitness intervention studies, which have reported enhanced functional connectivity within brain networks mediating executive function (e.g., frontoparietal network) and memory (e.g., default mode network) (Voss et al. 2010a, 2010b), we examined whether aerobic fitness-sensitive brain regions' influence over specific ICNs (measured by connectivity strength) can reliably predict individual's fluid intelligence. This analysis entailed multiple steps: (1) administering a neuropsychological test of fluid intelligence (Figure Series); (2) deriving a single measure of total connectivity strength for aerobic-fitness sensitive regions; and (3) implementing a linear regression framework to predict fluid intelligence scores from the connectivity strength metric. We describe each step in further detail below.

1. Cognitive Test Measuring Fluid Intelligence: A canonical neuropsychological measure of fluid intelligence, the Figure Series test, was administered. In this task, participants are presented a series of items (figures) and must infer the rule that determines the sequence in order to select the correct item that completes the pattern. A response time limit of 60 s per item was employed and performance was measured with respect to accuracy (i.e., the total number of correct responses). Test scores from 239 participants were available from the sample size of $N = 242$. The raw test scores were adjusted for age and gender to represent fluid intelligence scores.

2. Total Connectivity Strength Metric: In order to compute total connectivity strength, the positive Bonferroni-corrected rescaled and normalized connection weights of aerobic fitness-sensitive brain regions (MDMR nodes) were first correlated with fluid intelligence scores. Only connections weights between MDMR nodes and ICN nodes, which were significantly correlated with fluid intelligence scores were added together to produce the total connectivity strength metric. This correlation-based approach to select the connection weights was conducted to improve prediction accuracy when estimating fluid intelligence scores based on the total connectivity strength metric.

3. Predicting Fluid Intelligence Scores From Total Connectivity Strength: A leave-one-out cross-validation (LOOCV) linear regression framework was used to predict fluid intelligence scores from total connectivity strength computed across all MDMR nodes linked to each ICN. In the LOOCV method, a model is built by fitting linear regressions between fluid intelligence scores and the total connectivity strength from $N-1$ participants with respect to each ICN. The total connectivity strength metric from the excluded participant is then used as input into the trained model to generate a predicted fluid intelligence score. This was iterated N times so that we obtained predicted fluid intelligence scores across all participants. We then evaluated the predictive power of each model by correlating predicted and observed fluid intelligence scores across all participants.

Results

Individual Differences in the Functional Connectome That are Associated With Aerobic Fitness

Table 1 presents the clustered brain regions demonstrating individual differences in functional connectivity that are associated with aerobic fitness ($P < 0.05$, cluster corrected using GRF theory). A broadly distributed pattern of cortical regions was observed, including brain structures that have been widely implicated in sensory and motor processing (left thalamus, and the left and right V and IV lobes of the cerebellum), in addition to regions that support executive function (left and right frontopolar regions) and memory (right precuneus, right middle temporal gyrus, right inferior temporal gyrus, and left temporal fusiform cortex) (Table 1 and Fig. 1). Thus, rather than engaging only aerobic fitness-related sensory and motor regions, the functional connections associated with aerobic fitness engaged brain regions that are central to executive function and memory.

Investigating the Influence of Aerobic Fitness-Sensitive Brain Regions on Core ICNs

To further characterize the influence of aerobic fitness-sensitive regions (MDMR regions identified in Table 1) on core ICNs, we assessed network measures of connectivity strength. When examined across all MDMR regions, aerobic fitness demonstrated the strongest influence on individual differences in functional connectivity within ICNs for executive function (frontoparietal network), attention and learning (dorsal and

ventral attention networks), and memory (default mode network) (Fig. 2). Furthermore, we investigated the influence of aerobic fitness on individual differences in network connectivity by examining the connectivity profiles for each MDMR region within each of the 7 ICNs (Fig. 3). The observed pattern of connectivity indicates that the MDMR regions have broad influence over the network of nodes across multiple ICNs. The left frontopolar region, for example, was not only functionally coupled to the frontoparietal network, but also demonstrated strong bilateral connectivity with occipital regions within the visual network as well as the inferior and superior parietal regions of the dorsal attention network. The right frontal pole, on the other hand, showed moderate influence on 2 ICNs; namely, the frontoparietal network and the default mode network. However, its functional projections were not as extensive as those observed in the left frontal pole. Our findings indicate that the frontopolar regions have broad influence on networks that subserve executive control, attentional, and visuospatial processing.

MDMR also revealed individual differences in functional connectivity within the right precuneus and the right middle temporal gyrus, which were functionally integrated with several ICNs (Fig. 3). The right precuneus, for example, is functionally coupled with several regions within the visual network spanning the inferior temporal cortex, which is an area that plays a critical role in the visual recognition of objects. It also has functional projections to inferior parietal regions within the frontoparietal network as well as superior temporal regions of the ventral attention network. The right middle temporal gyrus, on the other hand, exhibited broad influence on several ICNs, with strong functional projections extending to regions within the default mode network (right middle frontal gyrus, parietal and temporal cortex), the frontoparietal network (dorsolateral and medial prefrontal cortex), the ventral attention network (lateral prefrontal area) and the limbic network (temporal and inferior frontal gyrus). The inferior temporal gyrus also exhibited moderate influence on several ICNs. Similar to the right middle temporal gyrus, this region had functional projections with the frontoparietal, dorsal attention, ventral attention, and default mode networks. Strong functional connections were located in parietal and middle frontal regions of the ICNs. It is not surprising that the inferior temporal gyrus has links to multiple ICNs as this region is involved in integrating information from different senses and is also associated with visual recognition and memory.

MDMR also revealed individual differences in functional connectivity within the left thalamus, the left temporal

Table 1. MDMR results.

Region	Z stat	Cluster size	x	y	z
L/R Cerebellum IV, V (CBL)	2.95	1568	16	−68	−30
L Thalamus (THAL)	2.85	184	−8	−26	0
R Inferior Temporal Gyrus (ITG)	2.35	176	59	−26	−21
L Frontal Pole (FP)	2.23	192	−24	56	13
R Middle Temporal Gyrus (MTG)	2.08	496	60	−60	−4
L Temporal Fusiform Cortex (TFC)	1.98	136	−34	−32	−19
R Frontal Pole (FP)	1.82	232	40	53	10
R Precuneus (PCUN)	1.67	304	12	−80	43

Eight clustered brain regions were identified (using FSL "autoaq" tool) from the MDMR output map demonstrating individual differences in functional connectivity that are associated with aerobic fitness ($P < 0.05$, cluster corrected using GRF theory). Each region name is presented in column 1, and the region's significance value, cluster size and the cluster COM in MNI coordinates are presented in columns 2–6, respectively. L, left; R, right; Z stat, test statistic.
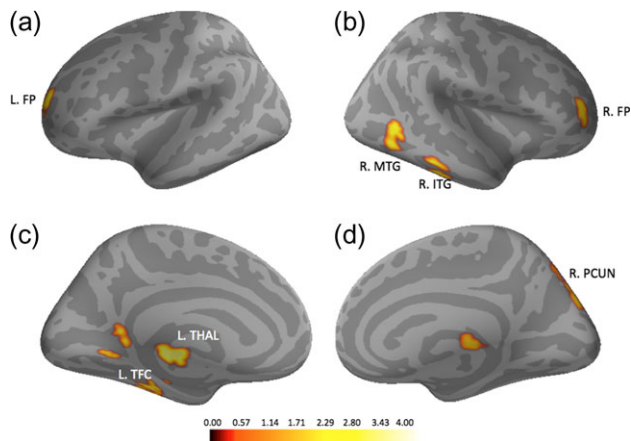
Figure 1. MDMR Results. Panels (*a*)–(*d*) illustrate the MDMR statistical z-score map indicating brain regions whose inter-individual variation in connectivity is significantly associated with aerobic fitness (as measured by fat-free VO_2max). Clustered regions listed in Table 1 are also shown using the following abbreviations: left frontal pole (L. FP), right inferior temporal gyrus (R. ITG), left thalamus (L. THAL), left temporal fusiform cortex (L. TFC), right frontal pole (R. FP), right middle temporal gyrus (R. MTG), and right precuneus (R. PCUN). (Note: cerebellar regions are not displayed.)
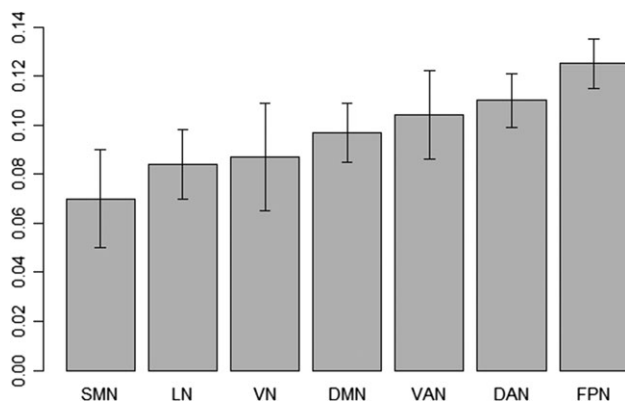
Figure 2. Connectivity strength results by network. Bar graph illustrates the global mean connectivity strength (*y*-axis) for all MDMR nodes with respect to each intrinsic connectivity network. Standard error of the mean is also displayed on each bar plot. Somatomotor network (SMN), limbic network (LN), visual network (VN), default mode network (DMN), ventral attention network (VAN), dorsal attention network (DAN), and frontoparietal network (FPN).

fusiform cortex and the right cerebellar regions. The left thalamus had functional projections to networks such as the dorsal attention network and the limbic network. The left temporal fusiform cortex, on the other hand, was weakly coupled to the frontoparietal network and also the dorsal and ventral attention networks. Similarly, a number of weaker functional projections were observed between the cerebellar regions and the middle frontal regions associated with the default mode, the frontoparietal and the ventral attention networks.

Based on the observed findings, we can conclude that aerobic fitness is associated with individual differences in functional connectivity within multiple cortical and subcortical areas (Table 1 and Fig. 1) and that these aerobic fitness-sensitive regions engage ICNs that support executive function, attentional processes, learning, and memory (Figs 2 and 3).

Predicting Fluid Intelligence From Connectivity Strength

Table 2 shows the correlations between the predicted and actual fluid intelligence scores based on the leave-one-out cross-validation linear regression framework. We found that total connectivity strength for aerobic sensitive brain regions associated with the frontoparietal network significantly predicted the fluid intelligence scores after correction for multiple comparisons ($r = 0.18$, $P = 0.005^*$). While the total connectivity strength with respect to the other ICNs were not reliable for model prediction, the correlation between the predicted and actual fluid intelligence scores did pass the 5% significance level for the default mode network when uncorrected for multiple comparisons ($r = 0.16$, $P = 0.013$). The findings suggest that functional interactions between brain regions associated with aerobic fitness and specific ICNs are predictive of individuals' fluid intelligence.

Discussion

By conducting a comprehensive investigation based on connectome-wide association study methods, the present study examined the respects in which the functional brain connectome—spanning all regions, functional connections, and ICNs—is associated with aerobic fitness. By applying MDMR methods to address this question, we add to the growing body of literature on the relationship between aerobic fitness and functional connectivity and plasticity (Chaddock-Heyman et al. 2013; Demirakca et al. 2016), offering a multivariate perspective on the nature of global network structure as it relates to fitness. The results revealed several brain regions within frontal, temporal, parietal, and cerebellar cortex, whose functional connectivity reliably explained variation in aerobic fitness. Notably, the underlying functional connectivity pattern of regions associated with individual differences in aerobic fitness were not restricted to motor regions most commonly associated with physical exertion and performance. Nor did aerobic fitness account for individual differences in functional connectivity within a discrete brain network. Instead our findings demonstrated that the association between aerobic fitness and the functional brain connectome reflects broad and system-wide effects. Our results provide novel evidence that aerobic fitness accounts for individual differences in connectivity within brain regions for executive function (left and right frontopolar regions) and memory (right precuneus, right middle temporal gyrus, right inferior temporal gyrus, and left temporal fusiform cortex), in addition to brain structures that have been widely implicated in sensory and motor processing (left thalamus, and the left and right V and IV lobes of the cerebellum). Indeed, previous studies demonstrate that aerobic fitness may confer beneficial effects on executive function, learning, and memory (Colcombe et al. 2006; Erickson et al. 2011; Chapman et al. 2013). Furthermore, specific regions, such as the precuneus, have been identified as brain health biomarkers in physically fit older adults (Thomas et al. 2013); frontopolar regions have been shown to increase in functional activation and to have greater grey matter volumes with improvements in aerobic fitness (Colcombe et al. 2004; Erickson et al. 2014); and subcortical structures, such as cerebellum and the thalamus, have been reported to have grey matter densities that are positively correlated with aerobic fitness (Motl et al. 2015; Zlatar et al. 2015). Aerobic fitness training intervention has also been shown to enhance connectivity within the middle temporal and inferior temporal gyri (Vidoni et al. 2012; Voss et al. 2013a).
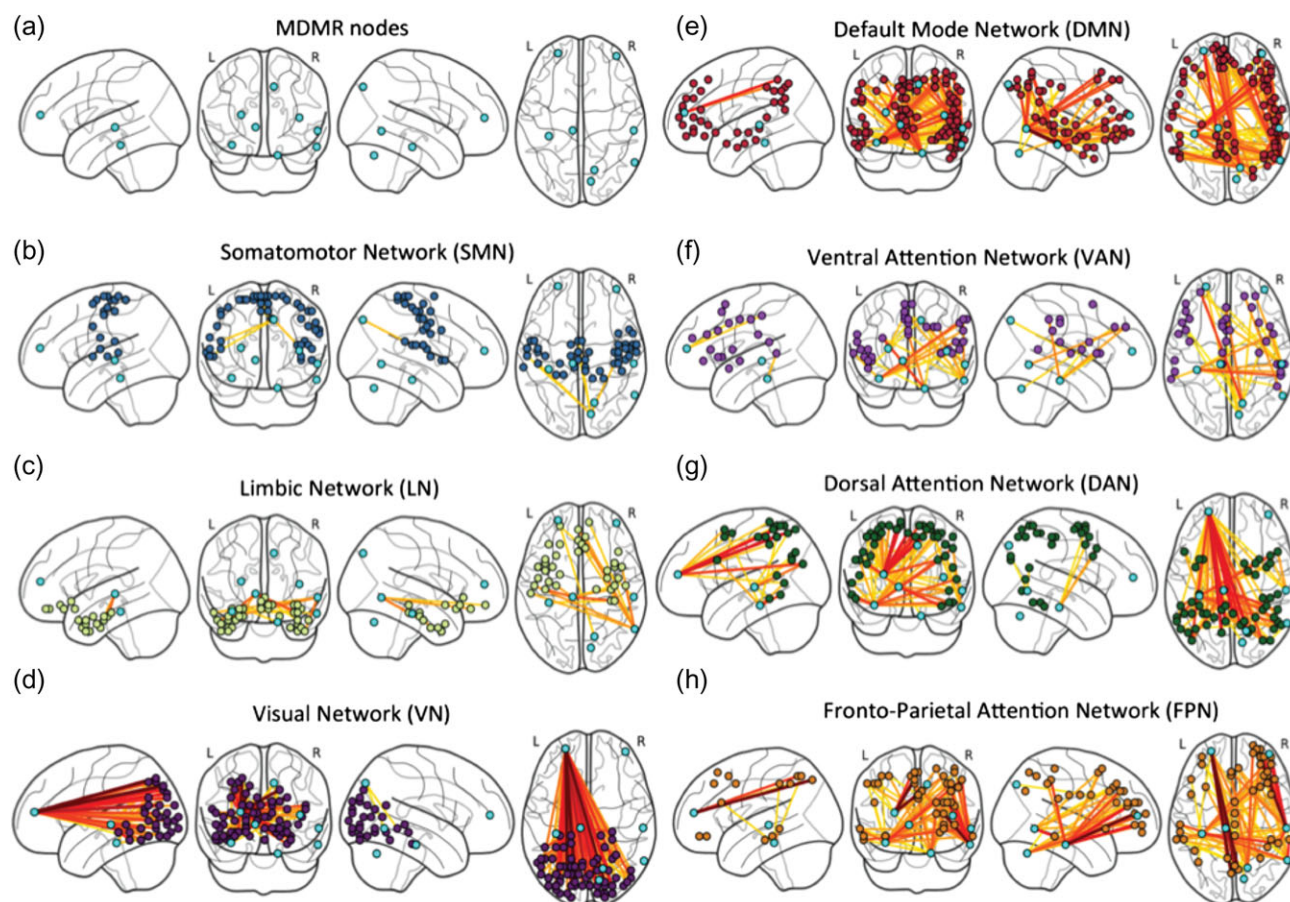
Figure 3. Connectivity profile for each aerobic fitness-sensitive region by network: glass brain plots illustrating connectivity between MDMR nodes in cyan (*a*) and ICN nodes (color coded within each subnetwork, panels (*b*)–(*h*)). The edges represent significant connection weights above the Bonferroni-corrected statistical threshold $Z > 5$ (yellow to red color map reflects increasing weights).

Table 2. Predicting fluid intelligence using total connectivity strength between aerobic fitness sensitive regions and ICNs.

ICN	r	P
Fronto-parietal	0.18	0.005*
Default mode	0.16	0.013
Visual	0.12	0.079
Ventral attention	0.07	0.277
Dorsal attention	0.06	0.338
Limbic	0.04	0.527
Motor	0.02	0.798

Correlation (*r*) between predicted and actual fluid intelligence scores for each ICN and corresponding *P*-values (*P*). (Note: * indicates statistical significance after correction for multiple comparisons at the 5% significance level.)

Our results further demonstrated that the influence of each MDMR region on the 7 ICNs is graded (rather than uniform), reflecting a priority for networks underlying executive function (frontoparietal network), attention and learning (dorsal and ventral attention networks) and memory (default mode network) (Fig. 2). Thus, aerobic fitness was associated with individual differences in functional connectivity within core ICNs that are known to mediate the beneficial effects of physical activity on executive function (frontoparietal network), attention and learning (dorsal and ventral attention network), and memory (default mode network) (Kane and Engle 2002; Ranganath et al. 2004; Barbey et al. 2012, 2014).

Furthermore, the aerobic fitness-sensitive regions also displayed strong functional connections to nodes that largely fell outside their core functional network topology. For example, the right inferior temporal gyrus, which is also part of the default mode network was functionally coupled to the ventral attention network (middle frontal regions) as well as the frontoparietal network (parietal and frontal regions). This broad pattern of connectivity of the right inferior temporal gyrus to multiple ICNs is indicative of its role in multimodal sensory integration (Mesulam 1998). Similarly, the right middle temporal gyrus, associated with the default mode network (Buckner et al. 2008; Uddin et al. 2009; Andrews-Hanna 2012) had functional projections to the ventral attention and frontoparietal networks, which is consistent with the role of this region in attentional and executive and processes (e.g., the retrieval of task-relevant information for goal-directed behavior (Davey et al. 2015, 2016). We also observed functional projections from the right precuneus that extended beyond its functional core in the default mode network (Utevsky et al. 2014). This region had functional connections with other ICNs, such as the visual network, frontoparietal network, and the ventral attention network suggesting a role in mental representations of the self that enable executive function (e.g., personal agency and goal-directed social behavior) and memory (e.g., visuospatial imagery and episodic memory retrieval) (Cavanna and Trimble 2006). In addition, subcortical structures such as the left thalamus was found to have functional projections to the dorsal

attention network and the limbic network. While the thalamus is involved in transmitting signals between other subcortical structures in the brain, recent evidence indicates that it also plays important roles cognitive processes, including attention, speed of information processing, and memory (Van Der Werf et al. 2003).

Our results from the regression analysis for predicting fluid intelligence scores from network connectivity strength provide evidence that functional connections between brain regions implicated in aerobic fitness and specific ICNs such as the frontoparietal network are reliable biomarkers of fluid intelligence. The frontoparietal network mediating executive functions has been implicated in several aerobic fitness studies, which have reported increase in activity within its regions (frontal and parietal) in higher fit individuals performing cognitive tasks requiring executive control (Chaddock et al. 2011, 2012; Voss et al. 2011). Notably, physical activity and aerobic fitness have been shown to largely impact executive function and enhance cognitive abilities (Barnes et al. 2003; Ble et al. 2005; Hillman et al. 2008).

Limitations

Although the present study provides a rigorous examination of individual differences in functional connectivity that are associated with aerobic fitness—conducting the largest and most comprehensive study to date—there are several limitations and questions this study raises for future research. First, the literature on the association between aerobic fitness, brain, and cognition has applied univariate methods that are designed to characterize group level effects on sampled population. Therefore, it will be important to determine the extent to which findings from this literature generalize to the study of individual difference, and vice versa. Indeed, this program of research will require even broader individual difference studies that capture multivariate associations between aerobic fitness, the structural and functional connectome, and measures of cognitive performance. Second, most of the prior literature has been conducted with older adults and children. Thus, it will be important to determine in future studies whether the pattern of connectivity results found in the current study with young adults also apply to other age groups. Third, the present study focused on cross-sectional data; that is data was obtained at a single point in time. Clearly, it will be important in future studies to examine whether the same regions that were associated with fitness in our static sample are also those brain regions that are amenable to change in fitness.

Conclusion

In this study we discovered brain regions that are sensitive to aerobic fitness based on a data-driven exploratory method, which mapped significant associations between functional connectivity patterns—measured across the entire connectome—and measures of fat-free VO_2max. Several of the observed brain regions were within the frontal, temporal and parietal cortex and have been implicated in prior studies investigating exercise-induced changes in brain plasticity. These regions were also functionally coupled to different ICNs and demonstrated the largest influence over networks engaged in executive control, attentional and memory processes. Furthermore, these regions and their influence across specific networks such as the frontoparietal network were shown to reliably predict fluid intelligence. This suggests that aerobic fitness could

moderate functional connections between specific brain regions and functional networks that support executive control. Hence in the near future, it would be important to investigate whether aerobic fitness training systematically alters the functional engagement of these regions and their influence on specific ICNs, which would in turn affect cognitive ability.

While this study is cross-sectional in nature, our findings provide the basis for targeting specific brain regions in longitudinal studies investigating the effects of physical activity and aerobic fitness on brain plasticity. Future longitudinal studies should examine the functional connectivity patterns within these regions and how they change over the course of a fitness intervention—in an effort to further elucidate how the functional brain connectome is shaped by physical activity and aerobic fitness to produce beneficial effects on cognition. These discoveries will help increase our ability to identify abnormalities in aerobic fitness-related neural circuits and networks relevant to health, aging, and disease. Future investigations of the neural circuits identified through fitness intervention studies will enhance our understanding of their functional significance, ultimately improving our ability to diagnose and possibly treat a wide range of health and age-related neurological disorders.

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