Exercise-related changes in between-network connectivity in overweight/obese adults

Kristina T. Legget, Ph.D.[a], **Korey P. Wylie, M.D.**[a], **Marc-Andre Cornier, M.D.**[b,c], **Edward L. Melanson, Ph.D.**[b,c,d], **Courtnie J. Paschall, B.S.**[a], and **Jason R. Tregellas, Ph.D.**[a,e]

[a]Department of Psychiatry, University of Colorado School of Medicine, Anschutz Medical Campus, Aurora, CO, United States

[b]Division of Endocrinology, Metabolism and Diabetes, Department of Medicine, University of Colorado School of Medicine, Anschutz Medical Campus, Aurora, CO, United States

[c]Anschutz Health and Wellness Center, University of Colorado Anschutz Medical Campus, Aurora, CO, United States

[d]Division of Geriatric Medicine, Department of Medicine, University of Colorado School of Medicine, Anschutz Medical Campus, Aurora, CO, United States

[e]Research Service, VA Medical Center, Denver, CO, United States

Abstract

Understanding how exercise affects communication across the brain in overweight/obese individuals may provide insight into mechanisms of weight loss and maintenance. In the current study, we examined the effects of a 6-month exercise program in 11 overweight/obese individuals (mean BMI: 33.6 ± 1.4 mg/kg^2; mean age: 38.2 ± 3.2 years) on integrative brain "hubs," which are areas with high levels of connectivity to multiple large-scale networks thought to play an important role in multimodal integration among brain regions. These integrative hubs were identified with a recently developed between-network connectivity (BNC) metric, using functional magnetic resonance imaging (fMRI). BNC utilizes a multiple regression analysis approach to assess relationships between the time series of large-scale functionally-connected brain networks (identified using independent components analysis) and the time series of each individual voxel in the brain. This approach identifies brain regions with high between-network interaction, i.e., areas with high levels of connectivity to many large-scale networks. Changes in BNC following exercise were determined using paired t-tests, with results considered significant at a whole-brain level if they exceeded a voxel-wise threshold of $p < 0.01$ and cluster-level family-wise error (FWE) correction for multiple comparisons of $p < 0.05$. Following the intervention, BNC in the posterior cingulate cortex (PCC) was significantly reduced ($p < 0.001$). The changes driving the observed effects were explored using Granger causality, finding significant reductions in both

Corresponding author: Kristina T. Legget, Ph.D., Department of Psychiatry, University of Colorado School of Medicine, Anschutz Medical Campus, 13001 E. 17th Place, Mail Stop F546, Bldg. 500, Rm. E4315, Aurora, CO 80045, Phone: (303) 724-5809, Fax: (303) 724-6227, Kristina.Legget@ucdenver.edu.

outgoing causal flow from the PCC to a number of networks ($p < 0.05$; language network, visual network, sensorimotor network, left executive control network, basal ganglia network, posterior default mode network), in addition to reductions in ingoing causal flow to the PCC from a number of networks ($p < 0.05$; ventral default mode network, language network, sensorimotor network, basal ganglia network). Change in BNC was related to changes in aerobic fitness level (VO2 max; $p = 0.008$) and perceived hunger (Three Factor Eating Questionnaire; $p = 0.040$). Overall, the impact of exercise on communication between large-scale networks may contribute to individual responsivity to exercise.

Keywords

exercise; obesity; posterior cingulate cortex; default mode network; between-network connectivity; fMRI

1. Introduction

Exercise confers numerous health benefits, including reduced risk of cardiovascular disease, type 2 diabetes, and cancer [1, 2]. The effects of exercise on weight loss and obesity prevention are, however, variable [3-7]. A potentially key factor involved in successful weight loss and maintenance with exercise is the effect of exercise on the brain. Exercise has been associated with alterations in brain structure [8-10] and neuronal responses to food cues in brain regions important in food reward [11-13]. Furthermore, a strong link has been established between physical fitness and/or exercise and improved cognitive performance [9, 14-16]. These effects may also relate to weight loss and maintenance, as numerous studies have suggested links between obesity and reduced cognitive control [17-20]. However, the mechanisms through which exercise exerts beneficial neuronal effects are unclear.

Previous studies have investigated exercise effects in discrete brain regions or networks. For example, following chronic exercise interventions, a small number of studies have observed alterations in functional connectivity within large-scale brain networks, such as the default mode network [21, 22], cognitive control networks [21, 22], and motor networks [22]. Specifically, in normal weight older adults, exercise has been associated with increased functional connectivity within the default mode and cognitive networks [21]. In overweight children, exercise has been associated with decreased synchrony within default, cognitive control, and motor networks, suggesting increased network efficiency [22]. As our ability to study brain function has improved, it has become apparent that a more complete understanding of the neurobiology of exercise requires consideration of neuronal activity not only *within* these large-scale brain networks, but also the transfer of information *between* them. Much of this information transfer occurs at integrative brain "hubs," which are areas with high levels of connectivity to multiple large-scale networks that are thought to play an important role in multimodal sensory and cognitive integration [23-25]. Identifying how exercise influences communication between large-scale networks at these hubs may be a key part of understanding the neurobiology of exercise effects. Based on previous findings of network-specific alterations in functional connectivity following exercise, the current study

tested the hypothesis that chronic exercise would result in overall altered information flow between large-scale functionally-connected networks at key integrative hubs in the brain.

To examine the effects of a 6-month exercise program on integrative brain hubs, the current study used a novel between-network connectivity (BNC) metric [26]. This data-driven approach allowed an examination of the degree to which key integrative hubs simultaneously interact with all identified large-scale networks, rather than simply focusing on relationships between specific networks and *a priori* regions of interest. This technique, which measures the amount of integration between large-scale networks at particular voxels, has the advantage of capitalizing upon the full spatial resolution provided by functional magnetic resonance imaging (fMRI), allowing examination of connectivity within cortical subregions not included in current anatomical atlases. Following identification of these key integrative areas, the effect of exercise on the areas was examined. The specificity and directionality of hub information flow to and from specific networks driving connectivity effects was then evaluated. Finally, the relationship between neuronal effects and behavioral measures of exercise effects was examined.

2. Methods

2.1. Participants

A subgroup of eleven individuals participating in a larger study evaluating exercise effects on total daily energy expenditure were recruited for the current study. One participant only completed fMRI measures at baseline, so complete data for ten overweight/obese adults were analyzed (five women, five men; mean body mass index (BMI) 33.6±1.4 mg/kg^2; mean age 38.2±3.2 years). Participants were free of metabolic and psychiatric disease and eating disorders and were not actively dieting. Participants provided written informed consent and all procedures were in accordance with and approved by the Colorado Multiple Institutional Review Board.

2.2. Experimental design

Participants were recruited from the larger study, as has been described previously [11, 27]. Participants performed a 6-month supervised treadmill-walking program that gradually increased in intensity (60% to 75%) and duration (~15-20 min/day to 40-60 min/day) to achieve a target workload (500 kcal/day at 75% of VO2 max) by week 18. Individualized exercise prescriptions targeted 2500 kcal per week. Prescriptions were calculated from a maximal aerobic capacity test at baseline and updated according to submaximal tests every 6 weeks. Participants were required to attend more than 75% of the scheduled exercise sessions. Behavioral, hormonal and body composition measures were completed before and after the intervention, following an overnight fast and no exercise for 24 h, on a separate day from fMRI measures.

2.3. Behavioral, hormonal and body composition measures

Body composition was assessed by dual-energy X-ray absorptiometry (DPX whole-body scanner, Lunar Radiation Corp.). Resting metabolic rate (RMR) was measured by standard hood indirect calorimetry (TrueOne 2400 metabolic cart, Parvometrics). Fasting blood

sampling was performed and analyzed for leptin concentration as determined by radioimmunoassay (Linco Research, Inc.). Participants completed the Three Factor Eating Inventory (TFEQ [28]), Power of Food Scale (PFS [29]), Craving and Mood Questionnaire (CMQ [30]), and Food Craving Inventory (FCI [31]). Hunger, satiety, and prospective food consumption ratings were assessed by visual analog scale (VAS) before and every 30 min for 180 min following a test meal breakfast. The test meal was served at 7:30 AM and provided 30% of daily energy intake (50% carbohydrate, 35% fat, 15% protein), estimated using baseline RMR and lean body mass plus an activity factor of 1.4. The entire meal was required to be consumed and was prepared by the University of Colorado Clinical Translational Research Center kitchen.

Maximal aerobic capacity (VO2 max) was measured on a motor-driven treadmill, on which participants walked to volitional exhaustion using the Balke treadmill protocol [32], performed at a constant speed but increasing grade. Expired gasses were collected and analyzed throughout the test using standard indirect calorimetry. Heart rate and rhythm were monitored continually using a 12-lead electrocardiogram. The test was considered successful if oxygen consumption plateaued or the participant met three of the following criteria, as per American College of Sports Medicine (ACSM) guidelines [32]: (1) maximum heart rate within 20 beats/min of the age-predicted maximal heart rate (220-age); (2) perceived exertion rating greater than 17; (3) respiratory exchange ratio greater than 1.15, and (4) volitional exhaustion. Maximal oxygen consumption was determined as the highest observed value during the test.

2.4. fMRI data acquisition

Within a week of behavioral, hormonal, and body composition measures, participants completed fMRI the morning after an overnight fast (approximately 8:00 AM; asked to not consume any food after 10:00 PM the night before). Fasting VAS appetite measures were performed prior to scanning. fMRI was performed using a GE 3.0T MR scanner. A high-resolution, T1-weighted 3D anatomical scan was acquired for each participant, after which functional images were acquired with an echo-planar gradient-echo T2* blood oxygenation level dependent (BOLD) imaging contrast technique, with TR = 2000 ms, TE = 30 ms, 64^2 matrix, 240 mm^2 FOV, 27 axial slices angled parallel to the planum sphenoidale, 2.6 mm thick, 1.4 mm gap. An inversion-recovery echo-planar image (IR-EPI; TI = 505 ms) volume was acquired to improve coregistration between the echo-planar images and gray matter templates used in preprocessing. Participants completed fMRI during 10 minutes of rest with eyes open.

2.5. Data analysis

2.5.1. fMRI preprocessing—fMRI data were preprocessed and analyzed using SPM8 (Wellcome Dept. of Imaging Neuroscience, London, UK). Functional data were realigned to the first echo-planar image, normalized to the Montreal Neurological Institute (MNI) EPI template, using the gray-matter-segmented IR-EPI as an intermediate to improve registration, and smoothed with an 8 mm full width at half maximum (FWHM) Gaussian kernel.

2.5.2. Between-network connectivity (BNC)—The method used to assess between-network connectivity (BNC) has been explained in detail previously [26]. Briefly, this technique measures the amount and diversity of connectivity between all large-scale networks occurring at a single voxel. BNC is calculated using simple and multiple correlation coefficients, along with each network's time series estimated for each subject (Figure 1). A voxel with high BNC indicates that the voxel is strongly connected (i.e., correlated) to many networks, suggesting a high degree of information flow between the networks at that voxel. In contrast, low BNC could indicate either that a voxel's connections to many intercommunicating resting-state networks are negligible, or that the voxel's connections are to networks that are not communicating with one another. Either case would result in a low BNC, indicating that this voxel would not be considered an integration hub.

Large-scale networks were identified using group independent components analysis (ICA) within the GIFT toolbox (http://icatb.sourceforge.net). Data for each session (pre- and post-exercise intervention) were processed jointly to identify networks present in both sessions. The dimensionality of the data from each subject was reduced to 70 components using principle component analysis and concatenated into an aggregate dataset for input into ICA. Fifty independent components were estimated using information-theoretic criteria [33], extracted using the infomax algorithm [34]. Individual subject components and time series were back-reconstructed using GICA3 [35]. Fourteen artifactual components corresponding to white matter, cerebral spinal fluid or head movement were identified based on spatial distributions and frequency characteristics, and excluded from further analysis.

Voxel time series were processed to remove sources of noise and minimize the influence of movement. Time series were detrended and band-pass filtered between 0.1 and 0.01 Hz. Signals for white matter, cerebral spinal fluid, and six movement parameters were regressed out. Additional movement control was provided by removing volumes with excessive framewise displacement [36].

BNC was calculated using the resulting non-artifactual ICA time series and denoised voxel time series. For each voxel, BNC was measured by subtracting the total amount of variance explained by the ICA component time series (the multiple correlation coefficient) from the sum of individual squared correlations with the ICA time series. All resulting raw BNC values were standardized to z-scores to facilitate comparison between subjects, by subtracting the whole-brain mean for each subject and dividing by the whole-brain standard deviation. The distribution of BNC throughout the entire brain was examined using a one-sample t-test in SPM8. Pre- and post-intervention conditions were compared using a paired t-test. Results were considered significant at a whole-brain level if they exceeded a voxel-wise threshold of $p < 0.01$ and cluster-level family-wise error (FWE) correction for multiple comparisons of $p < 0.05$.

2.5.3. Granger causality—Effective connectivity of local peaks of high BNC was analyzed using time-delayed Granger causality (GC) implemented in the Granger Causality Connectivity Analysis toolbox [37]. ICA time series were centered to a mean of zero, linear trends were removed, and time series were concatenated across subjects within each group. After concatenation, model order was determined using Bayesian information criteria.

Conditions were compared with a random permutation test, using the assumption of exchangeability of conditions under the null hypothesis. Condition labels were randomized for all subjects, the resulting time series were concatenated, and GC was calculated as above, for 1000 permutations in total. Significance level was set at alpha < 0.05.

2.5.4. Behavioral, hormonal, and body composition measures—Analyses for behavioral, hormonal, and body composition measures were performed with SPSS 22.0 (IBM Corp.). Total area under the curve for appetite VAS ratings using all post-meal time points was used. Effects of exercise as compared to baseline were compared with a paired t-test (alpha of 0.05). For correlations between fMRI and behavioral data, regression analyses were performed in SPSS using standardized BNC z-scores reflecting network activity extracted from SPM at the local maxima within the significant cluster. To explore relationships between individual ICA network connectivity at BNC hubs and behavioral data, voxel-to-network connectivity between the peak voxel of each integrative hub of interest and each ICA network was first calculated as a Pearson's correlation between these time series. Connectivity at this voxel-to-network level was then correlated with behavioral data.

3. Results

3.1. Behavioral, hormonal, and body composition measures

Percent body fat was significantly reduced in this group of participants following the exercise intervention (mean±SEM: 36.4±2.3 to 34.5±2.3%, $t = 2.50$, $p = 0.034$), with a trend towards a reduction in fat mass (35.6±3.1 to 33.1±3.6 kg, $t = 1.85$, $p = 0.098$) and no significant reduction in body weight (98.4±5.6 to 95.9±6.4 kg, $p > 0.05$). There were significant reductions in fasting blood leptin concentration following the intervention (33.0±6.9 to 21.7±4.9 ng/ml, $t = 2.72$, $p = 0.026$). Additionally, a significant increase in VO2 max was observed after the exercise intervention (27.02±1.24 to 32.03±1.61 ml/kg/min, $t = 3.87$, $p = 0.004$). No changes were observed in behavioral measures (Table 1).

3.2. fMRI

3.2.1. Between-network connectivity (BNC)—At baseline, high BNC was observed in a number of regions, including the posterior cingulate cortex, insula, precentral gyrus, postcentral gyrus, cuneus, superior temporal gyrus, and lingual gyrus (Table 2). These findings are consistent with prior observations [26]. Following the 6-month exercise intervention, BNC in the posterior cingulate cortex (PCC; x = −3, y = −43, z = 40) was significantly reduced, $t = 6.34$, $p < 0.001$ (Figure 2).

3.2.2. Granger causality—Significant changes in outgoing causal flow from the PCC following exercise were identified (change in weighted out-degree = 0.22, significant at $p < 0.05$ by permutation testing; Figure 3). This was driven by reduced connection strength in a number of networks, including a language network, visual network, sensorimotor network, left executive control network, basal ganglia network, and posterior default mode network (DMN). Ingoing causal flow to PCC was also altered post-intervention (change in weighted in-degree = 0.07, significant at $p < 0.05$ by permutation testing; Figure 4), driven by

reductions in causal influence from a ventral default mode network, language network, sensorimotor network, and basal ganglia network.

3.2.3. Correlations between fMRI and behavioral measures—Baseline BNC was not significantly correlated with any baseline body composition, hormonal, or behavioral measures, $p > 0.05$. Post-intervention change in VO2 max was significantly correlated with post-intervention change in PCC BNC, $r = 0.67$, $p = 0.035$. Further exploration using voxel-to-network connectivity suggests that connectivity between PCC and a ventral DMN network contributed to this effect, as changes in PCC/ventral DMN connectivity were significantly correlated with VO2 max change, $r = 0.78$, $p = 0.008$. As the PCC is a main component of the posterior DMN, this could also be interpreted as changes between ventral and posterior components of the DMN. Post-intervention change in hunger, as measured by the TFEQ, was also significantly correlated with post-intervention change in BNC, $r = -0.78$, $p = 0.041$. Change in connectivity between PCC and a visuospatial network was associated with the change in hunger score, $r = 0.91$, $p = 0.005$.

4. Discussion

The current study utilized a novel between-network connectivity (BNC) method [26] to determine effects of an exercise intervention on whole-brain integrative information flow in overweight/obese adults. This approach identified exercise-related changes in communication between large-scale neuronal networks and integrative "hub" regions. We have previously reported reductions in activity *within* the default mode network following exercise in this group [27]. However, the effects of exercise on whole-brain BNC have not previously been investigated. Thus, the current study expanded upon our previous work [11, 27] to examine exercise effects on large-scale network communication with individual voxels across the brain. Following the 6-month exercise intervention, reduced BNC was observed for the posterior cingulate cortex (PCC), a region identified as having high BNC at baseline. High BNC indicates that a region is functionally connected to numerous large-scale networks, and is thus likely important in information integration [26]. Reduced BNC in the PCC following exercise suggests that the intervention impacted information flow at a whole-brain level and between multiple large-scale networks.

The PCC is a prominent integrative hub and a key region of the default mode network (DMN) [38-44]. The DMN is a network of brain regions thought to reflect a baseline state of brain function most active when people are focused on internal mental states, such as in self-referential thinking and autobiographical memory, and during external unfocused attention (i.e., monitoring the environment) [39-41, 43-45]. Previous studies by our group and others have found that PCC DMN activity is increased in obese and overweight individuals [46, 47], and that activity in the region is reduced following chronic exercise [27]. Because these previous studies only examined activity *within* the DMN, the interpretation of the findings were necessarily limited to the primary functions of the network. As such, it was suggested that increased PCC DMN activity may reflect increased attention to internal states, such as appetite, an effect that may be lessened by exercise. The current study, however, suggests that exercise effects extend far beyond a single network.

The observed extensive interactions between the PCC, DMN and other brain networks is perhaps not surprising, given the extensive connections to and from this region. The PCC is the only node that directly interacts with all other DMN nodes, supporting this region's central role in integration of intrinsic activity [39, 40, 43, 44]. It also has structural and functional connections with myriad other non-DMN brain regions [42, 48-50]. The region has been implicated in a large number of processes requiring coordinated integration, including self-related processing [40, 41, 51], autobiographical memory [41, 52, 53], mind wandering [54, 55], emotional stimulus processing [56], evaluating personal significance [40, 41], reward outcome monitoring [57], and allocating neuronal resources to salient stimuli [38, 44, 50]. Likely as a component of these types of processes, PCC involvement has been observed in a number of processes related to food-intake behaviors and/or weight regulation. For example, PCC activation has been observed during presentation of visual food cues [58-60] and during food tasting [61, 62]. Furthermore, previous studies have identified a relationship between body mass index (BMI) and PCC responsivity to food cues [63], as well as altered PCC response to food cues in obese, compared to lean, individuals [64, 65].

To better understand the effects driving the observed BNC differences, an exploratory Granger causality analysis was performed to examine alterations in connection strength in both outgoing and ingoing causal information flow between the PCC and large-scale networks. These findings suggest that exercise may refine the flow of information between the PCC and a subset of large-scale networks. Observed reductions in outgoing connectivity from the PCC to other components of the DMN, such as the precuneus, and networks involved in various aspects of sensory processing (sensorimotor network, visual network) could relate to the role of the PCC in monitoring the external environment and accordingly allocating neuronal resources to salient stimuli [38, 44, 50]. The observed reduction in incoming information flow to the PCC from receptive components of language and sensorimotor networks could reflect a similar refinement in monitoring incoming sensory information. Changes in outgoing information flow from the PCC to the left executive control network could relate to improvements in cognitive function associated with exercise and physical fitness [9, 14-16]. Supporting this, exercise has been associated with altered neuronal responses during cognitive task performance in overweight children (decreased activation in precentral gyrus and posterior parietal cortex; increased activation in anterior cingulate and superior frontal gyrus) [66]. Furthermore, in older adults, exercise-associated alterations in functional connectivity have been associated with increases in brain-derived neurotrophic factor (BDNF) and other growth factors involved in synaptic plasticity, neuroprotection, and neurogenesis [67]. Specifically, increased connectivity within the DMN (between parahippocampal gyrus and middle temporal gyrus) following 12 months of exercise in older adults was associated with increased blood serum levels of BDNF, insulin-like growth factor-1 (IGF-1), and vascular endothelial growth factor (VEGF).

Change in aerobic fitness, as measured by VO2 max, was related to change in PCC BNC following the exercise intervention, such that greater improvements in fitness were associated with greater reductions in BNC. This effect was driven by changes in connectivity between the PCC and other components of the DMN. Voss et al. previously reported a link between VO2 max and DMN connectivity, including evidence that the

relationship between aerobic fitness and cognitive performance may be mediated by functional connectivity among various DMN regions [68]. The observed relationship between BNC change and VO2 max change in the current study further supports this hypothesis. As Voss et al. observed increased connectivity within the DMN to be associated with aerobic fitness and improved cognitive function, the present finding could suggest that exercise exerts differential effects on *within-network* connectivity versus *between-network* connectivity. Previous studies have posited that network refinement results from both increased within-network connectivity and decreased between-network connectivity [22, 69, 70].

Post-intervention change in perceived hunger, as measured by the TFEQ, was also associated with change in BNC, with less BNC reduction related to greater decreases in hunger. This was driven by changes between the PCC and a visuospatial network, possibly indicating altered salience of external visual cues post-intervention. Although there was no significant change in hunger scores following the intervention, the relationship between BNC change and hunger change could potentially relate to observed variability in appetite changes and compensatory energy intake following chronic exercise [71].

A potential limitation of the current study is sample size. Even with this limitation, however, the observed BNC changes suggest that the sample size was sufficient to detect effects. Subsequent studies with larger sample sizes may allow for detection of behavioral effects and a more in-depth examination of relationships between brain and behavioral effects. A session effect is another potential limitation, with the possibility that change in BNC could be due to scanning sessions simply being spaced 6 months apart, rather than due to exercise effects. Previous studies, however, have determined activity in large-scale brain networks, including the DMN, to be reliable and consistent across recording sessions, up to as long as 16 months between sessions [72-74]. Nonetheless, because reliability of the BNC metric used in the current study has not yet been reported, we investigated the possibility of session effects by identifying a group of individuals (N =10) who were not part of the current study, but who had completed resting-state fMRI scans spaced between 6 months to 1 year apart. As they were not included in the current study, this group of participants (mean BMI: 29.3 ± 7.1 mg/kg^2; mean age: 38.5 ± 11.6 years) did not participate in the exercise intervention. This group did not significantly differ from the intervention group in age, BMI, or BNC at baseline (p > 0.05). No significant between-session effects on BNC were observed in this group, suggesting that effects observed in the current study were not simply due to time between sessions. While this control group is helpful for examining potential session effects, future studies should include a group that participates in a control intervention for the same length of time as the exercise intervention, such as a diet or stretching group.

In conclusion, the exercise-associated reduction in between-network connectivity observed in the current study suggests an impact of exercise on information flow across the brain. Identifying the influence of exercise on communication between large-scale neuronal networks could be important for understanding how exercise causes neuronal and behavioral change. The current study represents an initial step in establishing these effects, by suggesting an impact of exercise on whole-brain communication involving the PCC, a

critical integrative hub, in overweight/obese individuals. Future studies are warranted to determine if exercise effects on BNC are similar in lean individuals, and if effects on BNC may be related to the variability of weight loss observed in response to exercise. Given that changes in obesity-related measures (e.g., BMI, percent body fat) were not related to BNC change, and that baseline BNC was not related to these measures at baseline, it seems likely that these effects could be generalizable to a non-obese population. Supporting this, our results are consistent with previous studies, focusing on within-network connectivity, that suggest exercise can improve network refinement and efficiency in populations different from the overweight/obese adults in the current study, specifically lean older adults [21, 68] and overweight children [22]. It is also possible that the impact of exercise on large-scale network communication at integrative hubs may contribute to individual responsivity to exercise, an effect that should be examined in future studies.

Acknowledgments

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Highlights

-Between-network connectivity (BNC) assessed exercise effects on brain connectivity.

-BNC in the posterior cingulate cortex was reduced following chronic exercise.

-Change in BNC was related to changes in aerobic fitness level and perceived hunger.

-Exercise effects on BNC may contribute to individual responsivity to exercise.
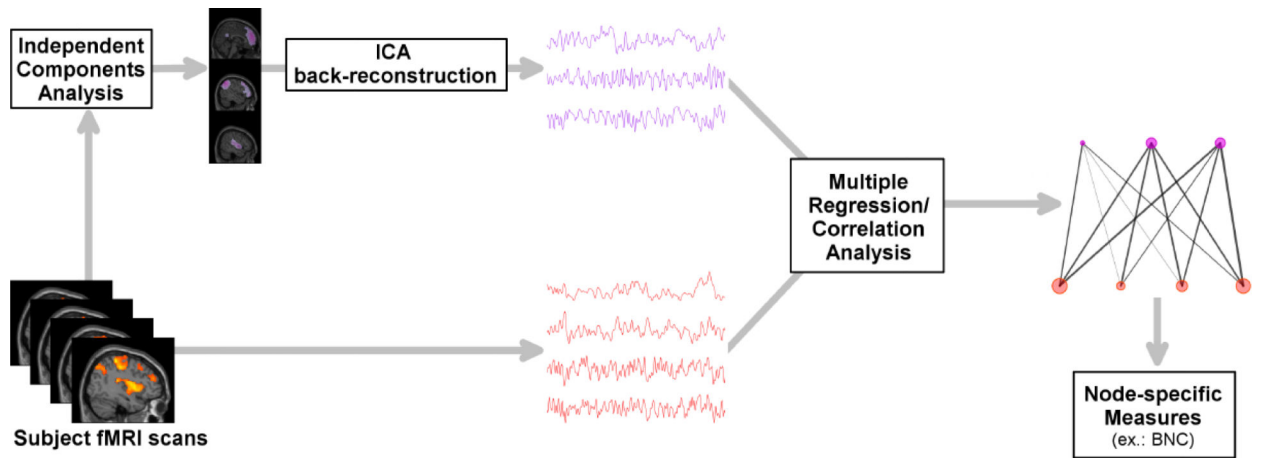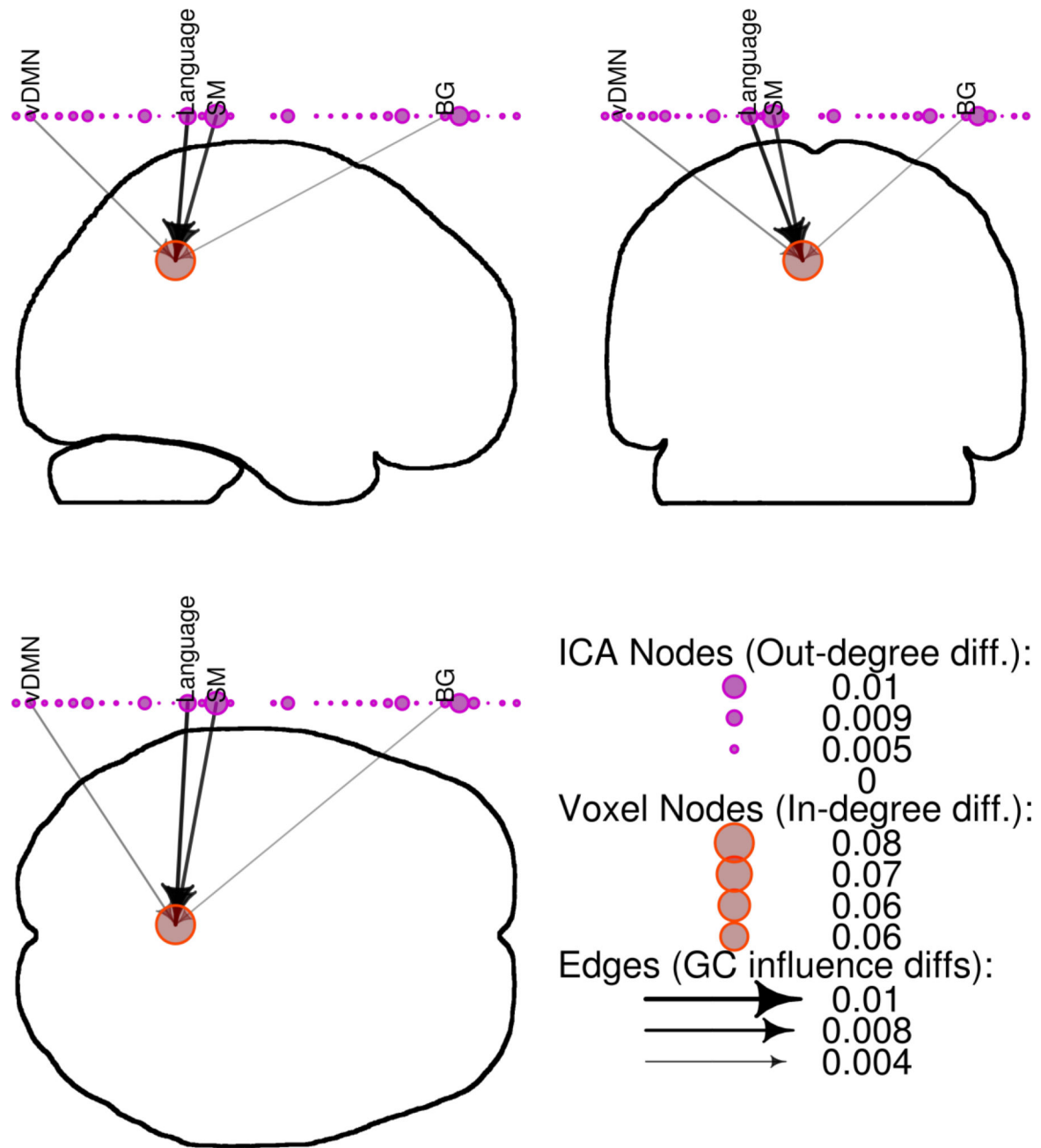
Figure 1.
Between-network connectivity (BNC) analysis pathway. fMRI: functional magnetic resonance imaging; ICA: independent components analysis; BNC: between-network connectivity.
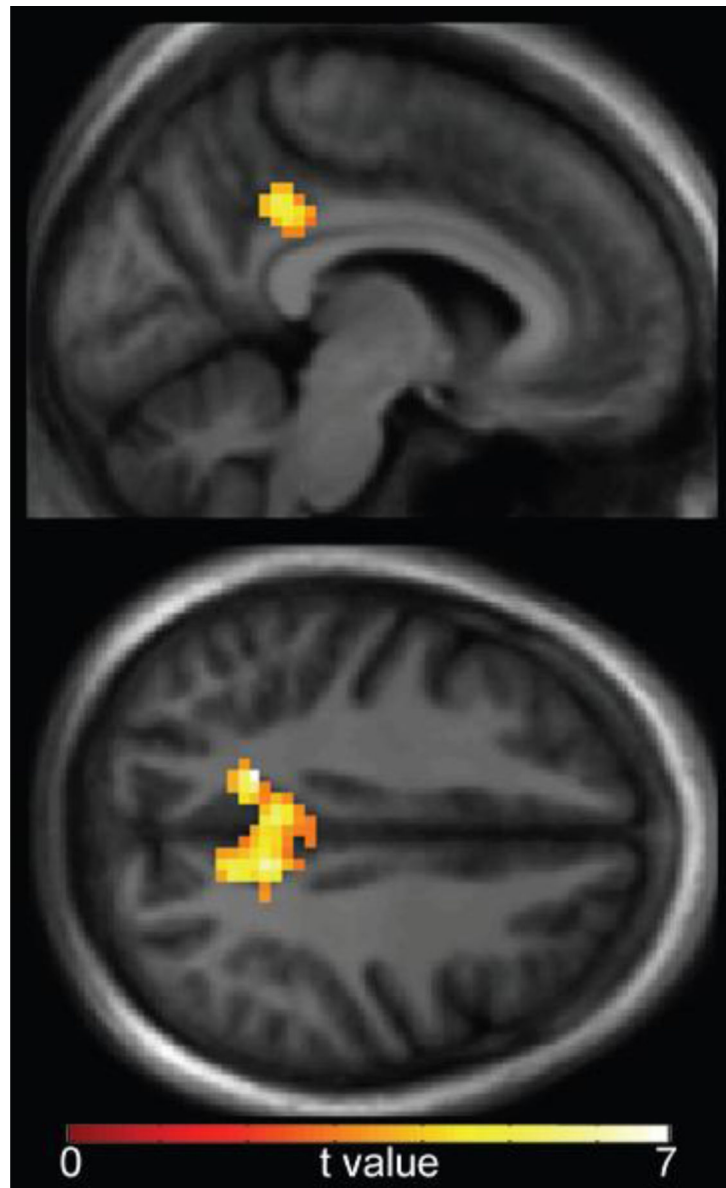
Figure 2.
Reduction in posterior cingulate cortex (PCC) between-network connectivity (BNC) post-intervention, compared to baseline. Data are thresholded at a voxel-wise threshold of p < 0.01 and a cluster-extent threshold of p < 0.05 (family-wise error-corrected for multiple comparisons), and overlaid onto a group-average anatomical image for visualization.
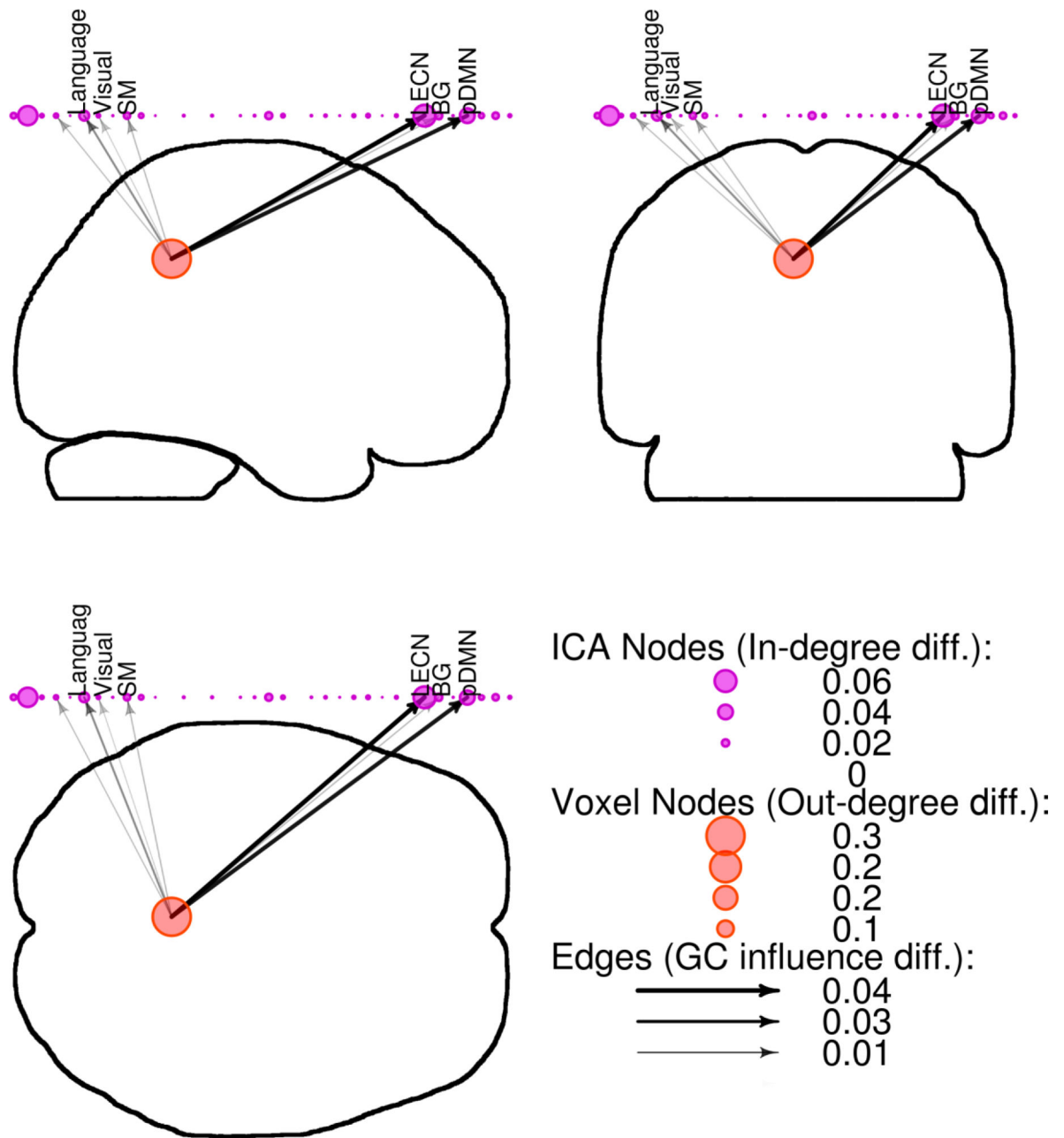
Figure 3.

Reductions in outgoing causal flow at the posterior cingulate cortex (PCC) following exercise. Granger causality (GC) results were displayed on whole-brain silhouettes ("glass brain") from three viewpoints, with PCC voxels represented by red circles, independent components analysis (ICA) networks represented by purple circles above the brain with descriptive labels, and GC strength and direction represented by black arrows. Language: language network; Visual: visual network; SM: sensorimotor network; LECN: left executive control network; BG: basal ganglia network; pDMN: posterior default mode network.

Figure 4.
Reductions in ingoing causal flow at the posterior cingulate cortex (PCC) following exercise. Granger causality (GC) results were displayed on whole-brain silhouettes with PCC voxels represented by red circles, independent components analysis (ICA) networks represented by purple circles above the brain with descriptive labels, and GC strength and direction represented by black arrows. vDMN: ventral default mode network; Language: language network; SM: sensorimotor network; BG: basal ganglia network.

Table 1

Eating behaviors and appetite measures, at baseline and post-exercise intervention.

Measure	Baseline		Post-Exercise	
	Mean	**SEM**	**Mean**	**SEM**
TFEQ: Restraint	9.1	1.2	9.0	1.4
TFEQ: Disinhibition	8.8	1.3	8.0	1.1
TFEQ: Hunger	5.9	1.0	4.9	1.0
CMQ	37.6	8.1	34.1	7.0
FCI	40.8	4.4	35.4	4.7
PFS	51.6	7.5	41.7	6.4
Hunger AUC	133.9	16.4	187.4	44.1
Satiety AUC	441.0	44.1	399.4	53.8
PFC AUC	192.4	24.5	236.4	40.7

TFEQ: Three Factor Eating Questionnaire; CMQ: Craving and Mood Questionnaire; FCI: Food Craving Inventory; PFS: Power of Food Scale; AUC: area under the curve in response to a meal; PFC: prospective food consumption.

Table 2

Between-network connectivity (BNC) peaks at baseline.

Region	Local maxima coordinates[a]			t value[b]	cluster size	p value[c]
	x	y	z			
Precentral gyrus (R)	42	−19	43	8.08	4168	<0.001
Postcentral gyrus (R)	54	−16	49	6.90		
Superior frontal gyrus (L)	−24	−7	58	6.35		
Posterior cingulate cortex	0	−28	31	5.35		
Anterior insula (R)	36	17	4	9.18	315	<0.001
Posterior insula (R)	33	−13	10	3.44		
Anterior insula (L)	−36	8	4	5.80	209	0.004
Insula (L)	−36	−1	7	5.03		
Insula (L)	−36	−7	−8	3.16		
Cuneus (L)	−12	−79	31	4.89	1435	<0.001
Cuneus (R)	9	−82	28	4.74		
Lingual gyrus (L)	−15	−70	−11	4.62		
Parietal operculum (R)	48	−19	16	5.21	190	0.006
Superior temporal gyrus (R)	66	−22	7	3.98		
Superior temporal gyrus (R)	63	−34	16	3.77		

[a] Stereotactic coordinates in MNI space.

[b] t values reported for local maxima within clusters.

[c] p values for significant clusters, corrected for multiple comparisons across the entire brain volume.