Physiology & Behavior 158 (2016) 60–67

Contents lists available at ScienceDirect

Physiology & Behavior

journal homepage: www.elsevier.com/locate/phb

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

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

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.

ARTICLE INFO

Article history:
Received 18 October 2015
Received in revised form 15 February 2016
Accepted 22 February 2016
Available online 23 February 2016

Keywords:
Exercise
Obesity
Posterior cingulate cortex
Default mode network
Between-network connectivity
fMRI

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 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.

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

---

[*] Corresponding author at: 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, United States.
E-mail address: Kristina.Legget@ucdenver.edu (K.T. Legget).

http://dx.doi.org/10.1016/j.physbeh.2016.02.031
0031-9384/

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 > 17; (3) respiratory exchange ratio > 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 3.0 T 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 min of rest with eyes open.